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Immunology Taught by Viruses

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The survival of viruses depends on the survival of susceptible hosts. The vertebrate immune system and viruses have therefore coevolved complementary facets. Evidence from various balanced virus-host relationships illustrates that immunological specificity and memory may best be defined biologically and that the mature immune system does not discriminate between "self" and "nonself." Rather, B cells distinguish antigen patterns, whereas T cell responses depend on localization, transport, and kinetics of antigen within lymphatic organs.

Historically, immunology developed from studies of the pathogenesis and prevention of infectious disease (*1*). The need for purified antigens, which were not available from infectious agents until recently, led to the introduction of model antigens into immunology. Responses to model antigens, proteins, haptens, and synthetic oligopeptides have been instrumental in identifying many of the ground rules underlying the immune responses (*2*, *3*); however, generalization on the basis of some of these results may be inappropriate, because the responses are not important for the survival of the host. Definitions of specificity, memory, and tolerance, the key parameters of the immune response (*1*), can now be reevaluated in infectious disease models owing to enormous methodological progress in biochemistry, molecular biology, embryology, and animal physiology. These parameters are reviewed here with the aim of arriving at a concept of immunobiology that reflects the coevolutionary balance reached between the immune system and viruses to guarantee survival of both virus and host (*4*–*10*). Three basic scenarios are presented: (i) immunity dominates cytopathic virus, (ii) noncytopathic viruses dominate the immune system, and (iii) the two scenarios are delicately balanced during acute or chronic infections (*5*, *11*–*15*) (Fig. 1). The nature of the interaction is influenced by viral parameters, such as cytopathogenicity, kinetics, cell and tissue tropism, susceptibility to other resistance mechanisms (for example, interferons), and host reservoirs; and by variables of the immune system, including the specificity, kinetics, and duration of humoral and cell-mediated immunity (*1*, *4*–*10*), in association with nonspecific effector mechanisms such as complement, hormone-like factors (interleukins), and phagocytes.

Specific humoral immunity is mediated by antibodies, which are produced and released into the blood by plasma cells, which in turn are derived from B cells (*1*, *9*, *12*–*16*). These antibodies recognize conformational determinants on proteins, carbohydrates or particulate antigens (such as viruses and bacteria) on mucosal membranes, and in the blood. However, with the exception of lesions, they cannot enter solid tissues. Cellular immunity is mediated by T cells, which differentiate in the thymus to express T cell receptors that are specific for small peptides presented by major histocompatibility complex (MHC) molecules (*17*, *18*). Peptides derived from internal proteins—components of the cell itself or of a virus infecting the cell—are, in general, presented by MHC class I molecules; they are recognized by $CD8^+$ T cells, which may destroy cells by cytotoxicity or release cytokines (or both). Peptides derived from phagocytized proteins—originating in the host or from infectious agent—are digested and presented by MHC class II molecules. These peptides are recognized by cytokine-releasing $CD4^+$ T helper cells, which usually are nonlytic. Because of this MHC-restricted recognition, T cells monitor only cell-associated alterations. This characteristic, together with their capacity to recirculate and, after activation, to emigrate into peripheral organs, renders T cells well suited for the surveillance of cellular integrity in solid tissues. Specific recognition of antigen by antibodies and T cells usually initiates powerful nonspecific effector mechanisms that control and eliminate infectious agents by complement activation, recruitment of inflammatory cells, phagocytosis, cell destruction, and interference with cellular function (*1*).

The critical effector mechanisms for recovery from primary infection, resistance against reinfection, or protection of physiologically immunodeficient young offspring are summarized in Table 1. Cytopathic viruses are stopped most efficiently by soluble, diffusing antiviral interleukins (*19*) that halt virus replication by rendering surrounding

Table 1. Critical immunological effector mechanism for recovery from and resistance to infection.

