A Reappraisal of Humoral Immunity Based on Mechanisms of Antibody-Mediated Protection Against Intracellular Pathogens

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Abstract

Sometime in the mid to late twentieth century the study of antibody-mediated immunity (AMI) entered the doldrums, as many immunologists believed that the function of AMI was well understood, and was no longer deserving of intensive investigation. However, beginning in the 1990s studies using monoclonal antibodies (mAbs) revealed new functions for antibodies, including direct antimicrobial effects and their ability to modify host inflammatory and cellular responses. Furthermore, the demonstration that mAbs to several intracellular bacterial and fungal pathogens were protective issued a serious challenge to the paradigm that host defense against such microbes was strictly governed by cell-mediated immunity (CMI). Hence, a new view of AMI is emerging. This view is based on the concept that a major function of antibody (Ab) is to amplify or subdue the inflammatory response to a microbe. In this regard, the "damage-response framework" of microbial pathogenesis provides a new conceptual viewpoint for understanding mechanisms of AMI. According to this view, the ability of an Ab to affect the outcome of a host–microbe interaction is a function of its capacity to modify the damage ensuing from such an interaction.

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In fact, it is increasingly apparent that the efficacy of an Ab cannot be defined either by immunoglobulin or epitope characteristics alone, but rather by a complex function of Ab variables, such as specificity, isotype, and amount, host variables, such as genetic background and immune status, and microbial variables, such as inoculum, mechanisms of avoiding host immune surveillance and pathogenic strategy. Consequently, far from being understood, recent findings in AMI imply a system with unfathomable complexity and the field is poised for a long overdue renaissance.

1. Introduction

The classical view of antibody-mediated immunity (AMI) is that specific antibody (Ab) produced during the immune response to a microbial infection helps to clear the microbe by enhancing the efficacy of innate immune mechanisms and then confers immunity to subsequent encounters with the microbe. Consistent with this view, historically established mechanisms of AMI include viral and toxin neutralization, complement activation, phagocytosis, and antibody-dependent cellular cytotoxicity (ADCC) (Janeway *et al.*, 2001). The correlation between a defined amount of serum Ab and immunity against certain viral, bacterial, and toxin-mediated diseases provided proof that AMI is protective (Robbins *et al.*, 1995). Unfortunately, this tidy view of AMI does not apply to many infectious diseases, particularly those caused by intracellular pathogens such as *Mycobacterium tuberculosis* and *Listeria monocytogenes*. In fact, it is difficult to establish a role for AMI in host defense against many pathogenic microbes based on correlations between serum Ab levels and disease prevention and/or efficacy of passive Ab administration (Casadevall, 2004). The difficulty in establishing a role for AMI against intracellular microbes, evidence that the effective tissue response against many intracellular bacteria and fungi is granuloma formation, and that individuals with defects in cell-mediated immunity (CMI) are at increased risk for disease with such microbes, led to the paradigm that AMI and CMI have dichotomous roles, whereby AMI protected against extracellular and CMI protected against intracellular pathogens, respectively (Casadevall, 2003). However, studies with monoclonal antibodies (mAbs) and mice deficient in B cells and Fc receptors suggest that AMI is remarkably complex and poorly understood and that the time is ripe not only just for a paradigm shift but also for a major rethinking of the role of AMI in health and disease. Consequently, the reevaluation of AMI for intracellular pathogens is serving as a major catalyst for revising certain long-held concepts in immunological thought.

2. Intracellular and Extracellular Pathogenic Microbes: How Distinct Are They?

When immunologists consider the relative efficacy of AMI and CMI against a microbe, they often focus on whether it is an intracellular or extracellular pathogen. A major impetus for the classification of microbes as intracellular or extracellular was to ground the understanding of host defense against microbes with different pathogenic strategies in known and emerging immunological mechanisms. Based on what were believed to be fundamental mechanisms of AMI and CMI, AMI was viewed as the essential mediator of protection against extracellular microbes. As such, AMI was considered to be incapable of protecting against intracellular microbes because immunoglobulins are largely confined to the extracellular space. On the other hand, the discoveries that T cells only recognize antigen (Ag) in the context of Ag-presenting molecules and that infected cells express microbial Ags on their surface provided a mechanistic rationale for separating the roles of AMI and CMI based on the availability of microbial ligands and microbial localization during infection. The paradigm of a duality in function for AMI and CMI that has dominated thinking in immunology since the 1960s made sense in light of the inability to demonstrate efficacy of AMI against many intracellular pathogens and the prevailing understanding of mechanisms of Ab and T cell function. By the late twentieth century, this view of a division of labor for AMI and CMI was rather universally accepted, leading to it being used as the intellectual and basic scientific framework for research on host defense and vaccine design against many pathogenic microbes. However, closer scrutiny of the concept that AMI protects against extracellular pathogens and CMI protects against intracellular pathogens reveals numerous flaws in this paradigm.

A central problem in separating microbes into extracellular and intracellular groups has been the ambiguity, uncertainty, and inconsistency of these designations. First, the classification of microbes as intracellular or extracellular is almost exclusively applied to pathogenic bacteria and fungi. Paradoxically, viruses are usually not considered within the rubric of intracellular pathogens, although they have an absolute requirement of intracellular replication. Similarly, certain protozoa with intracellular phases in their growth cycles, such as *Plasmodium* spp., are not usually viewed through the intracellular versus extracellular immunological lens. In fact, microbes that are not full-time intracellular or extracellular inhabitants pose a problem for the AMI/CMI duality, since AMI is known to be effective against many viral diseases and is acknowledged as an important component of protection against *Plasmodium*-related diseases (Pleass and Holder, 2005). Second, all microbes, with the possible exception of endogenous retroviruses, have an extracellular phase

during which they exist outside the cell membrane. Even microbes capable of cell-to-cell spread, such as *L. monocytogenes* and *Shigella flexneri*, inhabit extracellular spaces when they first infect a host. Of relevance, AMI can be active and effective during this period, even if brief, as evidenced by the finding that Ab-mediated protection for the obligate intracellular pathogen *Ehrlichia chaffeensis* occurs during the brief period of extracellular life phase (Li and Winslow, 2003). Third, some authorities base their definitions of intracellular and extracellular on whether replication occurs predominantly in the intracellular or extracellular space. Such distinctions are often based on either *in vitro* observations of infected monolayers or pathological examination of infected tissues. Hence, the fungus *Histoplasma capsulatum* is considered an intracellular pathogen because it is found almost exclusively inside macrophages in infected tissues. On the other hand, *Streptococcus pyogenes* and *Staphylococcus aureus* are never considered intracellular pathogens, despite the fact that both have been found to persist in phagocytes (Gresham *et al.*, 2000; Medina *et al.*, 2003). Fourth, encapsulated organisms, such as *Streptococcus pneumoniae*, *Neisseria meningiditis*, and *Haemophilus influenzae*, are often considered extracellular pathogens because their capsules are antiphagocytic *in vitro*, which allows them to survive in the extracellular space (Collins, 1979). However, each of these organisms is often found inside phagocytic cells in tissue. In fact, the presence of a capsule cannot be used as definitive criterion for intracellular versus extracellular classification. The pathogenic fungus *Cryptococcus neoformans* has a large polysaccharide capsule yet replicates inside macrophages *in vivo* and *in vitro* (Feldmesser *et al.*, 2000) and, as noted above, *S. pyogenes* and *S. aureus* persist without being killed in neutrophils (Gresham *et al.*, 2000; Medina *et al.*, 2003). On the other hand, *M. tuberculosis* has an outer polysaccharide capsule, yet is considered a prototypic intracellular pathogen (Daffe and Etienne, 1999).

The classification of microbes as intracellular or extracellular pathogens lacks rigorous definitional boundaries and on close examination reflects a certain degree of circular reasoning. For example, one argument for the paradigm that AMI protects against extracellular pathogens whereas CMI protects against intracellular pathogens was that AMI could not be demonstrated to protect many intracellular pathogens, despite serious limitations in the methodologies available for evaluating AMI (Casadevall, 2004). This led to the tendency to use a lack of AMI against a microbe as a criterion for classifying it as an intracellular pathogen from an immunological perspective. In fact, it was argued that one criterion for assessing the efficacy of CMI in host defense was demonstrating lack of protection by AMI (Mackaness, 1977). However, in retrospect it is clear that serious limitations in the available methodologies for evaluating AMI, including their dependence on heterogeneous, impure reagents, made

it impossible to conclude that negative results meant that AMI was ineffective (Casadevall, 2004). Furthermore, it is noteworthy that the AMI versus CMI paradigm for extracellular and intracellular pathogens, respectively, was derived from the examination of a relatively small number of microbes. For example, the enormously authoritative and influential reviews of Mackaness and Collins that posited the importance of CMI for intracellular pathogens were focused on a small subset of pathogenic microbes such as *Mycobacterium* spp., *L. monocytogenes*, and *Salmonella* spp. (Collins, 1979; Mackaness, 1971, 1977). Nonetheless, it is noteworthy that the proposal that CMI was protective against these organisms emerged from a struggle to establish a role for CMI in the mid-twentieth century immunological world that often equated Ab with immunity. Hence, the focus on a few organisms for which AMI could not be demonstrated made sense in the context of establishing the field of cellular immunity. As such, the investigators who pioneered those studies left us a legacy of outstanding science and a greater understanding of host defense. However, the problem arose when the principles derived from a few microbes were generalized to the larger set of pathogenic microbes. There have always been microbes with intracellular pathogenic strategies for which AMI appeared to be important, including *Bacillus anthracis* and *Legionella pneumophilia*. AMI is protective against anthrax (Beedham *et al.*, 2001; Little *et al.*, 1997), although *B. anthracis* is not considered an intracellular pathogen in an immunological context. Although *B. anthracis* is a free-living spore that does not require a host for survival, it replicates within macrophages after escaping from the phagosome to the cytosol (Dixon *et al.*, 2000), making it a classical intracellular pathogen by most definitions. AMI also contributes to host defense against *L. pneumophilia* (Brieland *et al.*, 1996; Eisenstein *et al.*, 1984a; Rolstad and Berdal, 1981), a free-living bacterium in water sources capable of replicating inside macrophages and amoebae. These examples and the aforementioned ability of gram-positive organisms to persist in phagocytes illustrate that neither the ability for intracellular replication nor phylogenetic derivation nor the relative efficacy of AMI and CMI can be used as a singular or definitive criterion for designating a microbe as extracellular or intracellular. Consequently, the distinction between intracellular and extracellular, as the terms are most commonly used, appears to be more microbe specific, than based on shared or common microbiologic or pathogenic characteristics. Hence, our view is that the paradigm of a dichotomous role for AMI and CMI for extracellular and intracellular microbes, respectively, is logically inconsistent and inadequate to serve as a pillar of immunological theory and thought. Nonetheless, the separation of microbes into intracellular and extracellular pathogens has formed the basis of much immunological thought and was central to the development of current views of the relative efficacy of AMI and CMI (Collins, 1974;

Mackaness, 1971). Therefore, this chapter will discuss AMI from the vantage point of this distinction. Cognizant of the limitations of the term intracellular, we will use it to refer to microbes that have significant intracellular growth phases and for which CMI is generally considered to be the primary host defense mechanism.

3. Components of AMI

The term AMI is used here to encompass all the protective effects associated with Ab, including those mediated by "naturally occurring Ab," passively transferred Ab, and acquired Ab (Ab generated by an immune response). When considering the function of AMI, it is worthwhile to remember that serum contains a high concentration of immunoglobulin proteins that include many different microbial and self-specificities and isotype compositions. This immunoglobulin pool reflects the host response to endogenous microbiota as well as the immunological memory of the host for a variety of acquired microbial agents. Understanding the role of AMI in protection against infectious diseases involves developing an appreciation for the differences in function between Abs referred to as "naturally occurring," those that are passively administered, and those that are induced by a specific agent.

