EDITORIAL

What is Immunologic Competence? An Attempt to Define the Attributes of the Immunologically Functioning Cell

By Arthur M. Silverstein and Robert A. Prendergast

The recent appearance of editorials by Dameshek and by Berman on the morphology, functions, and interrelationships among immunologically active cells has served as a new focus for the continuance of the important debate about the origin and role of these cells. On the theory that any good argument can only be improved and hopefully clarified by open discussion and even by respectful disagreement, several questions are raised that seem to deserve further consideration.

The first point involves the inevitable question of acceptable nomenclature. What precisely is meant by immunologic competence? It must be recognized that this term is employed at times with two distinct meanings. The first usage, more prevalent in Europe but employed here also, involves cells which, as the dictionary defines competence, are “qualified” or “capable” of reacting with antigen to become immunocytes. The second meaning encompasses those cells which have already experienced antigenic stimulus and now possess immunologic memory, i.e., cells that are primed for some sort of rapid secondary response to antigen. These latter will henceforth be termed immunocytes. (The thinness of the ice under this position is apparent, since the immunologic selectionist would recognize no valid distinction between these two cells. Until selection theories become more firmly founded than at present, however, this distinction should be kept in mind and will be retained in the following discussion, without necessarily implying irrevocable acceptance of an alternative instructionist approach.)

The next question to be asked is—which cells are able to give rise to immunocytes? Which cells are competent to respond to antigenic stimulus and to incorporate immunologic memory? Berman suggests that the lymphocyte, arising ultimately from the thymus, is the forbear of all immunocytes. With the recent implication of the bursa of Fabricius, and possibly of the appendix, this view has been somewhat diluted (so that the apparently flip-pant comment that the thymicologists are in danger of rediscovering the reticuloendothelial system may ultimately be shown to contain the seed of truth). Dameshek, on the other hand, appears willing to attribute a readiness to respond to antigen to both the lymphocyte and the reticuloendothelial cell or histiocyte. Though far from conclusive, there is also a suggestive body of literature implicating perithelial and perhaps other fixed mesenchymal cells as potential precursors of antibody-producing plasma cells. It is difficult to conceive that these cells, arising from the primitive mesenchyme, orig-
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mate from thymic seed. Thus, if Maximow's concept of the ubiquity and multipotentiality of the mesenchymal system still carries any validity, one must be prepared for the possibility that any primitive mesenchymal cell may be able to assume immunologic function, some perhaps less readily than others and some perhaps involving a preliminary transformation or modulation.

It may next be asked—what morphologically recognizable cell types can function as immunocytes; that is, which cells may carry and utilize immunologic memory? Both Dameshek and Berman indicate that the immunocyte system comprises the lymphocyte, the plasma cell, and intermediate stages back to the "immunoblast" or basophilic lymphoblastoid cell. Again, it may be suggested that this is not adequately comprehensive. The passive transfer of delayed hypersensitivity with peritoneal exudate cells (predominantly macrophages) certainly implicates the circulating macrophage as a carrier of immunologic information, and there is reason to suspect that the reticulum cell of lymphoid tissue may be able to participate in an anamnestic antibody response.

Along these same lines, another point deserves consideration. This concerns the fate of those cells which actively participate in the immune response. Some of them seem also to differentiate into other mesenchymal forms, so that numerous two-way arrows would appear necessary in any diagram of the immunocyte complex, indicating the great extent of the cellular interchange that is probable. In this regard, most formulations treat the mature plasma cell as an end-of-the-line form (as the small lymphocyte was once treated). They suggest, either implicitly or explicitly, that the plasma cell dies in situ. But careful examination of plasmacytic infiltrates consistently fails to furnish evidence of dying plasma cells. This calls to mind the familiar question of where elephants go to die, since their corpses are seldom seen. If the plasmacytic elephant does not die on the spot and instantaneously vanish, and if it does not leave the scene in its original form to return to the circulation, then perhaps it changes from an elephant into some other familiar and ubiquitous local animal like a hippopotamus (lymphocyte and/or histocyte?) and leaves the scene in this new guise.13

These considerations lead to perhaps the most significant question of all. What are the attributes conferred upon a cell by virtue of its immunologic training, and precisely how far do they dictate its structure and govern its activities? From another standpoint, the question takes the form—how uniquely immunologic is the immunocyte, and how highly committed is it to a purely immunologic function? It has become quite clear recently that the greater proportion of the cells at the site of an immunogenic lesion (delayed hypersensitivity or homograft reaction) are not carriers of specific immunologic knowledge.14,15 But what of those which are true immunocytes? Do they pass their time waiting only for the reappearance of the antigen to which they are committed? All evidence points to a negative answer to this query. The very manner of performing passive transfer experiments with buffy coat cells, with thoracic duct lymphocytes, or with peritoneal exudate cells, points to the fact that the lymphocytes and monocytes responsible for the transfer not only circulate normally, but even participate in nonspecific
inflammatory responses unrelated to their immunologic prowess. This would suggest that despite their immunologic knowledge, these cells nevertheless may fulfill some more general biological function.