Recovery from first infection	Resistance against reinfection	
Lymphoid and peripheral organs	Lymphoid organs	Peripheral organs
Cytopathic virus		
T-dependent cytokines and neutralizing antibodies, both amplifying antiviral effects beyond individual effector cells	Neutralizing antibodies	Activated T cells releasing cytokines
Noncytopathic virus		
Cytolytic T cells individually lyse cells and stop virus replication; released viral antigens induce additional immune responses. Protection causes host cell damage	Increased neutralizing antibodies, cytotoxic T cell precursors	Activated cytolytic T cells

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cells resistant against viral replication and direct damage caused by virus. Noncytopathic virus is stopped by $CD8^+$ cytotoxic T cells (CTLs) that destroy infected host cells before they release their progeny; this mechanism also releases viral antigens that induce T helper and antibody responses. Because the cytotoxic protective T cell response causes damage to infected host cells, the balance between viral spread and the kinetics of this T cell response determines whether immune protection—that is, elimination of the virus—or immunopathology will predominate. Neutralizing antibodies are very efficient in preventing reinfection and hematogenic spread of virus (*16*).

Specificity

Specificity for antigen is determined by the binding forces between antibodies and three-dimensional protein or carbohydrate structures (*11–15, 20, 21*), and between T cell receptors and MHC-peptide complexes (*22*). Although such parameters are measurable in vitro, it is often unclear how they correlate with protection against infectious agents or toxins in vivo. Specificity is therefore best defined operationally, by the capacity of antibodies or T cells to distinguish between structures—peptides or crucial antigens of infectious agents, such as distinct viral serotypes that do not cross-react—relevant for host survival.

The definition of specificity depends on the method of measurement used. Neutralization activity in vitro against a virus usually correlates well with protective activity in vivo and depends on an antibody affinity (avidity) of about 10^8 to 10^{10} liter mol^{-1} (*11–15, 20*). In contrast, antibody-binding assays may detect considerably lower affinities (down to 10^6 liter mol^{-1}) and are therefore less stringent. Protective specificity based on in vitro assays for T cells is even more difficult to define, because binding affinities cannot easily be measured (*17, 22*). Nevertheless, studies suggest that functional readouts of T cells in vivo are considerably more stringent than several in vitro methods, such as detecting thymidine uptake as a monitor of proliferation, or the release of interleukins into culture supernatants (*23*). It can therefore be argued that immunological specificity is best tested directly in vivo: for antibodies, by the presence or absence of cross-protection (*11–15*); for cross-reactive or specific helper ($CD4^+$) T cells, by the switch from immunoglobulin M (IgM) to IgG production or by activation of macrophages (*1*); and for ($CD8^+$) CTLs, by reduction of virus titers and protection from immunopathological host cell damage in solid organs (*24, 25*). However, the precise nature of a protective response or the key parameter of that response is often unknown. For example, where T cell cytolysis, interleukin production, and antibody responses are all produced, which is the most critical? For an antibody response, is it the affinity (binding of one antibody-binding site), the avidity (the combined binding strength of the molecularly interlinked binding sites), or the concentration of antibody in serum or in tissue that is most important? And what is the role of somatic mutation of antibodies for immune protection?

Germline-encoded antibodies versus affinity maturation. Cytopathic viruses must not be too successful in killing the host, otherwise they may jeopardize their own survival. Because of this coevolution, it is debatable whether the antibody germline genes have coevolved to comprise relevant specificities or whether the cytopathic infectious agents, using great numbers and mutations, have adapted to the available basic immunological repertoire. One mechanism whereby the host antibody response adapts to variation of infectious agents may be by affinity maturation of antibodies. This process occurs by selection of somatic point mutations, mostly in the binding areas of specific IgG receptors of B cells, and has been shown to result in an overall increase in affinities (avidities) of IgG against hapten antigens with time (*3–10*).

For neutralizing antibodies against cytopathic viruses, affinity maturation may not be possible (because the host would die too soon), or it may have to occur very early (*15, 20, 21*). In contrast, slow affinity maturation of the antibody response to noncytopathic viruses may permit wider spread and prolonged transmission of the virus. It has been proposed that affinity maturation establishes antibody memory more economically and that it may allow immunological responses to "catch up" with virus mutants during an ongoing infection, but these ideas remain to be demonstrated (*26*).

Some of the finest examples of immunological specificities are serologically distinct virus mutants that evolve, under the pressure of an ongoing or established immune response, to escape either neutralizing antibodies or cytotoxic T cell recognition. Influenza viruses represent the best studied examples of how viruses, by modulating viral antigen, and how various host species, by varying neutralizing antibodies, have coevolved (*12, 13, 27*).