The term naturally occurring is inexact and vague. This designation was probably meant to differentiate preexisting Ab from that generated during an immune response, which is often referred to as "specific" or "acquired" Ab. In fact, a rise in titer in serological assays is sometimes used to try to distinguish naturally occurring Ab from specific Ab produced in response to a specific agent. Important caveats to this approach are that the heterogeneous nature of serum precludes knowing whether the Abs detected before contact with an agent recognize the same determinants as those that are detected afterward and that many methods of detecting Ab can measure some degree of reactivity with the agent of interest. Issues of detection notwithstanding, a problem with the term naturally occurring Ab is that the actual agent/s that elicited such Abs is/are essentially unknown. Further, the naturally acquired Ab repertoire also consists of Abs that can be shown to be cross-reactive with a multitude of microbial and even self-determinants, making their origin even more elusive. In this chapter, we will use the term naturally occurring to refer to preexisting Abs that are found in the serum of a host prior to contact with a new microbial agent and/or immunogen.

Naturally occurring Ab has the capacity to bind pathogenic microbes even when the host has not encountered the microbe in question. Although the interaction of naturally occurring Ab with a microbe is often a low-affinity interaction, the principle of mass action is likely to enable some immunoglobulin

binding to microbial surfaces since the concentration of immunoglobulins in serum is high. Since Ab binding is sufficient to induce B cell activation, low-affinity interactions between an Ab and Ag have the potential to induce biologically relevant Ab activity. Contrary to prevailing thought, it has been proposed that low-affinity Abs have a better potential to discriminate between, and as such be more specific for given antigenic determinants, since they are more likely to dissociate than high affinity Abs (Van Regenmortel, 1998).

Consistent with a biological role for such Abs, there is increasing evidence that naturally occurring Abs provide a key layer of early protection against many pathogenic microbes by virtue of their capacity for low-affinity interactions. The importance of preexisting Abs in resistance to numerous pathogens, including bacteria, viruses, and parasites, in animal models of infectious diseases has been increasingly recognized (Boes *et al.*, 1998a; Brown *et al.*, 2002; Couper *et al.*, 2005; Rajan *et al.*, 2005). Some of these models rely on the use of secretory IgM (sIgM)-deficient mice, which have a defect in IgM secretion that results in their having normal serum levels of other isotypes but no serum IgM (Boes *et al.*, 1998b). Preexisting IgM is crucial for resistance to pneumococcus in mice (Brown *et al.*, 2002), despite the fact that serum levels of IgG are considered a surrogate for vaccine efficacy against this microbe. IgM derived from a defined repertoire of memory B cells has been strongly implicated in protection against pneumococcal disease in humans (Carsetti *et al.*, 2005; Kruetzmann *et al.*, 2003; Shi *et al.*, 2005). This population of B cells is reduced in patients at high risk for pneumococcal disease, including HIV-infected individuals and the elderly (Chong *et al.*, 2004; Shi *et al.*, 2005). The activity of germline and/or early acquired IgM against viral pathogens, such as influenza and *West Nile virus*, and other agents, such as pneumococcus (Brown *et al.*, 2002; Diamond *et al.*, 2003; Harada *et al.*, 2003; Mehlhop *et al.*, 2005), implicates naturally occurring IgM as an important component of innate immune responses to and complement-mediated protection against these agents. One mechanism by which naturally occurring AMI could contribute to host defense is by amplifying complement activation and providing opsonins. This function suggests that AMI could play a proinflammatory role, shortening the response time when the host encounters a pathogenic microbe. On the other hand, IgM has been shown to inhibit complement activation without compromising opsonic activity, in some instances by blocking classical but not alternative complement pathway activation (Walpen *et al.*, 2004; Werwitzke *et al.*, 2005). Given that our appreciation of the importance of naturally occurring Abs in host defense against infectious diseases is in its infancy, future studies are likely to reveal a fuller understanding of the mechanisms that govern the efficacy of naturally occurring AMI in host defense.

Passively administered Ab confers a form of AMI that is different than either naturally occurring or AMI that is induced by a specific Ag/agent. Most passively administered Abs have either known specificity or protective properties that are already known to confer a state of immediate immunity. However, pooled, nonspecific immunoglobulin preparations are in use as anti-inflammatory therapy for diseases as diverse as inflammatory myopathies and streptococcal toxic shock (Dalakas, 2003; Norrby-Teglund *et al.*, 2003). The efficacy of nonspecific immunoglobulin in toxic shock syndrome has been attributed to toxin neutralization (Darenberg *et al.*, 2003). IgM-enriched immunoglobulin preparations (pentaglobulin) were found to be cost effective in treatment of severe septic shock (Neilson *et al.*, 2005), an effect that could reflect the ability of certain IgMs to bind endotoxin (Bennett-Guerrero *et al.*, 1997; Maury *et al.*, 2003) or to inhibit complement activation (Rieben *et al.*, 1999; Walpen *et al.*, 2004). When used as antimicrobial therapy against experimental infection, passive Ab is most effective when administered before microbial challenge. In fact, passive Ab is often ineffective against established infection. Hence, passive Ab preparations must be able to be effective in the context of early innate and cellular immune responses. Passive Ab is often ineffective against established infection. This raises a fundamental problem that has never been adequately explained, since Ab presumably contributes to host defense in natural infection even though it is made in response to infection. For example, clinical improvement from pneumococcal pneumonia in the preantibiotic era was associated with the appearance of specific serum Ab. One explanation for this phenomenon, which is consistent with the observation that recovery from many infections occurs sooner than the time it takes for a specific Ab response to develop, is that the Abs that protect against acute infection are part of the natural, preexisting repertoire and that these Abs are different from acquired Abs, protect against reinfection, or downregulate the inflammatory response by engaging inhibitory Fc receptors. In these scenarios, naturally occurring AMI would cooperate with innate immune mechanisms and the nascent CMI response to contain infection, while the secondary IgG response is made later for long-lasting immunity (Fig. 1). Hence, the efficacy of passively administered specific Ab in a naïve host may recapitulate conditions that mimic the immune response or reencounter with a microbe more than the naïve response.

Specifically induced or acquired AMI involves the production of IgM, IgA, or IgG in response to a microbial agent or immunization. A paradoxical observation involving AMI is that specific IgG is often made after the host has recovered. In fact, a rise in serum IgG titer is a time-honored method for diagnosing many infectious diseases. This observation begs the question of why IgG is made after recovery from most infectious diseases. Invoking a need to

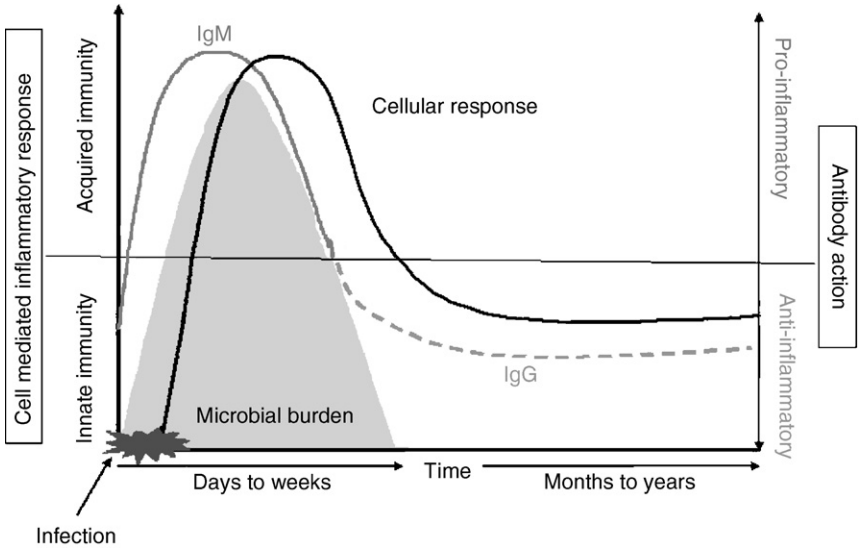

Figure 1 The proposed role of Ab as an regulator of the inflammatory and cellular response (Casadevall and Pirofski, 2003). The scheme is idealized for a host–microbe interaction whereby the immune system can contain and eradicate the microbe. The left hand *y*-axis depicts the cellular inflammatory response to a microbe. The right hand *y*-axis depicts Ab action shown as pro-inflammatory and anti-inflammatory effects. In this schema, IgM functions predominantly in a proinflammatory role, which augments the innate cellular immune response to and pathogen clearance, and IgG functions predominantly in an anti-inflammatory role, which decreases the cell-mediated inflammatory response that follows pathogen clearance. This is depicted on the right hand *y*-axis. According to this view, Ab helps to confer the state of immunity by downregulating the CMI of a primed host on a subsequent encounter with the same microbe (Casadevall and Pirofski, 2003).

prevent recurrences is a somewhat unsatisfactory answer if the initial innate and cellular response was adequate to clear the first bout of disease. Nevertheless, an adaptive response that avoids recurrent bouts of a particular disease would have a significant survival advantage. The presence of serum IgG is a marker of immunity for many infectious diseases, even if IgG may not have been responsible for control of the initial infection.

4. AMI in the Context of the "Damage-Response Framework"

Given that AMI is a host defense mechanism against pathogenic microbes, an attempt to understand its function should account for Ab action in the context of principles of microbial pathogenesis. Unfortunately, until recently we lacked a unified theory that incorporated the contribution of the host response as well

as the microbe into microbial pathogenesis. We have proposed the damage-response framework (Casadevall and Pirofski, 1999, 2003) as a unified theory of microbial pathogenesis. This theory is grounded by the proposal that the common denominator in all cases of microbial pathogenesis, irrespective of the causative microbial agent, is damage to the host. This view provides a universal, yet flexible, construct to account for microbial pathogenesis without the need for separate categories for different types of microbes. According to the damage-response framework, damage is defined as a perturbation of host homeostasis that disrupts or alters tissue integrity, function, physiology, biochemistry, or hemodynamics or cellular function, secretion or inflammation.

The damage-response framework is built on the following three tenets: (1) microbial pathogenesis is the outcome of an interaction between a host and a microbe, (2) the relevant outcome of host–microbe interaction is damage in the host, (3) damage can be the result of host factors, microbial factors, or both (Casadevall and Pirofski, 1999, 2003). Consequently, the outcome of host–microbe interaction can be plotted on a u-shaped curve, whereby the *y*-axis represents the amount of host damage and the *x*-axis represents the host response from weak to strong going from left to right (Fig. 2). The terms weak and strong are relative and include both quantitative and qualitative parameters (Casadevall and Pirofski, 1999). Although we recognize that plotting an immune response along a single axis is an oversimplification of an enormously

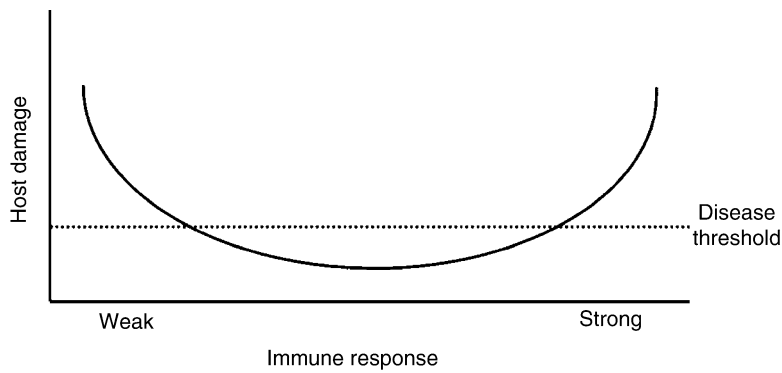

Figure 2 The basic curve of microbial pathogenesis as proposed by the damage-response framework is a parabola whereby host damage from the host–microbe interaction occurs primarily at the extremes of immune response (Casadevall and Pirofski, 1999, 2000, 2003). One can modify this curve to generate classify known pathogens into six groups (Casadevall and Pirofski, 1999). The curve can also be modified to account for commensal host–microbe interactions. Most of the classical intracellular pathogens considered in this chapter are class 3 pathogens (Casadevall and Pirofski, 1999) and are represented by the curve shown here.

complex process, the continuum from weak to strong provides a first approximation for developing systematic approach to understanding microbial pathogenesis. Certain infectious diseases are the result of excessive (strong, inappropriate) immune responses that require downregulation of inflammation, whereas others are the result of insufficient (weak, inappropriate) immune responses that require bolstering. Hence, it is logical to assess Ab function based on its impact on host damage and the nature of the immune response to a microbial agent.