If the immunocyte is not uniquely oriented while awaiting a new antigenic stimulus, is its response to antigen biologically unique? On the basis of present knowledge, the antibody-forming immature and mature plasma cell appear to be unique in this sense, at least so long as it remains a plasma cell—later, it may change its form, go elsewhere, and function differently. (Whether plasma cells are invariably concerned with antibody formation, or may function in a non-immunologic manner, is presently unclear. Suggestive along these lines is the occurrence of plasma cell neoplasias, virus-induced plasma cell hyperplasias, and fetal production of "normal" gamma globulin, all involving plasma cell and globulin production with no demonstrable antibody specificity. An immunologic basis for these phenomena has yet to be provided.)

But what of the response of the circulating immunocytes? How does antigen direct their activities? Despite the early suggestion of Rich and Lewis, recent evidence has indicated that these cells do not die upon contact with antigen in the development of a delayed lesion or a homograft infiltrate. Nor do they appear able to phagocytize and destroy antigen or antigen-bearing cells more competently than their nonsensitized fellows. But if this be true, wherein lies the special attribute of the immunocyte? The only specific effect of antigen upon these cells demonstrated conclusively appears to be a stimulus toward proliferation and differentiation. The result of this induced activity is the accelerated production of more of the same types of cells. In the lymph node undergoing an anamnestic antibody response, many of these daughter cells are undoubtedly immunocytes, since plasmacytosis follows rapidly. In the local immunogenic inflammatory site, information is largely lacking as to whether all of the descendants are also immunocytes. Under certain conditions, some of them do differentiate into plasma cells (perhaps the local analog of the anamnestic antibody response). Those newly arisen cells at the delayed lesion or graft rejection site which do not finally become plasma cells may in fact play no further immunologic role but rather may merely satisfy the more general biologic function of lymphocytes and phagocytes alluded to earlier.

All of these considerations point to the fact that, local plasma cell formation apart, the effect of antigen upon the circulating immunocyte population is to accelerate all phases of the development of the chronic inflammatory infiltrate. Beyond this, all subsequent events in the delayed hypersensitivity lesion would appear to be nonspecific. If phagocytosis occurs, and especially if it is accelerated by the opsonizing activity of antibody (and that produced locally by plasma cells at the lesion would be most effective), then it seems to occur after the immunologic fact and not as a manifestation of specific immunocytologic function.

Thus, the attributes of the immunologically functioning cell may not confer as far-reaching potentialities as had earlier appeared probable, nor, in the main, do they imply as much biological uniqueness. The possibilities which
do suggest themselves from the above discussion are: (1) that the circulating mononuclear cells may fulfill some such general biological role as defense, via the inflammatory reaction in the sense of Metchnikoff; (2) that the immunologic response, including the phenomenon of delayed hypersensitivity, may have evolved by natural selection as nothing more than an improved adaptation of the defensive inflammatory response. This would involve the accelerated accumulation of inflammatory cells including the all-important phagocyte and a more rapid proliferation of these cells both at the local site where they would be most effective and in the lymphoid tissue supporting the defense reaction; (3) that the most highly involved immunocyte of all, the plasma cell, may present a further evolutionary refinement of the defense mechanism. Among the protective roles generally accorded to antibody is its function as a detoxifying agent, a bacteriocidal and bacteriostatic agent, and perhaps most importantly as an opsonin to accelerate phagocytosis. But in addition, the interaction of antibody with antigen accelerates almost all cellular and vascular phases of inflammation, and evokes the nonspecific assemblage of yet another phagocytic cell type, the neutrophil leukocyte. It will be recognized that the ability of the circulating immunocyte to differentiate into a plasma cell at the site of a lesion in response to appropriate antigenic stimulus brings all of these benefits of the antibody to bear where they are most needed.

Implicit in the above is the suggestion that the immunologic response is not unique in the sense of Burnet, and further, that the usual dichotomy set up in immunology between immunity (protective) and hypersensitivity (destructive) may be artificial and deceiving. All of the reactions associated with the immune response may be viewed as mediating or catalyzing the general biological phenomenon of defense. If the outcome is sometimes the development of an "allergic" lesion to a bland antigen, this may not constitute a distinct mechanism. Rather it may only indicate the potential problems associated with any biological system and the fact that, after all, the organism does not distinguish pathogenic from non-pathogenic antigens and responds indiscriminately and to the best of its fairly limited abilities to both.

REFERENCES


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