Noncytopathic viruses (but obviously not cytopathic ones) may escape protective CTL responses by mutating the peptides that comprise the relevant T cell epitope (or epitopes) (*28, 29*). Whereas antibodies strongly influence the evolution and the worldwide epidemics of serologically distinct viruses, mutant viruses that escape CTL recognition have been observed to arise in individual hosts only. This is because T cell recognition is restricted by the MHC, an extremely polymorphic set of genes. MHC restriction–dependent escape mutations of noncytopathic viruses may, nevertheless, slowly accumulate in a population in order to escape most MHC presentations and T cells; noncytopathic virus-

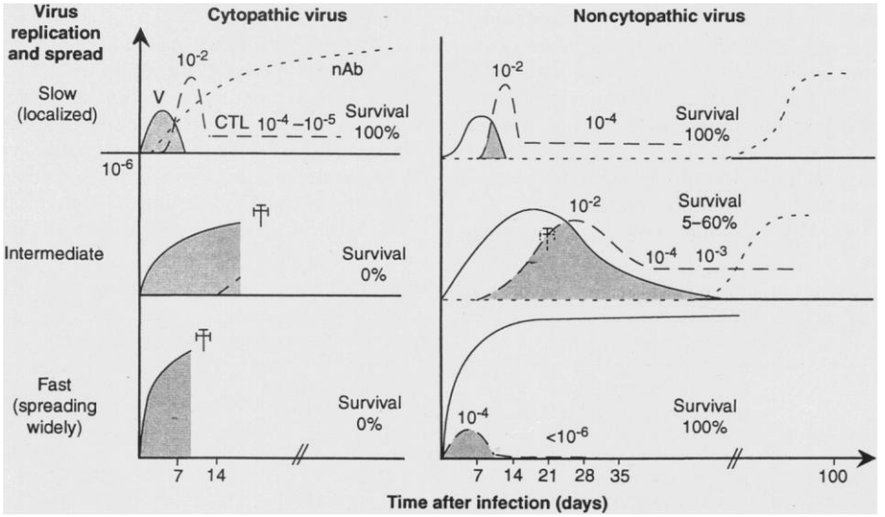

Fig. 1. Paradigms of virus and immune response kinetics. Idealized summary of cytopathic or noncytopathic virus kinetics versus kinetics of the immune responses as they determine disease evolution. Comparison of virus titers (V, solid line), $CD8^+$ T cells (CTL, long dashed line; precursor frequencies in spleen are indicated as 10^{-2} to 10^{-6} values), or neutralizing antibody titers (nAb, short dashed line) dependent on time after infection. Shaded area indicates the period of disease. In this scheme only the virus kinetics were changed from slow to fast, but the overall equilibrium between virus and immune response can also vary similarly if immune responses shift from fast and extensive to slow or quantitatively reduced.

es may, therefore, eventually reduce disease-causing immunopathology in otherwise susceptible hosts.

Immunological Discrimination: T Cells

The immune system reacts against foreign antigens, but usually not against self antigens. Because autoimmune diseases are relatively rare in young humans (up to 30 years of age), the immune system (that is, T cells) has been defined by Burnet, Fenner, Medawar, and Lederberg as distinguishing self from nonself. The decision as to what the immune system accepts as self and as foreign is classically considered to be made in the thymus during T cell differentiation. This "central tolerance" is very efficient and suggests that maturing thymocytes are particularly susceptible to deletion by self antigens expressed in the thymus; this mechanism is in place by the time immunocompetence is reached by T cells, at about 7 to 10 weeks of gestation in humans and at birth in mice (*1, 30*). However, although not all self-encoded antigens are represented in the thymus, mature T cells are nevertheless unresponsive. In addition, certain locations are not readily accessible to T cells; at these immunologically privileged sites, self-encoded as well as foreign antigens are usually not recognized and not reacted against. To explain these findings, mechanisms of "peripheral tolerance," such as anergy, vetoing, suppression, and deletion, have been postulated (*31–35*). Peripheral T cell tolerance is now usually discussed in terms of two-signal models of lymphocyte induction (*9, 10, 34, 35*). According to the two-signal model, antigen (signal 1) without an additional lymphokine or other form of signal 2 turns T cells off; antigen together with a helpful signal 2, optimally provided by professional antigen-presenting cells (APCs, such as dendritic cells), induces T cells.