The damage-response framework is a new schema for understanding the role of AMI in health and disease. In the context of the damage-response framework, a protective Ab is one that shifts the curve depicting host damage as a result of the immune response in favor of the host by reducing damage. This can occur as a result of Ab-mediated reduction of an exuberant inflammatory response (shift to the left) or enhancement of a weak inflammatory response (shift to the right) (Fig. 3). Often, host damage in the setting of a weak immune response is a result of microbial factors, whereas damage in the setting of a strong immune response reflects an excessive inflammatory response. Hence, in the setting of a weak host response to a microbe, a protective Ab might enhance the immune response. This could be mediated by an Ab with the ability to augment the inflammatory response. This type of phenomenon was described for an IgM to the polysaccharide capsule of *S. pneumoniae*, which promoted earlier recruitment of neutrophils to the lungs of mice with pulmonary infection (Burns *et al.*, 2005). However, later in the course of infection, when control mice had high levels of proinflammatory mediator expression, the same Ab led to downregulation of chemokine expression in lung. Hence, Abs can mediate protection by downregulating the immune response in the setting of strong immune responses, during which high levels of inflammatory mediators are major contributors to host damage. Along these lines, Ab-mediated protection to *C. neoformans* in mice has been associated with downregulation of IFN-γ and, in some mouse strains, increased levels of IL-4 and IL-10 (Feldmesser *et al.*, 2002; Rivera and Casadevall, 2005; Rivera *et al.*, 2002, 2005). However, in certain conditions, Ab administration to mice with chronic *C. neoformans* infection can result in catastrophic cardiovascular collapse associated with release of platelet-activating factor and other proinflammatory mediators (Lendvai *et al.*, 2000; Savoy *et al.*, 1997). Furthermore, experiments with human cells *in vitro* have clearly demonstrated the same type of antibodies can promote the release of proinflammatory mediators under certain conditions (Vecchiarelli and Casadevall, 1998; Vecchiarelli *et al.*, 1998a,b) (52–54). Consequently, a given Ab can mediate proinflammatory or anti-inflammatory changes depending on the specific host–microbe interaction.

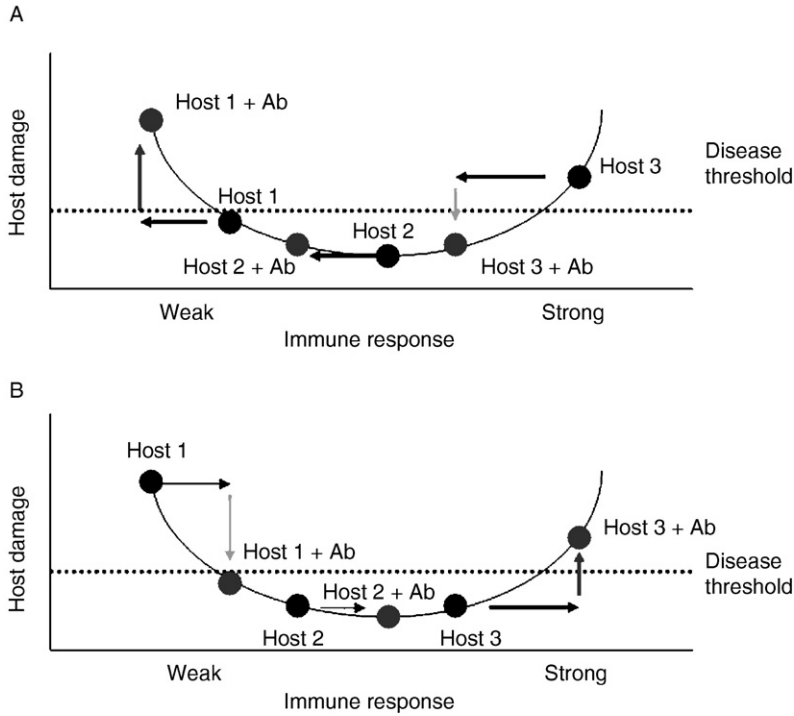

Figure 3 Conceptual representation of Ab that enhances or diminishes the immune response in the context of the damage-response framework of microbial pathogenesis. (A) An Ab that diminishes the immune response would be protective for host 3, disease enhancing for host 1, and have no clinical effect on host 2. (B) An Ab that enhances the immune response would be protective for host 1, disease enhancing for host 3, and have no clinical effect on host 2.

In contrast to protective Abs, a disease-enhancing Ab would shift the curve such that host–microbe interaction resulted in greater host damage. In this regard, immune complexes to *Leishmania* have been proposed to contribute to virulence by promoting the secretion of IL-10 that downregulates the immune response (Miles *et al.*, 2005), thereby shifting the curve to the left. However, Ag–Ab complexes can also shift the curve to the right as evidenced by the observation that Ab administration to certain mice with chronic *C. neoformans* infection caused cardiovascular collapsed from secretion of the inflammatory mediator platelet-activating factor (Lendvai *et al.*, 2000; Savoy *et al.*, 1997). Hence, it is increasingly apparent that, rather than being inherently good or bad, the effects of Abs are either beneficial or deleterious in a host, depending on the type of microbe–host interaction, including the setting in which damage

occurs as a function of the host immune milieu and response. A logical extension of this concept is that an Ab that is protective in one host may not be protective in another if the nature of their immune responses to the relevant agent places them on different parts of the damage-response curve (Fig. 3). These concepts have important ramifications for vaccine design since vaccine efficacy could depend on enhancement of the immune response for those with weak immune responses, but enhanced responses could be detrimental in those who naturally generate strong immune responses. An excessive inflammatory response mediated by immune complexes could have been in part responsible for the failure of the killed measles vaccine, which was associated with the development of atypical measles (Polack *et al.*, 1999). Hence, more than one type of vaccine may be needed to prevent infectious diseases that can develop in the setting of either weak or strong immune responses.

Toxin-mediated diseases are viewed by the damage-response framework as a special case whereby damage occurs across a range of host responses. Bacterial toxins, such as those produced by *Clostridium tetani* and *Corynebacterium diphtheriae*, cause host damage without eliciting a significant immune response as evidenced by the fact that neither tetanus nor diphtheria confers immunity to recurrent disease (Spenney *et al.*, 1971). AMI protects against these diseases through toxin neutralization, a phenomenon that would reduce the incidence of disease without necessarily altering the prevalence of infection.

Another important principle of the damage-response framework is that the state of the host–microbe interaction is a function of time (Casadevall and Pirofski, 2003). The damage-response framework sees no fundamental difference between the states of colonization, commensalism, latency, and disease except for the amount of host damage that results from the host–microbe interaction over time (Casadevall and Pirofski, 2003). Hence, Abs that are protective in some host–microbe interactions could prevent host damage that would otherwise lead to progression from colonization or latency to disease. This provides a functional explanation for how vaccines for microbes that often exist in a state of colonization prevent disease; protective Ab responses would control host damage, keeping it below the threshold that would result in disease. Abs that promote or maintain a state of latency could contribute to protective responses because they decrease the likelihood that disease will ensue. Although Abs that maintain latency have not been identified, they have not been looked for, raising the question of whether certain naturally occurring and/or specifically induced Abs that bind latent microbes, such as *M. tuberculosis*, herpesviruses, or *C. neoformans*, have a role in maintaining latency. This concept is supported in principle by serological studies that showed a decline in IgM to cryptococcal capsular polysaccharide in individuals

at high risk for the development of disease (Fleuridor *et al.*, 1999; Subramanian *et al.*, 2002). Further, the demonstration that vaccination of elderly individuals against varicella-zoster virus prevented herpes zoster suggests that the elicited Abs helped to maintain the latent and prevent the development of disease (Oxman *et al.*, 2005). Perhaps Abs similar to those that were elicited by the vaccine are already present in individuals who do not develop herpes zoster.

In contrast to Abs that mediate protection, Abs that enhance disease or are deleterious are those that contribute to progression of damage and/or disease. Examples of such Abs are those that are part of damaging immune complexes or those that enhance uptake of microbes, which improves their ability to replicate and damage host cells, such as certain Abs to *Dengue virus* (Sullivan, 2001). In summary, the damage-response framework provides a flexible schema by which to characterize Ab efficacy, which, despite the complexity of the interactions that underlie host–microbe relationships and Ab function, can be reduced to assessment of how Ab affects two relationships: host damage as a function of the host immune response and host damage as a function of time.

5. Abs as Enhancers of Innate Immunity

The importance of naturally occurring Abs, predominantly of the IgM isotype, in enhancing innate immune responses to a multitude of pathogens is being increasingly recognized. In addition to the aforementioned animal models in which microbial virulence is reduced in the absence of serum IgM (see earlier), naturally occurring IgMs enhance complement-mediated and complement-independent antimicrobial mechanisms. For example, naturally occurring swine IgM promoted complement-mediated lysis of pseudorabies virus–infected cells (Hayashi *et al.*, 2005) and naturally occurring human serum IgM that lacked the ability to promote complement-mediated lysis *in vitro* protected infant rats against *N. meningiditis* serogroup B, a serogroup against which an effective vaccine has not yet been developed (Toropainen *et al.*, 2005). The mechanism by which such protection is mediated is not known. However, in light of the discovery that the efficacy of a nonopsonic IgM to pneumococcal polysaccharide was associated with downregulation of the proinflammatory response to pulmonary pneumococcus infection (Burns *et al.*, 2005), a similar mechanism could be operative against other microbes. Such a mechanism appears to allow innate host defense mechanisms to combat the microbe, while reducing the damage that might result from the inflammation induced by this process. Consistent with the idea that naturally occurring Abs can regulate the inflammatory response, natural IgM was found to promote granuloma formation in an experimental model of filarial infection (Rajan *et al.*, 2005). One clue to the mechanism by which some such Abs might work

is the discovery of a natural IgM Ab that enhanced the Ag-presenting ability of dendritic cells by binding to B7 (Radhakrishnan *et al.*, 2003), suggesting that an Ab ligand can link receptors of innate and acquired immunity. Another mechanism by which naturally occurring Abs could enhance the potential of innate immunity to microbial pathogens is through the catalytic activity that has been demonstrated for some such molecules (Nathan, 2002; Paul *et al.*, 2005). The ability of certain Abs to mediate catalysis has been attributed to variable region nucleophilic sites with the capacity for covalent binding (Paul *et al.*, 2005). Although whether the rate of catalysis mediated by catalytic Abs is sufficient to confer biological activity *in vivo* has been debated, higher levels of catalytic IgG correlated with better survival in patients with septic shock (Lacroix-Desmazes *et al.*, 2005).

6. Abs as Direct and Indirect Effector Molecules

Abs can promote host defense by direct or indirect mechanisms (Table 1). Direct Ab functions are those that are manifest when an Ab binds a microbe and/or a microbial component and mediates an antimicrobial or antitoxin effect. Direct Ab functions include those classically associated with AMI such as complement activation, agglutination; toxin and viral neutralization. With the exception of toxin and viral neutralization, these direct effects are facilitated by Abs but mediated in concert with other components of the immune system. However, a considerable body of evidence has accumulated indicating that certain Abs can mediate direct effects against bacteria and fungi by themselves. Specific IgM can be bactericidal to *Borrelia* in the absence of complement by killing the bacteria through surface effects (Connolly and Benach, 2001; Connolly *et al.*, 2004). Abs that mimic the action of a yeast killer toxin have been shown to be directly microbicidal to a variety of different classes of microbes, including *Leishmania* spp. (Savoia *et al.*, 2002), *Candida albicans* (Polonelli *et al.*, 1996), *Aspergillus* (Torosantucci *et al.*, 2005) and *M. tuberculosis* (Conti *et al.*, 1998). Abs to *C. albicans* surface Ags inhibited hyphal formation and growth (Moragues *et al.*, 2003). In fact, a single mAb to *C. albicans* has been shown to mediate multiple antifungal effects including inhibition of germination and attachment to host cells in addition to having direct candidicidal activity *in vitro* (Moragues *et al.*, 2003). A list of direct Ab effects is provided in Table 2.

In contrast, indirect Ab functions are antimicrobial effects mediated through actions with effector cells and/or by changes in the inflammatory and immune response. Indirect Ab functions classically associated with AMI are phagocytosis and ADCC. AMI can have profound effects on the inflammatory response through a variety of mechanisms that include activation of

Table 1 Direct and Indirect Antimicrobial Activities of Abs

Ab mechanism and/or action	Type	Reference
Opsonization	Direct	Janeway *et al.*, 2001
Complement activation	Direct	Janeway *et al.*, 2001
Viral neutralization	Direct	Janeway *et al.*, 2001
Toxin neutralization	Direct	Janeway *et al.*, 2001
ADCC	Direct	Janeway *et al.*, 2001
Bactericidal	Direct	Connolly and Benach, 2001; Connolly *et al.*, 2004; Goel and Kapil, 2001
Fungistatic	Direct	Moragues *et al.*, 2003; Rosas *et al.*, 2001; Torosantucci *et al.*, 2005
Interference with antigen release	Direct	Martinez *et al.*, 2004
Interference with biofilm formation	Direct	Martinez and Casadevall, 2005
Interference with iron acquisition	Direct	Fitzgerald and Rogers, 1980
Generation of oxidants	Direct	Wentworth *et al.*, 2002
Oxidative burst	Indirect	Johnston *et al.*, 1976; Mozaffarian *et al.*, 1995
Changes in cytokine expression	Indirect	Anderson and Mosser, 2002; Gerber and Mosser, 2001; Marsh *et al.*, 1994, 1995, 1997, 1998; Vecchiarelli *et al.*, 1998b
Release of prostaglandins	Indirect	Neuwirth *et al.*, 1988
Changes in costimulatory molecule expression	Indirect	Vecchiarelli *et al.*, 1998c
Changes in FcγR expression	Indirect	Rivera and Casadevall, 2005
Enhancement of lysosome-phagosome fusion	Indirect	Armstrong and Hart, 1975

inhibitory FcR receptors, modulating the release of proinflammatory and anti-inflammatory cytokines, promoting release of prostaglandins, and clearance of microbial molecules with immunomodulatory effects (Casadevall and Pirofski, 2003). In addition, intravenous immunoglobulin (IVIG) has been shown to induce neutrophil apoptosis via an Fc receptor-dependent H_2O_2-dependent pathway (Takeshita *et al.*, 2005), a function that could contribute to its anti-inflammatory activity. Indirect Ab functions may be beneficial or detrimental to the host, depending on the type of host–microbe interaction. Ab effects that reduce host damage due to the inflammatory response can be expected to translate into Ab-mediated protection, whereas proinflammatory changes that increase damage can be expected to result in no protection or disease-enhancing

Table 2 Facultative and Obligate Intracellular Pathogens for Which Ab Can Affect the Outcome of Experimental Infection

Organism[a]	Reference[b]
Anaplasma marginale	Tebele *et al.*, 1991
Brucella abortus	Bowden *et al.*, 1995; Elzer *et al.*, 1994
Chlamydia spp.	Cotter *et al.*, 1995; Zhang *et al.*, 1987
Cryptococcus neoformans	Dromer *et al.*, 1987; Fleuridor *et al.*, 1998; Mukherjee *et al.*, 1992; Sanford *et al.*, 1990
Ehrlichia chaffeensis	Kaylor *et al.*, 1991; Li *et al.*, 2001, 2002
Histoplasma capsulatum	Nosanchuk *et al.*, 2003
Legionella pneumophilia	Brieland *et al.*, 1996; Eisenstein *et al.*, 1984a
Leishmania spp.	Anderson *et al.*, 1983; Savoia *et al.*, 2002
Listeria monocytogenes	Edelson and Unanue, 2001; Edelson *et al.*, 1999
Mycobacteria tuberculosis	Chambers *et al.*, 2004; Hamasur *et al.*, 2003, 2004; Pethe *et al.*, 2001; Teitelbaum *et al.*, 1998; Williams *et al.*, 2004
Rickettsia typhi	Gambrill and Wisseman, 1973
Salmonella spp.	Eisenstein *et al.*, 1984b; Ornellas *et al.*, 1970; Robbins and Robbins, 1984; Watson *et al.*, 1992
Shigella flexneri	Phalipon *et al.*, 1995
Toxoplasma gondii	Cha *et al.*, 2001; Johnson and Sayles, 2002; Johnson *et al.*, 1983; Mineo *et al.*, 1994; Pavia *et al.*, 1992

[a]The strength of the evidence for the protective role of AMI varies for the different pathogens listed below.

[b]Not a complete listing.

effects. Although the distinctions between direct and indirect effects are somewhat artificial and simplistic and there is some overlap of these effects, they provide a useful construct to categorize mechanisms of AMI. Nonetheless, it must be recognized that the interrelatedness of components of the immune system is such that any action mediated by an Ab is likely to affect other aspects of the immune response.

Considering Ab-mediated effects to be part of direct or indirect effector categories can provide clues as to why it has been so difficult to demonstrate the efficacy of AMI against intracellular pathogens. Historically, immunological concepts of Ab-mediated protection have largely focused on direct Ab effects that apply primarily to toxins and extracellular microbial pathogens, with less emphasis on considering indirect effects of Ab action, such as modulation of the inflammatory response. This was undoubtedly a consequence of the fact that the tools for studying mediators of inflammation have become available relatively recently. Furthermore, the view that Ab molecules were confined to the extracellular space by cell membranes encouraged the view that AMI was not a major contributor to host defense against intracellular pathogens.

However, when indirect Ab functions are taken into account, it is clear that there are numerous mechanisms by which AMI can affect the outcome of host–microbe interactions with intracellular pathogens.

An important burgeoning role for AMI is found in the emerging understanding that Ab can be required for resistance to reinfection, even though it may not be required for primary resistance. For example, specific Ab mediated resistance to reinfection with *Candida*, although B cell-deficient mice were resistant to primary infection (Montagnoli *et al.*, 2003). This finding was attributed to the ability of Ab to prime dendritic cell–mediated antifungal immunity. This is consistent with the concept that AMI is important for the establishment and maintenance of certain memory responses, particularly those that depend on $CD8^+$ T cells. The memory response to *Helicobacter pylori* and cytotoxic lymphocytes (CTLs) to *Lymphocytic choriomeningitis virus* (LCMV) is enhanced by B cell presentation and or activation (Azem *et al.*, 2005; Homann *et al.*, 1998; Klenerman, 2004; Matter *et al.*, 2005). Similarly, B cells, which play an insignificant role in the primary response, were required for the development of a memory response to *L. monocytogenes* Shen *et al.*, 2003) and reinfection with *Francisella tularemia* (Bosio and Elkins, 2001). The demonstration of B cells in granulomatous skin lesions of patients with *Coccidiodes immitis* underscores the importance of B cells in the immune response to fungi, microbes that were formerly believed to depend solely on CMI, and supports their emerging role as immunoregulators (Li *et al.*, 2005). The exact role of immunoglobulin in these processes remains to be determined.

7. AMI as a Regulator of the Inflammatory Response

As discussed previously, Ab can be a positive or negative regulator of the inflammatory response. The ability of an Ab to function in a positive or negative regulatory capacity is a function of the Ab isotype, amount, and specificity. Proinflammatory activities of Abs are complement activation, FcR engagement with the release of proinflammatory mediators such as cytokines, chemokines, platelet-activating factor, and chemokines, neutralization of microbial components that interfere with an inflammatory response, and the capacity to promote phagocytosis and enhance Ag presentation. For IgG, many proinflammatory and anti-inflammatory functions are mediated by interaction with activating (FcγRI and FcRγRIII) and inhibitory (FcγRII) FcγRs (Ravetch and Bolland, 2001; Ravetch and Lanier, 2000). These receptors have different affinities for the various IgG subclasses (Nimmerjahn and Ravetch, 2005). Consequently the proinflammatory or anti-inflammatory activity of a given isotype is in part inherent, depending on the type of receptor with which it interacts. In mice, IgG1 interacts exclusively with FcRγRIII, whereas a new

fourth IgG FcR has been described (FcγRIV) that has specificity for IgG2a and IgG2b, but does not bind to IgG1 or IgG3 (Nimmerjahn *et al.*, 2005). The inhibitory (FcγRII) FcR has been implicated in the anti-inflammatory effect of IVIG and innate resistance to pneumococcus (Clatworthy and Smith, 2004). There is an emerging literature showing that the types of Fc receptors activated can have a profound effect on the development of immune responses. In this regard, differences in the degree of stimulation of activating and inhibitory receptors on dendritic cells may tilt the response toward tolerance or immunity (Boruchov *et al.*, 2005). Specific IgM probably has a greater proinflammatory capacity than specific IgG by virtue of its greater complement-activating activity and the absence of inhibitory IgM Fc receptors. However, IgM also has anti-inflammatory effects, which could in part be due to the ability of certain naturally occurring IgMs to neutralize endotoxin, clear apoptotic cells, and/or to inhibit classical complement pathway activation (Peng *et al.*, 2005; Reid *et al.*, 1997; Reith *et al.*, 2004; Rieben *et al.*, 1999; Walpen *et al.*, 2004).

Anti-inflammatory activities of Abs include their ability to reduce a microbial inoculum by promoting microbial clearance by phagocytosis, FcγR engagement to produce anti-inflammatory cytokines such as IL-10 (Tripp *et al.*, 1995), and binding to proinflammatory microbial components such as lipopolysaccharide (LPS). Acute LCMV infection was attenuated by an Ab-mediated reduction in T cell-mediated host damage that was associated with a reduction in viral replication (Wright and Buchmeier, 1991). IgG is probably a more anti-inflammatory Ig class than IgM by virtue of its ability to engage the inhibitory FcγR and its requirement for multiple molecules in activating complement. Consistent with this property, IgG administration is commonly used clinically to treat inflammatory conditions. However, IgM (pentaglobulin) was beneficial in patients after abdominal surgery and in those with septic shock (Buda *et al.*, 2005; Pul *et al.*, 2002; Reith *et al.*, 2004). In summary, IgM and IgG can each be proinflammatory or anti-inflammatory depending on their amount, specificity, and access to FcRs. Proinflammatory and anti-inflammatory functions of Ig are listed in Table 3. The ability of AMI to function in both proinflammatory and anti-inflammatory roles, depending on the variables mentioned above, implies that it is an integral part of the host response and that its net effect will be a function of the conditions that prevail for the relevant host–microbe interaction.

Another mechanism by which Ab can function as an immunodulator is by the ability of certain Abs to alter the immune response to an Ag when they are complexed with that Ag (Brady, 2005). This phenomenon has been extensively studied with mAbs to the *Streptococcus mutans* Ag P1. Complexes of mAb and P1 altered the isotype and specificity of the serum Ab response to P1 when administered mucosally or systemically (Brady *et al.*, 2000; Oli *et al.*, 2004).