An alternative model of discrimination is presented here (Table 2), in which the immune system does not distinguish between self and nonself but reacts against any antigen, according to the following six principles. (i) Antigen that is always present in the thymus and in lymphoid tissue deletes T cells. (ii) Induction of effector cells occurs only in organized lymphoid organs; therefore (iii) antigen must be brought into lymphoid organs by way of blood or mobile APCs, and (iv) antigen must enter the immune system in a localized fashion (that is, antigen reaches lymphoid organs from a localized peripheral infection and induces an immune response before spreading further, to avoid exhaustive induction). (v) The rules for T and B cell induction are not the same: B cells are essentially pattern recognizers. (vi) Antigen is the positive regulator of the immune system. If antigen is controlled or eliminated, immune responses disappear; if antigen persists at high levels, immunopathology results; and if antigen persists at very low levels, it helps to maintain protective immunological memory.

Rules for the induction of mature T cells. Cytopathic (and therefore dangerous) infectious agents, such as smallpox or polioviruses, are usually efficient inducers of T or B cell responses. They either infect migrating APCs in the periphery or in lymphoid organs directly, or release, by cytopathogenicity, antigens that are taken up by mobile APCs (dentritic cells) to induce T cells, or to induce B cells directly. In contrast, experimental induction of immune responses against soluble foreign antigens, and against some self-encoded antigens not expressed in the thymus, is usually difficult to achieve. It is much easier when monomeric antigen is rendered "infectious agent–like" by mixing directly with inflammatory granuloma-forming bacteria, or by aggregation or absorption onto particulate alum to enhance uptake by APCs (*1, 8, 36*).

Indifference of T cells. Antigens that are not present on migrating professional APCs and that stay outside of lymphoid organs are ignored by T cells. For example, cytopathic rabies virus in neuronal axons (a rare but usually lethal infection) or noncytopathic papilloma virus in keratinocytes (a common but harmless infection) is usually initially ignored by T cells. These viruses induce immune responses only after the relevant antigens have been released from destroyed cells and are taken up by mobile professional APCs (*37*). The same is probably true for many self-encoded antigens, which are neither expressed nor picked up in sufficient amounts by mobile professional APCs (*38*). These antigens therefore do not usually reach lymphoid tissues and are ignored (Table 2), and no autoimmunity is induced. This finding has been documented in a transgenic mouse model, where a viral glycoprotein was expressed in pancreatic β-islet cells. These mice did not develop diabetes and seemed to be tolerant. However, after infection also of some APCs with the relevant virus, CTLs were promptly induced; they destroyed the islet cells and caused diabetes within 10 days. There is therefore no obvious conceptual need for a special state of unresponsiveness for T cells with these specificities (*31–35*).

Exhaustive induction of T cells. There is a second, diametrically opposite situation in which mature T cells generally fail to react (Table 2) (*39*). During some generalized infections with noncytopathic viruses [for example, lymphocytic choriomeningitis virus (LCMV) in mice and hepatitis B or C virus (HBV, HBC) in humans], all antigen-specific T cells may be deleted. In the normal course of infections, only about 10 to 30% of potentially reactive T cells are induced and become effector cells; most of these die after 2 to 4 days, as soon as antigen has been eliminated. However, an excess of antigen on numerous APCs in lymphoid organs and spread throughout the periphery (such as may happen during overwhelming infection with noncytopathic viruses) may induce all antigen-specific responsive T cells. The matured effector T cells also all die off within a few days, resulting in the deletion of this specificity from the repertoire. An example is the infection of mice with rapidly spreading LCMV isolates that, by exhausting protective $CD8^+$ T cell responses and by spreading to the thymus, may readily establish a persistent virus infection (*39*) after rapidly spreading intravenous infections but not after localized subcutaneous challenges (Table 1). This may represent another example of successful coevolution

Table 2. Immune responses of mature T cells: Role of antigen localization and distribution kinetics. Antigen in periphery is defined here as associated only with nonlymphohematopoietic cells and not in lymphoid organs. Localized antigen is that in few lymphoid organs and is associated with a few APCs or nonhematopoietic cells. When antigen spreads throughout an organism, it can be found on APCs, in lymphoid organs, and associated with nonlymphohematopoietic cells.

	Antigen in periphery	Localized antigen	Antigen throughout system
Reaction of T cells	Indifference	Induction	Deletion
Examples			
Foreign (viruses)	Rabies virus in axons; papilloma virus in keratinocytes	Smallpox, measles in mucosa plus local lymph node; HBV, LCMV low dose localized infection	HBV or HCV (high dose) via blood transfusion, LCMV (high doses; rapidly replicating)
Self-encoded antigens	Sequestered myelin basic protein, eye lens, pancreatic islet cell	Myelin basic protein mixed with adjuvants	Self-encoded antigen already deleted in thymus

of virus and host: whereas cytopathic viruses must induce an effective T cell response early to prevent extensive viral pathology, noncytopathic viruses, by exhausting the antivirally protective $CD8^+$ T cell response, may avoid lethal, immunopathological destruction of infected cells. The mechanisms of exhaustion and the question of whether negative selection in the thymus is distinct from or similar to T cell exhaustion in the periphery remain to be evaluated.

$CD4^+$ T helper cells can be exhaustively induced experimentally with high or low doses of soluble model protein antigen (*1, 40*), but so far this has not been found to occur naturally after overwhelming infections with noncytopathic viruses. This difference between $CD8^+$ and $CD4^+$ T cell induction may reflect the fact that T helper cells do not directly lyse altered host cells and are essential for protective antibody responses against most cytopathic viruses; therefore, exhausive induction should be minimized. This result is achieved by confinement of MHC class II–associated antigens largely to lymphoid organs, where sufficient levels of the necessary interleukins are available. In contrast, $CD8^+$ T cells may encounter specific antigen in nonlymphoid organs, where they may die of interleukin deprivation. In the absence of $CD8^+$ T cells, and because T helper and B cell responses alone are often insufficient to eliminate noncytopathic viruses, chronic immune responses of T helper and B cells may be maintained; these can generate excessive amounts of interleukins and antigen-antibody complexes, resulting in chronic inflammatory immunopathological disease (*41*).

A redefinition of mature T cell discrimination. The vastly different host-virus relationships observed indicate that there is no difference in the physical-chemical characteristics of antigens that render them self or nonself, infectious or noninfectious, dangerous or harmless. Such characteristics, as a result of coevolution, are determined by the biology of the antigen, whether self-encoded or foreign. Therefore, for mature T cells, antigen localization, transport, and distribution kinetics determine whether immune reactivity is induced, maintained, or aborted. By coevolutionary necessity, cytopathic viruses induce protective immunity efficiently, to avoid elimination of the essential host species. Against noncytopathic viruses, control of virus is only indirectly relevant; it is more important to control the immunopathological immune responses, which are harmful to the host.

This concept extends and changes that of "self-nonself discrimination" defined by Burnet and Lederberg (*30*) and recent proposals based on two-signal theories by Bretscher, Cohn, and Langman, by Lafferty, by Schwartz, by Janeway, and by Matzinger (*9, 10, 34, 35*). According to these postulates, the following rules explain T cell responsiveness: T and B cells must be tolerizable (or anergizable). Inducible immune cells become anergic, or die, if the antigenic signal (signal 1) is received without costimulation (signal 2). Signal 2 can only be delivered by professional APCs. By using these rules, it was postulated that the immune system discriminates "infectious-dangerous-nonself" from "noninfectious-harmless-self." In contrast, not only toxic or cytopathic antigens, but also normally harmless antigens (such as noncytopathic viruses) can be dangerous, because they induce dangerous immunopathology. Therefore, antigens differ not with respect to whether they are self or nonself, infectious or noninfectious, dangerous or harmless; rather, antigen localization (in lymphoid tissue versus outside) and transport via migrating cells (distribution-concentration kinetics) determine whether mature immune cells will be induced to react and for how long.