Table 3 Effect by Which Ab Can Affect Inflammatory Responses

Effect	Mechanism(s)	Outcome proinflammatory	Anti-inflammatory
Complement activation	Phagocytosis Microbial damage Production of proinflammatory complement split products	Increased recruitment of inflammatory cells Microbial damage releases proinflammatory products	Reduction of inoculum IgM-mediated reduction of complement activation
Direct antimicrobial effects	Bactericidal activity Fungistatic activity Inhibition of biofilm formation	Microbial damage releases proinflammatory products	Reduction of inoculum
Formation of Ag–Ab complexes	FcγR cross-linking Complement activation Immunization	Release of proinflammatory mediators such as cytokines and platelet activation factor	Removal of antigens with immunomodulatory effects Release of anti-inflammatory cytokines such as IL-10 Inhibition of proinflammatory cytokines such as IL-12
FcγR activation	Cellular signal transduction following interaction with activating and inhibitory FcγR	Release of proinflammatory mediators such as cytokines, prostaglandins, and platelet activation factor Phagocytosis Enhanced antigen presentation Oxidative burst Expression of costimulatory molecules Reduced inoculum	Release of anti-inflammatory cytokines such as IL-10 Inhibition of proinflammatory cytokines such as IL-12

The mechanism(s) responsible for this phenomenon are not fully understood. mAb-directed alterations in the Ab response, which depended on the amount, isotype, and specificity of the P1-reactive mAb (Oli *et al.*, 2004), could reflect alterations in P1 processing and presentation since mAb binding to P1 induced changes in proteolytic cleavage of P1 (Rhodin *et al.*, 2004). Such a mechanism predicts that mAb–Ag complexes could broaden the response to the Ag to include determinants that induce a more heterogenous array of Abs (Nie *et al.*, 1997), perhaps reactive with a larger number of determinants and or with more favorable biological activity. In this regard, complexes of induced Ab with residual or newly introduced Ag could drive the Ab response toward cryptic or determinants that are underrepresented or poorly antigenic on the native Ag. The possibility that the response to some vaccines may be enhanced by this mechanism is suggested by evidence that passive Ab therapy can drive somatic mutation and affinity maturation of Abs to its relevant Ag (Song *et al.*, 1999). In summary, Ab-mediated immunomodulation is a multifacted function that can depend on Fc dependent or independent, T cell dependent or independent mechanism (Brady, 2005), or as yet unknown processes that may converge in their ability to alter the Ag determinant and/or Ag signaling on which the immune response depends.

There is overwhelming evidence from many systems that Ab and CMI cooperate and are interdependent. For both *Francisella tularensis* (Rhinehart-Jones *et al.*, 1994) and *C. neoformans* (Yuan *et al.*, 1997), the efficacy of passive Ab is dependent on both IFN-γ and T cells. For *Salmonella typhimurium*, the efficacy of passive Ab correlates with the inherent resistance of the mouse strain, suggesting a dependence on cellular and/or innate immune mechanisms for Ab action (Eisenstein *et al.*, 1984b). Similarly, the efficacy of passive Ab against Friend leukemia virus is dependent on the major histocompatibility complex (MHC) type of the host because of a requirement for both CD4 and CD8 T cells (Hasenkrug and Chesebro, 1997; Hasenkrug *et al.*, 1995), but sterilizing immunity requires the presence of neutralizing Ab (Messer *et al.*, 2004). For LCMV, sterilizing immunity required the action of both $CD8^+$ T cells and neutralizing Ab (Baldridge *et al.*, 1997). Synergy between AMI and CMI has also been described in the resolution of lymphoma (Vasovic *et al.*, 1997). Interdependency, cooperation, and the ability of Ab to affect the development of cellular responses suggest that for some systems the relative contribution of AMI and CMI is not easily separable. In fact, one could argue that attempts to separate these components through reductionistic experimental approaches may fail to yield an accurate and comprehensive view of the depth of host defense mechanisms. If this is the case new integrative approaches, perhaps including mathematical modeling, may be needed to achieve a better and more predictive understanding of AMI.

8. Dose-Response Conundrum

Early investigators noted that the efficacy of passive Ab therapy did not obey the law of multiple proportions (Goodner and Horsfall, 1935). Classic studies of passive Ab protection against *S. pneumoniae* revealed that the outcome of a passive Ab protection experiment was critically dependent on the amount of Ab administered (Felton, 1928; Goodner and Horsfall, 1935). The amount of Ab below which no protection occurred for a given inoculum was known as the "limiting titer zone," a phenomenon that could be understood in the context of a requirement for a certain amount of Ab in mediating protection. Furthermore, it was known that no amount of Ab would protect against massive inocula, and this inoculum was known as the German word "*Schwellenwert*" that translates to "threshold." Presumably the *Schwellenwert*-infective dose was so overwhelming that AMI was ineffective. Perhaps the most perplexing aspect of the mouse protection test for *S. pneumoniae* was a "prozone" phenomenon whereby the admistration of large amounts of Ab was accompanied by diminished or abolished protection. For *S. pneumoniae*, the prozone was shown to be caused by a reduction in phagocytosis at very high-Ab concentrations resulting in unchecked bacterial replication (Goodner and Horsfall, 1936). "Prozone-like" phenomena have been demonstrated in other systems, including Ab effects against viruses, bacteria, parasites, fungi, and even cancer cells *in vitro* and *in vivo* (Asano *et al.*, 1982; Flavell *et al.*, 1995; Kozel *et al.*, 2004; Lieberman *et al.*, 1988; Lowell *et al.*, 1980; Parker *et al.*, 1995; Peeling *et al.*, 1984). Prozone-like effects were reproduced using mAbs in two models of murine *C. neoformans* infection (Taborda and Casadevall, 2001; Taborda *et al.*, 2003). For *C. neoformans*, at least three mechanisms have been demonstrated by which high Ab concentrations produce prozone-like effects. First, a high concentration of Ab on the fungal capsule can interfere with nitrogen-derived oxidants that are used by phagocytic cells for microbicidal activity. Second, the cytokine response at high- and low-Ab doses is markedly different, and this effect was shown to be isotype related using a family of variable-gene identical mAbs that differed in constant region. Third, the interaction of complement with *C. neoformans* cells differs at high- and low-Ab concentrations such that the Ab amount can affect the likelihood of phagocytosis by the complement or Fc receptor.

The dependence of Ab efficacy on concentration, and the fact that high concentrations of Ab can render an Ab that was protective nonprotective, suggests the need for caution in drawing negative conclusions about the relative efficacy of AMI, unless a careful dose-response study over a range of Ab amounts is undertaken. The fact that Ab efficacy depends on both the Ig concentration and microbial innoculum (and possibly burden) suggests that

AMI is most effective along a relatively narrow range of Ab concentrations, especially in passive Ab experiments (Casadevall, 2004). Furthermore, since the amount of Ig produced during an immune response changes with time as a function of the rate of Ab production and consumption, and the microbial burden changes with time as a function of microbial and host characteristics that govern replication, infection, and the immune response, it is conceivable that Ab efficacy changes with time as a function of the Ig to microbe ratio. Hence, rather than being a static or stable characteristic, the ability of an Ab to mediate protection is likely to be dynamic, changing as a function of time, the host response, available host receptors and inflammatory mediators, and the state of the microbe in the host.

9. Ab-Mediated Protection Against Intracellular Pathogens

By the late twentieth century, the struggle between the cellularists and humoralists that began with the Ehrlich and Metchnikov debate on the relative importance of CMI and AMI nearly a century earlier (Silverstein, 1979) had settled into a sort of détente whereby each arm of the immune response was assigned a specific role in host defense against certain types of microbes. In this dichotomous view of immune function, AMI was considered to have a key role in protection against extracellular organisms, toxins, and certain types of viruses, while CMI protected against intracellular pathogens. A central problem in this division of labor was the common conclusion that negative data in Ab protection studies implied that Ab had no role in host protection against the relevant microbe (Casadevall, 1998, 2003, 2004). In the past decade, the results of studies with mAbs to various intracellular pathogens have challenged this assumption and established new functions for AMI (Casadevall, 1998, 2003, 2004; Casadevall and Pirofski, 2004). We will consider developments in AMI for several intracellular pathogens. Our goal is to highlight mechanisms by which AMI can protect without being exhaustive. We recognize that in selecting certain microbes for detailed discussion we regretfully will not cover seminal work in certain fields. For those microbes that are not covered in depth, such as *Salmonella* spp., *L. pneumophila*, *S. flexneri*, and others, we provide references in Table 2.

9.1. *Cryptococcus neoformans*

Like many other intracellular pathogens, such as *M. tuberculosis* and *L. monocytogenes*, it was not possible to assign an important role for AMI against *C. neoformans* by either passive administration of immune sera or demonstrating reduced susceptibility in the presence of *C. neoformans*-reactive serum Ab

(reviewed in Casadevall, 1995). Hence, by the late 1980s the prevailing view was that AMI had no role in protection and that host defense was the exclusive domain of CMI. This view was supported by the lack of association of cryptococcosis with B cell defects and the high prevalence of AIDS-related cryptococcosis in patients with CD4 counts <200 cells/cm^3. However, when mAbs were used in passive immunization studies some Abs were found to be protective (Dromer *et al.*, 1987; Fleuridor *et al.*, 1998; Mukherjee *et al.*, 1992; Sanford *et al.*, 1990). Furthermore, studies with individual mAbs revealed that there were protective, nonprotective, and even some disease-enhancing Abs (Maitta *et al.*, 2004; Mukherjee *et al.*, 1995). Ab-mediated protection against *C. neoformans* was shown to be dependent on such Ig-related variables as Ab amount (Dromer *et al.*, 1987), isotype (Yuan *et al.*, 1995, 1998), specificity of Ig (Mukherjee *et al.*, 1995). On the other hand, Ab-mediated protection was also dependent on host factors such as T cells (Yuan *et al.*, 1997), B cells (Rivera *et al.*, 2005), the presence of inducible nitric oxide (Rivera *et al.*, 2002), and both Th1- and Th2-associated cytokines (Beenhouwer *et al.*, 2001). IgM, but not IgG, required complement (Fleuridor *et al.*, 1998; Shapiro *et al.*, 2002). Hence, the outcome of Ab protection studies was determined by the interaction between Ab characteristics and immune parameters of the host such that certain Abs were protective in certain host immune milieus but not others and vice versa.

At present, our understanding of the factors that govern cryptococcal pathogenesis remains insufficient to consistently predict which Ab characteristics are required for protection in a given host immune or inflammatory milieu. However, it is reasonable to predict that Abs that require CD4$^+$ T cells to function might not be effective in HIV-infected individuals and that Fc receptor polymorphisms could affect the efficacy of Abs that bind the relevant receptor. In this regard, individuals who are homozygous for a low-affinity receptor for (human) IgG2 are more susceptible to menigococcal sepsis (Domingo *et al.*, 2004; van Sorge *et al.*, 2003). Further, available data suggest that Abs that mediate protection in wild-type mice fail to do so in mice with dysregulated cytokine responses such as NO-, cytokine-, and B cell-deficient mice (Beenhouwer *et al.*, 2001; Feldmesser *et al.*, 2002; Rivera *et al.*, 2002, 2005). Hence, the interplay between the host immune response and the way in which a given Ab affects the inflammatory response can govern whether an Ab will reduce host damage sufficiently to be protective.

9.2. *Mycobacterium tuberculosis*

Numerous studies over the past century found evidence for and against a role for AMI against *M. tuberculosis* (Glatman-Freedman, 2003; Glatman-Freedman

and Casadevall, 1998), yet by the 1990s the prevailing view was that AMI had little or no role in host defense. Consistent with this notion, B cell-deficient mice did not manifest great susceptibility to *M. tuberculosis* or *M. avium* infection (Bosio *et al.*, 2000; Johnson *et al.*, 1997; Sangari *et al.*, 2001; Vordermeier *et al.*, 1996), with the caveat that negative studies in this type of system cannot be used to exclude a role for AMI (Casadevall, 2004). However, in 1998 an mAb to the arabinomannan component of the mycobacterial surface was shown to mediate protection when coadministered with mycobacteria by the intratracheal route (Teitelbaum *et al.*, 1998). Subsequently, four independent groups have confirmed that different mAbs can mediate protection against mycobacteria in mouse models of infection (Chambers *et al.*, 2004; Hamasur *et al.*, 2004; Pethe *et al.*, 2001; Williams *et al.*, 2004). Protective mAbs to mycobacteria include those recognizing polysaccharide and protein Ags, indicating that different types of Ags have the potential to elicit useful AMI. Furthermore, one report showed that an F(ab) derived from an mAb to arabinomannan could mediate protection, implying that for certain Abs protection could be Fc independent (Hamasur *et al.*, 2004). The mechanism by which an F(ab) can mediate protection is uncertain. However, there are precedents for F(ab)-mediated protection against other bacterial and fungal pathogens (Matthews *et al.*, 2003; Ramisse *et al.*, 1996) through mechanisms that may include direct antimicrobial effects or immunization-type phenomena (Brady, 2005). The ability of AMI to protect against *M. tuberculosis* is further supported by the demonstration that polysaccharide-protein conjugate vaccines constructed with oligosaccharides from lipoarabinomannan elicited immune responses were protective in mice and comparable to BCG (Hamasur *et al.*, 2003). In another study, mice immunized with arabinomannan conjugated to recombinant *Pseudomonas aeruginosa* exoprotein A had a lower lung bacterial burden at day 7 of infection (Glatman-Freedman *et al.*, 2004).

Despite strong evidence that certain Ab responses can protect against mycobacteria, the mechanism of Ab action has not been fully elucidated. Mycobacterial polysaccharides are immunomodulators. Hence, the ability of specific Ab to promote clearance could confer an immunological benefit (Glatman-Freedman *et al.*, 2000; Schwebach *et al.*, 2001). Another potential mechanism includes modification of the outcome of intracellular infection by specific Ab, since phagocytosis in the presence of specific Ab was reported to promote the fusion of lysosomes with mycobacterial-containing phagosomes (Armstrong and Hart, 1975). Ab-mediated internalization of *M. tuberculosis* was shown to be associated with high Ca^{2+} concentrations that promoted phagosomal maturation and intracellular killing of mycobacteria (Malik *et al.*, 2000). This effect was different than complement-mediated phagocytosis and suggested that engagement of certain FcR could reverse mycobacterial

inhibition of Ca^{2+} fluxes that are associated with intracellular survival (Malik *et al.*, 2000).

Ab-mediated effects on intracellular survival and/or clearance of mycobacterial products can enhance the immune response, suggesting that Ab-mediated protection translates into reduced host damage. The possibility that Ab-mediated protection is associated with a reduction in the inflammatory response comes from the observations that mice given passive IgG3 had differences in the histology of lung inflammation and that B cell- and IgA-deficient mice (Rodriguez *et al.*, 2005) infected with *M. tuberculosis* manifested different immune responses.

The ability of certain mAbs to mediate protection against *M. tuberculosis* is in contrast to the historical difficulty in consistently demonstrating protection in passive Ab studies or in associating Ab responses with immunity to tuberculosis (Glatman-Freedman, 2003; Glatman-Freedman and Casadevall, 1998). However, the finding that some mAbs are protective while others are non-protective (Teitelbaum *et al.*, 1998) suggests that like the situation for *C. neoformans* the problem in demonstrating the efficacy of AMI against *M. tuberculosis* could reflect heterogeneity in and the complex nature of the Ab response. In fact, a serological study of Abs to arabinomannan in human sera revealed quantitative and qualitative differences in individual responses (Glatman-Freedman *et al.*, 2004). It is likely that differences in mechanisms of Ab action will be discovered for Abs to *M. tuberculosis*, since the heterogenous serum response is associated with resistance to disease in most individuals who experience an infection. However, understanding of the role of AMI in human *M. tuberculosis* infection must await the use of more sophisticated serological tools that can measure quantitative and qualitative aspects of the Ab response and establish correlations between serological responses and clinical endpoints ranging from latency to disease.

9.3. *Ehrlichia chaffeensis*

Several studies have conclusively established a role for AMI in host protection against *E. chaffeensis*, an obligate intracellular bacterium that infects monocytes and macrophages (Li and Winslow, 2003; Li *et al.*, 2002; Winslow *et al.*, 2000). *E. chaffeensis* infection is cleared in C57Bl/6 mice rapidly but produces lethal infection in severe combined immunodeficiency (SCID) mice. Passive administration of immune serum led to transient clearance of infection in SCID mice, implying the ability of specific Ab to control and eradicate this organism without T cell help (Winslow *et al.*, 2000). Most striking was the ability of immune serum to control established infection, although this effect was transient and required repeated administration for maintenance (Winslow

et al., 2000). Subsequent studies established that Ab-mediated protection could be conferred by passive administration of mAbs to the *E. chaffeensis* outer membrane protein 1-g (OMP-1g) and that Abs of this specificity were present in immune sera from both humans and mice (Li *et al.*, 2001). The comparison of mAb-mediated protection revealed isotype-related differences in efficacy with IgG2a > IgG3 = IgG2b ≫ IgM in a set of variable region matched Abs that recognized a linear epitope in the first hypervariable domain of OMP-1g (Li *et al.*, 2001, 2002). Ab efficacy was also found to be directly associated with half-life and picomolar affinity (Li *et al.*, 2002). The consistency of these observations became apparent when free *E. chaffeensis* was demonstrated in the serum of infected mice, implying the existence of an extracellular phase during which this obligate intracellular bacterium spread from cell to cell and was susceptible to AMI (Li and Winslow, 2003). Hence, the emerging story for AMI to *E. chaffeensis* indicates that a different mechanism than that described for other intracellular pathogens, which relies on the bactericidal capacity of Ab in serum, is responsible for Ab efficacy. However, there is also evidence that specific Ab to *E. chaffeensis* can modify the cytokine expression of host cells, suggesting that, like that to *C. neoformans*, Ab-mediated protection may be due to changes in the inflammatory response (Lee and Rikihisa, 1997).

Passive Ab administration is also protective against another *Erlichia* species *E. risticci*, an obligate intracellular bacterial pathogen of horses (Kaylor *et al.*, 1991). For this microbe, the F(ab) of horse immune serum blocked bacterial entry, while intact IgG allowed internalization of the host cell via the Fc receptor, which interfered with intracellular growth of the bacterium (Messick and Rikihisa, 1994).

9.4. *Listeria monocytogenes*

Immunological studies of host defense against the facultative intracellular gram-positive bacterium *L. monocytogenes* helped to formulate the paradigm whereby protection against intracellular bacterial microbes was the exclusive domain of CMI (Mackaness, 1971, 1977). For *L. monocytogenes*, passive Ab transfer experiments using immune serum did not provide protection (Miki and Mackaness, 1964). Comparison of the outcome of infection in B cell-deficient and normal mice suggested a role for B cells in the establishment of CMI that was independent of Ab production (Matsuzaki *et al.*, 1999). However, passive administration of an mAb to listeriolysin O (LLO) to mice before challenge with *L. monocytogenes* mediated protection by prolonging survival and reducing the tissue bacterial burden (Edelson *et al.*, 1999). One peculiar aspect of this phenomenon was the requirement for relatively high

Ab doses to achieve protection. The mechanism of Ab-mediated protection involved neutralization of LLO inside macrophages preventing passage of the bacteria from the phagosome to the cytoplasm (Edelson and Unanue, 2001). Hence, the requirement for large Ab doses was explained by the need to achieve high enough serum concentrations to deliver sufficient immunoglobulin to mediate toxin neutralization. Consistent with this mechanism, Ab-mediated protection was not dependent on FcγR (Edelson and Unanue, 2001). Abs with LLO-neutralizing activity were not found in the serum of infected animals, implying that this determinant was not antigenic in the course of experimental infection. Whereas this example of Ab-mediated protection could be explained by the classical mechanism of toxin neutralization, it extends this mechanism to phagosomal spaces, underscoring that AMI is not limited to the extracellular space.

9.5. *Histoplasma capsulatum*

This fungus is a facultative intracellular pathogen that is almost always found inside macrophages in tissue. Numerous studies have failed to demonstrate a role for AMI against *H. capsulatum* in mice passively immunized with immune sera (Tewari *et al.*, 1977) or B cell deficiency (Allendoerfer *et al.*, 1999). In contrast, there is overwhelming evidence that CMI is critical for host defense (Deepe and Seder, 1998). However, when the potential role of AMI was investigated by generating mAbs to *H. capsulatum* surface Ags, an mAb was identified that mediated protection when administered prior to experimental infection in mice (Nosanchuk *et al.*, 2003). The Ag recognized by this mAb was a histone-like protein that is expressed on the surface of fungal cells. Although the mechanism of Ab action was not fully clarified, there was evidence that it was opsonic *in vitro* and that Ab-treated mice had altered inflammatory responses, as shown by changes in tissue histology and cytokine expression (Nosanchuk *et al.*, 2003). Passive Ab was most effective when given with small amounts of amphotericin B, an antifungal agent that is a potent immunomodulator by virtue of its ability to stimulate Toll-like receptors (Nosanchuk *et al.*, 2003). This observation is consistent with the view that Ab-mediated protection in this system was a result of alterations in the inflammatory response (Nosanchuk *et al.*, 2003).

9.6. *Toxoplasma gondii*

Toxoplasma gondii is an intracellular pathogen that is able to infect all mammalian cells. After the parasite gains entrance to the cell, it forms a parasitophorous vacuole that effectively shields it from host cellular antimicrobial mechanisms.

Numerous studies have established the potential efficacy of AMI in protection against *T. gondii*. For this microbe, the evidence that AMI contributes to host defense includes studies showing greater susceptibility in hosts with impaired AMI, demonstration of protection in passive transfer studies, and association of vaccine-mediated protection with AMI (Pavia *et al.*, 1992). B cell-deficient mice (μMT) were significantly more susceptible to toxoplasmosis than wild-type mice and could be protected by the administration of polyclonal rabbit immune sera (Kang *et al.*, 2000). CD4-deficient mice manifest greater susceptibility to *T. gondii* that was ameliorated by the transfer of immune sera (Johnson and Sayles, 2002).

Several studies suggest possible mechanisms for Ab-mediated protection and a high likelihood that there are multiple Ags that can elicit protective and nonprotective Abs to *T. gondii*. Secretory IgA reactive with a 46-kD Ag was shown to inhibit the enterozyte infection *in vitro* (Mack and McLeod, 1992). However, not all specific IgG is protective, since other studies have shown no reduction in the ability of *T. gondii* to replicate in macrophages when opsonized by IgG (Fadul *et al.*, 1995). An mAb to a 97-kD Ag inhibited intracellular replication of *T. gondii* in macrophages by a complement-independent mechanism that did not involve interference with internalization or attachment (Mineo *et al.*, 1994). However, complement may be important for the action of certain *T. gondii*-specific Abs. mAbs to the dense granular proteins of *T. gondii* mediate protection when tachyozites were incubated with Ab and complement prior to murine infection while Ab alone had no effect (Cha *et al.*, 2001). Other protective mAbs recognize different Ag of 35 and 14 kD (Johnson *et al.*, 1983).

9.7. *Chlamydia* spp.