Immunological Discrimination: B Cells

Neutralizing antibody responses against viruses prevent reinfection against the most important acute cytopathic human viruses, such as polio, measles, and mumps. But antibodies may also be of critical importance in some primary infections. In several model infections, the absence of B cells or $CD4^+$ T helper cells (or both) results in impaired virus clearance and death [for example, vesicular stomatitis virus (VSV, a close relative of rabies virus) in mice]. Many viruses, including VSV, exhibit highly repetitive neutralizing determinants in a rigid, two-dimensional crystal–like form on their surface glycoproteins that trigger an early (days 3 and 4) and completely T cell–independent IgM response, which by day 6 switches to a protective IgG response only in the presence of T help (*11–16, 42, 43*). Because VSV is not a polyclonal B cell activator, these results suggest that in mature B cells, receptor cross-linking is critical to induce IgM responses (*42, 43*). In the absence of T help or signal 2 (Table 3), such efficient direct and early B cell induction and expansion are not maintained, but the enormously expanded B cell population is now a target for T help, thereby guaranteeing early, long-lasting, and highly protective IgG responses. Several other serologically distinct viruses exhibit neutralizing glycoprotein determinants in the viral envelope that are spaced about 5 to 10 nm apart. In bacterial and repetitive hapten antigens, this distance has been found to be optimal for the triggering of mature B cells (*44, 45*). In the case of VSV, only the VSV particles themselves—exhibiting a rigid, two-dimensional antigen pattern—are strictly T-independent antigens (that is, they induce B cells directly); other forms of VSV-G, such as purified recombinant protein (that is, antigen monomers) and vaccinia VSV recombinant virus (which induces VSV-G as a mobile cell surface antigen in a semifluid membrane) depend on varying forms and decreasing degrees of T help (*42–45*).

These findings indicate that rigid, densely arranged, and ordered repetitive antigens are a hallmark of infectious agents, including viruses, bacteria, and parasites; that is, they are a hallmark of harmful nonself. Thus, mature B cells can differentiate between harmless and harmful according to pattern or antigen organization (*42–44*). It is noteworthy that rigid, repetitive self antigens are hidden and are not usually accessible to B cells; therefore, direct IgM au-

Table 3. Discrimination by mature B cells between harmless and harmful antigen. NA, not applicable.

Antigen		Antibody response with			
Concentration	Origin	B cells only	T cell–independent IgM	T help present	T-dependent antigens
		Antigen on cell membranes			
High	Self	–	–	–	–
		Antigen in bone marrow			
Low	Self	+*	+*	–	+*
		Monomer			
High or Low	Self	+*	NA	–	–
	Foreign	+	NA	+	+
		Repetitive polymer, crystal-like			
	Self (rare)	+	(+)†	(+)	(+)
	Foreign (harmful)	+	+	+	++

*B cells are present and are triggered if antigen is repetitive and rigidly ordered in a paracrystalline fashion (T helper–independent type 1 configuration), but B cells do not respond if little (T helper–independent type 2) or conventional linked T help is necessary against mobile, poorly organized, or monomeric antigen (*42*). †Interpreted to be potentially present (variable responses dependent on antigen accessibility to B cells or induction of T help) (*42*).

toantibody induction is probably rare, but autoantibodies against DNA or collagen could fit the proposed concept. Autoantibody responses against monomeric or oligomeric self-encoded antigens are well controlled despite the availability of autoantigen-specific B cells because the necessary T cell help is unavailable as a result of its deletion in the thymus.

Immunological Memory

Besides specificity, immunological memory is probably the parameter most studied from a clinical perspective. However, it is still poorly understood. After infection or vaccination of a host, the immune system is "primed." This specific immunological memory results in improved immune performance (that is, enhanced protection against reinfection) (*1*, *16*) and is usually assessed as increased antibody titers or as increased frequencies of specific T cells measured in vitro (*1*, *47*). There is no doubt that immunological memory mediated by increased antibody levels is necessary, but also sufficient, to provide protection against cytopathic virus infections. Thus, one function of immunological memory at the population level is probably to keep the host and the population fitter, either directly or indirectly by regulating epidemics through herd immunity (*5–8*, *12–14*, *27*). However, the important primary function of increased memory antibody levels is the adoptive transfer of memory antibodies from mother to offspring; these provide protection from otherwise lethal infections of young immunoincompetent offspring while immune reactivity matures.

The importance of immunological memory mediated by antibodies and the lack of transfer of T cell memory may best be explained as an evolutionary necessity imposed by MHC-restricted T cell recognition (*42*). Because MHC molecules mutate in order to adapt to new infectious agents, the T cell receptor repertoire must remain adaptable and is not genetically linked to MHC. As a consequence, during T cell maturation, a "learning" process is required for T cell receptor expression, involving positive and negative selection in the thymus (*1*). This process leaves fetus and offspring temporarily immunodeficient. MHC polymorphism also causes histoincompatibility and immunological rejection of histoincompatible cells or organs. Therefore, in contrast to memory antibodies, immunological T cell memory cannot be transferred from mother to offspring.