Chlamydia trachomatis in an intracellular pathogen is the leading cause of sexually transmitted disease. For this organism, there is overwhelming evidence that both CMI and AMI contribute to host defense. The appearance of serum Abs correlates with clearance of experimental *C. trachomatis* infection in rabbits (Rank *et al.*, 1979) and serum Ab is a marker of immunity (Murray *et al.*, 1973; Rank and Barron, 1983). The presence of IgA in human vaginal secretions demonstrates a striking inverse correlation with the likelihood of cervical recovery of the organism in women (Brunham *et al.*, 1983). Passive transfer of immune serum protected guinea pigs against experimental genital infection (Rank and Batteiger, 1989). Passive administration of mAbs to the *C. trachomatis* outer membrane protein mediated protection against lethal infection in mice and neutralized chlamydial infectivity in a monkey model of

opthalmitis (Zhang *et al.*, 1987). In contrast, individual mAbs had variable efficacy in passive transfer studies (Cotter *et al.*, 1995), perhaps suggesting the need for multiple Ab specificities and isotypes to fully protect against *C. trachomatis* in various tissue compartments. However, studies with B cell-deficient mice have shown that Ab is not required for resolution of infection or resistance to reinfection (Ramsey *et al.*, 1988; Williams *et al.*, 1987). Hence, AMI contributes to host defense against *C. trachomatis* in the context of other antichlamydial immune mechanisms that cooperate and work in parallel.

10. Protective Efficacy of an Ab Molecule

Given that the efficacy of an Ab depends on its specificity, isotype, affinity, and the immune status and genetic background of the host, one cannot classify an Ab as protective, nonprotective, or disease enhancing solely on the basis of Ig structure. In fact, for each microbe Ab-mediated protection might be thought of as a complex function of: (1) Ab variables such as isotype, specificity, and amount; (2) host variables such as genetic background, immunization status, and immune competence; and (3) microbial variables such as virulence factors, inoculum, and pathogenic strategy. Furthermore, it is likely that this function will be different for each pathogenic microbe. For example, IgG3 to capsular polysaccharide is protective against *M. tuberculosis* in BALB/c and C57Bl/6 mice (Teitelbaum *et al.*, 1998) but not against *C. neoformans* (Yuan *et al.*, 1997). However, the same IgG3 that was not protective in C57Bl/6 or 129/Sv mice against *C. neoformans* was protective against experimental cryptococcosis in C57Bl/6 × 129/Sv mice (Rivera and Casadevall, 2005). In a polyclonal response, the efficacy of AMI can be expected to be a function of the combined effects of individual Ab molecules, each with its own protective function based on the characteristics listed earlier. Whether the net effect of each component on protective function is additive or multiplicative is unknown. Considering that the immune response to pathogenic microbes includes Abs to many Ags differing in the predominant isotype and amount, one can easily envision unfathomable complexity that becomes even more daunting if one considers host genetic variation in an outbred species. Clearly, defining protective efficacy of an Ab molecule in a predictive fashion is currently beyond the state of immunological science and may not be possible with current reductionistic approaches to scientific problems. Nevertheless, we remain optimistic that as the variables that impact Ab-protective efficacy are identified it may be possible to define algorithms that provide predictive information.

11. Some Emerging Concepts

1. Abs are both proinflammatory and anti-inflammatory and mediate some of their effects by modulating both innate and adaptive cellular responses.
2. Protective Abs can probably be made against many if not all pathogens for which current methods cannot demonstrate a clear role for AMI in host defense. The most efficient way to achieve this is to generate mAbs to the microbe in question with the caveat that immunological knowledge is insufficient to predict the Ab characteristics that will be protective. Therefore, in most instances, determining the efficacy of Ab remains an empiric rather than predictive discipline.
3. The inability to demonstrate a role for AMI against a particular pathogen using the classical methods of passive Ab administration and correlation of Ab titer with immunity does not rule out a role for AMI in protection or pathogenesis.
4. The efficacy of an Ab cannot be defined solely from the molecular characteristics of the Ig molecule or independently of the host in which it is tested.
5. Ab-mediated protection can be associated with enhanced or reduced inflammatory responses depending on the microbe in question.
6. Given the strong dependence of Ab function on the quantity and the nature of the host immune response, it is likely that for some microbes the function of AMI differs early and late in infection or in the context of reinfection.
7. Protective Abs can be used as probes in reverse vaccinology approaches to identify epitopes and design vaccines that induce Abs that mediate protection. Examples of this approach are provided by *C. neoformans* (Devi, 1996), *C. albicans* (Han *et al.*, 1999), and *M. tuberculosis* (Hamasur *et al.*, 2003) in which the identification of protective mAbs led to the identification of an Ag that elicited a protective Ab response that was then used to make an effective conjugate vaccine.
8. The relative contributions of AMI and CMI to host defense and microbial clearance may be inseparable for certain, particularly, intracellular pathogens, suggesting the need for new models and systems to identify and characterize mechanisms of Ab action.

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References

Allendoerfer, R., Brunner, G. D., and Deepe, G. S., Jr. (1999). Complex requirements for nascent and memory immunity in pulmonary histoplasmosis. *J. Immunol.* **162,** 7389–7396.

Anderson, C. F., and Mosser, D. M. (2002). Cutting edge: Biasing immune responses by directing antigen to macrophage Fcγ receptors. *J. Immunol.* **168,** 3697–3701.

Anderson, S., David, J. R., and McMahon-Pratt, D. (1983). *In vivo* protection against Leishmania mexicana mediated by monoclonal antibodies. *J. Immunol.* **131,** 1616–1618.

Armstrong, J. A., and Hart, P. D. (1975). Phagosome-lysosome interactions in cultured macrophages infected with virulent tubercle bacilli. Reversal of the usual nonfusion pattern and observations on bacterial survival. *J. Exp. Med.* **142,** 1–16.

Asano, Y., Albrecht, P., Stagno, S., and Takahashi, M. (1982). Potentiation of neutralization of Varicella-Zoster virus to antibody to immunoglobulin. *J. Infect. Dis.* **146,** 524–529.

Azem, J., Svennerholm, A. M., and Lundin, B. S. (2005). B cells pulsed with *Helicobacter pylori* antigen efficiently activate memory CD8(+) T cells from *H. pylori*-infected individuals. *Clin. Immunol.* **118,** 284–291.

Baldridge, J. R., McGraw, T. S., Paoletti, A., and Buchmeier, M. J. (1997). Antibody prevents the establishment of persistent arenavirus infection in synergy with endogenous T cells. *J. Virol.* **71,** 755–758.

Beedham, R. J., Turnbull, P. C., and Williamson, E. D. (2001). Passive transfer of protection against *Bacillus anthracis* infection in a murine model. *Vaccine* **19,** 4409–4416.

Beenhouwer, D. O., Shapiro, S., Feldmesser, M., Casadevall, A., and Scharff, M. D. (2001). Both Th1 and Th2 cytokines affect the ability of monoclonal antibodies to protect mice against *Cryptococcus neoformans*. *Infect. Immun.* **69,** 6445–6455.

Bennett-Guerrero, E., Ayuso, L., Hamilton-Davies, C., White, W. D., Barclay, G. R., Smith, P. K., King, S. A., Muhlbaier, L. H., Newman, M. F., and Mythen, M. G. (1997). Relationship of preoperative antiendotoxin core antibodies and adverse outcomes following cardiac surgery. *JAMA* **277,** 646–650.

Boes, M., Prodeus, A. P., Schmidt, T., Carroll, M. C., and Chen, J. (1998a). A critical role of natural immunoglobulin M in immediate defense against systemic bacterial infection. *J. Exp. Med.* **188,** 2381–2386.

Boes, M., Esau, C., Fischer, M. B., Schmidt, T., Carroll, M., and Chen, J. (1998b). Enhanced B-1 cell development, but impaired IgG antibody responses in mice deficient in secreted IgM. *J. Immunol.* **160,** 4776–4787.

Boruchov, A. M., Heller, G., Veri, M. C., Bonvini, E., Ravetch, J. V., and Young, J. W. (2005). Activating and inhibitory IgG Fc receptors on human DCs mediate opposing functions. *J. Clin. Invest.* **115,** 2914–2923.

Bosio, C. M., and Elkins, K. L. (2001). Susceptibility to secondary *Francisella tularensis* live vaccine strain infection in B-cell-deficient mice is associated with neutrophila but not with defects in specific T-cell-mediated immunity. *Infect. Immun.* **69,** 194–203.

Bosio, C. M., Gardner, D., and Elkins, K. L. (2000). Infection of B cell-deficient mice with CDC 1551, a clinical isolate of *Mycobacterium tuberculosis*: Delay in dissemination and development of lung pathology. *J. Immunol.* **164,** 6417–6425.

Bowden, R. A., Cloeckaert, A., Zygmunt, M. S., and Dubray, G. (1995). Outer-membrane protein- and rough lipopolysaccharide-specific monoclonal antibodies protect mice against *Brucella ovis*. *J. Med. Microbiol.* **43,** 344–347.

Brady, L. J. (2005). Antibody-mediated immunomodulation: A strategy to improve host responses against microbial antigens. *Infect. Immun.* **73,** 671–678.

Brady, L. J., Van Tilburg, M. L., Alford, C. E., and McArthur, W. P. (2000). Monoclonal antibody-mediated modulation of the humoral immune response against mucosally applied *Streptococcus mutans*. *Infect. Immun.* **68,** 1796–1805.

Brieland, J. K., Heath, L. A., Huffnagle, G. B., Remick, D. G., McClain, M. S., Hurley, M. C., Kunkel, R. K., Fantone, J. C., and Engleberg, C. (1996). Humoral immunity and regulation of intrapulmonary growth of *Legionella pneumophila* in the immunocompetent host. *J. Immunol.* **157,** 5002–5008.

Brown, J. S., Hussell, T., Gilliland, S. M., Holden, D. W., Paton, J. C., Ehrenstein, M. R., Walport, M. J., and Botto, M. (2002). The classical pathway is the dominant complement pathway required for innate immunity to *Streptococcus pneumoniae* infection in mice. *Proc. Natl. Acad. Sci. USA* **99,** 16969–16974.

Brunham, R. C., Kuo, C. C., Cles, L., and Holmes, K. K. (1983). Correlation of host immune response with quantitative recovery of *Chlamydia trachomatis* from the human endocervix. *Infect. Immun.* **39,** 1491–1494.

Buda, S., Riefolo, A., Biscione, R., Goretti, E., Cattabriga, I., Grillone, G., Bacchi-Reggiani, L., and Pacini, D. (2005). Clinical experience with polyclonal IgM-enriched immunoglobulins in a group of patients affected by sepsis after cardiac surgery. *J. Cardiothorac. Vasc. Anesth.* **19,** 440–445.

Burns, T., Zhong, Z., Steinitz, M., and Pirofski, L. A. (2003). Modulation of polymorphonuclear cell interleukin-8 secretion by human monoclonal antibodies to type 8 pneumococcal capsular polysaccharide. *Infect. Immun.* **71,** 6775–6783.

Burns, T., Abadi, H., and Pirofski, L. (2005). Modulation of the inflammatory response to serotype 8 pneumococcal infection by a human immunoglobulin in monoclonal antibody to serotype 8 capsular polysaccharide. *Infect. Immun.* **73,** 4530–4578.

Carsetti, R., Rosado, M. M., Donnanno, S., Guazzi, V., Soresina, A., Meini, A., Plebani, A., Aiuti, F., and Quinti, I. (2005). The loss of IgM memory B cells correlates with clinical disease in common variable immunodeficiency. *J. Allergy Clin. Immunol.* **115,** 412–417.

Casadevall, A. (1995). Antibody immunity and invasive fungal infections. *Infect. Immun.* **63,** 4211–4218.

Casadevall, A. (1998). Antibody-mediated protection against intracellular pathogens. *Trends Microbiol.* **6,** 102–103.

Casadevall, A. (2003). Antibody-mediated immunity against intracellular pathogens: Two-dimensional thinking comes full circle. *Infect. Immun.* **71,** 4225–4228.

Casadevall, A. (2004). The methodology for determining the efficacy of antibody-mediated immunity. *J. Immunol. Methods* **291,** 1–10.

Casadevall, A., and Pirofski, L. (1999). Host-pathogen interactions: Redefining the basic concepts of virulence and pathogenicity. *Infect. Immun.* **67,** 3703–3713.

Casadevall, A., and Pirofski, L. (2000). Host-pathogen interactions: The basic concepts of microbial commensalism, colonization, infection, and disease. *Infect. Immun.* **68,** 6511–6518.