Adoptive transfer of passive protection by maternal antibody via the placenta in humans, providing immunity against poliovirus, has been well studied (*48*). Calves are born without antibodies; because of the double-layered chorioepithelial placenta, antibodies cannot be transferred (therefore fetal calf serum is used in research). Newborn calves receive all necessary protection against infections through antibody concentrates in colostral milk during the first 24 hours after birth. In addition, antibodies are transferred to the eggs of birds and reptiles (*48*). Because infectious agents must not be too successful in killing the host, coevolution has probably selected cytopathic agents of epidemiological importance that can be checked efficiently by the accumulated maternal antibody experience (over at least 13 years by human and 8 weeks by murine mothers). To secure this goal, increased neutralizing memory antibody titers must be maintained by antigens either reencountered, cross-reacting, or stored in a stable fashion, for example, as IgG complexes on follicular dendritic cells (*49*). In addition, female hormones enhance antibody responses—but also susceptibility to autoantibody-mediated diseases—as compared with those in males (*49*).

In contrast to long-lasting, increased levels of protective memory antibody, CTLs are induced and disappear rapidly. $CD8^+$ T cell frequencies are low in a normal host, on the order of 10^{-6} before infection. During acute infection they increase to 10^{-2} for viruses that replicate rapidly and widely, and 10^{-3} to 10^{-4} for less well replicating viruses. Once virus has been eliminated, these frequencies usually decrease to about 10^{-4} to 10^{-5} (*47*, *50*). This decline demonstrates the strong influence of antigen in regulating immune responses and corresponds to the finding that, once activated, effector T cells die off within 2 to 3 days. Therefore, whether cytotoxic T cell memory is important and what role antigen plays in its maintenance—as persisting virus, through reinfection, in depots on MHC class I molecules, by cross-reactive antigens, or in some other form—are presently being investigated (*47*, *51*). The fact that maternal antibodies are successful in protecting offspring suggests that activated cytotoxic T cell memory plays a different role in immunocompetent hosts, that of controlling persisting noncytopathic viruses (which are harmless to immunoincompetent young hosts) and of limiting harmful T cell–mediated immunopathology.

The characteristics of immunological memory presented here indicate that antigen drives the immune response and is its most important (positive) regulator. Accordingly, there is probably no conceptual need for specific negative regulation of immune responses. An important negative illustration of this simple concept is that, if antigen is not eliminated and if lymphoid organ structures form chronically in peripheral damaged organs, then immunopathological disease, excessive lymphoid cell proliferation, or autoimmunity will develop. Once antigen is eliminated, or drastically reduced, activated effector T and B cells disappear because of their short life-span. Although T cells recirculating in the blood may persist, as measured by increased precursor frequency, they can emigrate into solid tissues only if they are activated by antigen. Similarly, B cells may recirculate in the blood in an immune host. However, only B cells that are restimulated by antigen on follicular dendritic cells are activated to become antibody-producing plasma cells that contribute to the maintenance of increased memory antibody levels. Thus, protective immunological memory seems to be antigen-dependent (*47*, *49*, *51*), and it becomes difficult to distinguish immunological memory from low-level, normal immune responses.

Conclusion

The forms of interdependence between viruses and immune responses, as summarized here, are necessarily incomplete, and generalization may still be difficult. Nevertheless, even the few well-studied examples illustrate an evolutionary balance. The analysis of immune responses against viruses has helped to extend concepts based on important immunological studies with model antigens in vitro and has revealed essential biological parameters of immunity in vivo, providing an operational definition of specificity, a concept of immunological memory, and a definition of the rules of T cell induction with which to replace the idea of immunological "self-nonself discrimination." The various forms of balance reached between different viruses and the immune system can teach us about immunology well indeed.

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52. The views summarized here are the results of many years of stimulating experimentation with H. Hengartner, H. P. Pircher, P. Aichele, A. Althage, M. Bachmann, M. Battegay, D. Kägi, Th. Kündig, D. Kyburz, Th. Leist, D. Moskophidis, B. Odermatt, P. Ohashi, K. Rosenthal, M. Schulz, and L. Stitz and fruitful collaborations with the labs of T. Mak, K. Bürki, D. Bishop, M. Aguet, H. Arnheiter, D. Mathis, and I. Horak and important help from many friends. Supported by grants from the Swiss National Science Foundation, the National Institutes of Health, the Jeantet Foundation, and the Kanton of Zurich.