Casadevall, A., and Pirofski, L. (2003). The damage-response framework of microbial pathogenesis. *Nature Microbiol. Rev.* **1,** 17–24.

Casadevall, A., and Pirofski, L. (2004). New concepts in antibody-mediated immunity. *Infect. Immun.* **72,** 6191–6196.

Casadevall, A., and Pirofski, L. A. (2003). Antibody-mediated regulation of cellular immunity and the inflammatory response. *Trends Immunol.* **24,** 474–478.

Cha, D. Y., Song, I. K., Lee, G. S., Hwang, O. S., Noh, H. J., Yeo, S. D., Shin, D. W., and Lee, Y. H. (2001). Effects of specific monoclonal antibodies to dense granular proteins on the invasion of *Toxoplasma gondii in vitro* and *in vivo*. *Korean J. Parasitol.* **39,** 233–240.

Chambers, M. A., Gavier-Widen, D., and Hewinson, R. G. (2004). Antibody bound to the surface antigen MPB83 of *Mycobacterium bovis* enhances survival against high dose and low dose challenge. *FEMS Immunol. Med. Microbiol.* **41,** 93–100.

Chong, Y., Ikematsu, H., Kikuchi, K., Yamamoto, M., Murata, M., Nishimura, M., Nabeshima, S., Kashiwagi, S., and Hayashi, J. (2004). Selective CD27+ (memory) B cell reduction and characteristic B cell alteration in drug-naive and HAART-treated HIV type 1-infected patients. *AIDS Res. Hum. Retroviruses* **20,** 219–226.

Clatworthy, M. R., and Smith, K. G. (2004). FcgammaRIIb balances efficient pathogen clearance and the cytokine-mediated consequences of sepsis. *J. Exp. Med.* **199,** 717–723.

Collins, F. M. (1974). Vaccines and cell-mediated immunity. *Bacteriol. Rev.* **38,** 371–402.

Collins, F. M. (1979). Cellular antimicrobial immunity. *CRC Crit. Rev. Microbiol.* **7,** 27–91.

Connolly, S. E., and Benach, J. L. (2001). Cutting edge: The spirochetemia of murine relapsing fever is cleared by complement-independent bactericidal antibodies. *J. Immunol.* **167,** 2032–3029.

Connolly, S. E., Thanassi, D. G., and Benach, J. L. (2004). Generation of a complement-independent bactericidal IgM against a relapsing fever Borrelia. *J. Immunol.* **172,** 1191–1197.

Conti, S., Fanti, F., Magliani, W., Gerloni, M., Bertolotti, D., Salati, A., Cassone, A., and Polonelli, L. (1998). Mycobactericidal activity of human natural, monoclonal, and recombinant yeast killer toxin-like antibodies. *J. Infect. Dis.* **177,** 807–811.

Cotter, T. W., Meng, Q., Shen, Z. L., Zhang, Y. X., Su, H., and Caldwell, H. D. (1995). Protective efficacy of major outer membrane protein-specific immunoglobulin A (IgA) and IgG monoclonal antibodies in a murine model of *Chlamydia trachomatis* genital tract infection. *Infect. Immun.* **63,** 4704–4714.

Couper, K. N., Phillips, R. S., Brombacher, F., and Alexander, J. (2005). Parasite-specific IgM plays a significant role in the protective immune response to asexual erythrocytic stage *Plasmodium chabaudi* AS infection. *Parasite Immunol.* **27,** 171–180.

Daffe, M., and Etienne, G. (1999). The capsule of *Mycobacterium tuberculosis* and its implications for pathogenicity. *Tuber. Lung Dis.* **79,** 153–169.

Dalakas, M. C. (2003). High-dose intravenous immunoglobulin in inflammatory myopathies: Experience based on controlled clinical trials. *Neurol. Sci.* **24**(Suppl. 4), S256–S259.

Darenberg, J., Ihendyane, N., Sjolin, J., Aufwerber, E., Haidl, S., Follin, P., Andersson, J., and Norrby-Teglund, A. (2003). Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: A European randomized, double-blind, placebo-controlled trial. *Clin. Infect. Dis.* **37,** 333–340.

Deepe, G. S., Jr., and Seder, R. A. (1998). Molecular and cellular determinants of immunity to *Histoplasma capsulatum*. *Res. Immunol.* **149,** 397–406.

Devi, S. J. N. (1996). Preclinical efficacy of a glucuronoxylomannan-tetanus toxoid conjugate vaccine of *Cryptococcus neoformans* in a murine model. *Vaccine* **14,** 841–842.

Diamond, M. S., Sitati, E. M., Friend, L. D., Higgs, S., Shrestha, B., and Engle, M. (2003). A critical role for induced IgM in the protection against West Nile virus infection. *J. Exp. Med.* **198,** 1853–1862.

Dixon, T. C., Fadl, A. A., Koehler, T. M., Swanson, J. A., and Hanna, P. C. (2000). Early *Bacillus anthracis*-macrophage interactions: Intracellular survival survival and escape. *Cell Microbiol.* **2,** 453–463.

Domingo, P., Muniz-Diaz, E., Baraldes, M. A., Arilla, M., Barquet, N., Pericas, R., Juarez, C., Madoz, P., and Vazquez, G. (2004). Relevance of genetically determined host factors to the prognosis of meningococcal disease. *Eur. J. Clin. Microbiol. Infect. Dis.* **23,** 634–637.

Dromer, F., Charreire, J., Contrepois, A., Carbon, C., and Yeni, P. (1987). Protection of mice against experimental cryptococcosis by anti-*Cryptococcus neoformans* monoclonal antibody. *Infect. Immun.* **55,** 749–752.

Edelson, B. T., and Unanue, E. R. (2001). Intracellular antibody neutralizes *Listeria* growth. *Immunity* **14,** 503–512.

Edelson, B. T., Cossart, P., and Unanue, E. R. (1999). Cutting edge: Paradigm revisited: Antibody provides resistance to *Listeria* infection. *J. Immunol.* **163,** 4087–4090.

Eisenstein, T. K., Tamada, R., Meissler, J., Flesher, A., and Oels, H. C. (1984a). Vaccination against *Legionella pneumophila*: Serum antibody correlates with protection induced by heat-killed or acetone-killed cells against intraperitoneal but not aerosol infection in guinea pigs. *Infect. Immun.* **45,** 685–691.

Eisenstein, T. K., Millar, L. M., and Sultzer, B. M. (1984b). Immunity to infection with *Salmonella typhimurium*: Mouse-strain differences in vaccine- and serum-mediated protection. *J. Infect. Dis.* **150,** 425–435.

Elzer, P. H., Jacobason, R. H., Jones, S. M., Nielsen, K. H., Douglas, J. T., and Winter, A. J. (1994). Antibody-mediated protection against *Brucella abortus* in BALB/c mice at successive periods after infection: Variation between virulent strain 2308 and attenuated vaccine strain 19. *Immunology* **82,** 651–658.

Fadul, C. E., Channon, J. Y., and Kasper, L. H. (1995). Survival of immunoglobulin G-opsonized *Toxoplasma gondii* in nonadherent human monocytes. *Infect. Immun.* **63,** 4290–4294.

Feldmesser, M., Kress, Y., Novikoff, P., and Casadevall, A. (2000). *Cryptococcus neoformans* is a facultative intracellular pathogen in murine pulmonary infection. *Infect. Immun.* **68,** 4225–4237.

Feldmesser, M., Mednick, A., and Casadevall, A. (2002). Antibody-mediated protection in murine *Cryptococcus neoformans* infection is associated with subtle pleotrophic effects on the cytokine and leukocyte response. *Infect. Immun.* **70,** 1571–1580.

Felton, L. D. (1928). The units of protective antibody in anti-pneumococcus serum and antibody solution. *J. Infect. Dis.* **43,** 531–542.

Fitzgerald, S. P., and Rogers, H. J. (1980). Bacteriostatic effect of serum; role of antibody to lipopolysaccharide. *Infect. Immun.* **27,** 302–308.

Flavell, D. J., Cooper, S., Okayama, K., Emery, L., and Flavell, S. U. (1995). Comparison of the performance of anti-CD7 and anti-CD38 bispecific antibodies and immunotoxins for the delivery of saporin to a human T-cell acute lymphoblastic leukemia cell line. *Hematol. Oncol.* **13,** 185–200.

Fleuridor, R., Zhong, Z., and Pirofski, L. (1998). A human IgM monoclonal antibody prolongs survival of mice with lethal cryptococcosis. *J. Infect. Dis.* **178,** 1213–1216.

Fleuridor, R., Lyles, R. H., and Pirofski, L. (1999). Quantitative and qualitative differences in the serum antibody profiles of human immunodeficiency virus-infected persons with and without *Cryptococcus neoformans* meningitis. *J. Infect. Dis.* **180,** 1526–1535.

Gambrill, M. R., and Wisseman, C. L. (1973). Mechanisms of immunity in typhus infections. III. Influence of human immune serum and complement on the fate of *Rickettsia mooseri* within human macrophages. *Infect. Immun.* **8,** 631–640.

Gerber, J. S., and Mosser, D. M. (2001). Reversing lipopolysaccharide toxicity by ligating the macrophage Fcγ receptors. *J. Immunol.* **166,** 6861–6868.

Glatman-Freedman, A. (2003). Advances in antibody-mediated immunity against *Mycobacterium tuberculosis*: Implications for a novel vaccine strategy. *FEMS Immunol. Med. Microbiol.* **39,** 9–16.

Glatman-Freedman, A., and Casadevall, A. (1998). Serum therapy for tuberculosis revisited: A reappraisal of the role of antibody-mediated immunity against *Mycobacterium tuberculosis*. *Clin. Microbiol. Rev.* **11,** 514–532.

Glatman-Freedman, A., Mednick, A. J., Lendvai, N., and Casadevall, A. (2000). Clearance and organ distribution of *Mycobacterium tuberculosis* lipoarabinomannan (LAM) in the presence and absence of LAM-binding IgM. *Infect. Immun.* **68,** 335–341.

Glatman-Freedman, A., Casadevall, A., Dai, Z., Jacobs, W. R., Jr., Li, A., Morris, S. L., Navoa, J. A., Piperdi, S., Robbins, J. B., Schneerson, R., Schwebach, J. R., and Shapiro, M. (2004). Antigenic evidence of prevalence and diversity of *Mycobacterium tuberculosis* arabinomannan. *J. Clin. Microbiol.* **42,** 3225–3231.

Goel, V. K., and Kapil, A. (2001). Monoclonal antibodies against the iron regulated outer membrane proteins of *Acinetobacter baumannii* are bactericidal. *BMC Microbiol.* **1,** 16.

Goodner, K., and Horsfall, F. L., Jr. (1935). The protective action of type I antipneumococcus serum in mice. I. Quantitative aspects of the mouse protection test. *J. Exp. Med.* **62,** 359–374.

Goodner, K., and Horsfall, F. L., Jr. (1936). The protective action of type 1 antipneumococcus serum in mice. IV. The prozone. *J. Exp. Med.* **64,** 369–375.

Gresham, H. D., Lowrance, J. H., Caver, T. E., Wilson, B. S., Cheung, A. L., and Lindberg, F. P. (2000). Survival of *Staphylococcus aureus* inside neutrophils contributes to infection. *J. Immunol.* **164,** 3713–3722.

Hamasur, B., Haile, M., Pawlowski, A., Schroder, U., Williams, A., Hatch, G., Hall, G., Marsh, P., Kallenius, G., and Svenson, S. B. (2003). *Mycobacterium tuberculosis* arabinomannan-protein conjugates protect against tuberculosis. *Vaccine* **21,** 4081–4093.

Hamasur, B., Haile, M., Pawlowski, A., Schroder, U., Kallenius, G., and Svenson, S. B. (2004). A mycobacterial lipoarabinomannan specific monoclonal antibody and its F(ab') fragment prolong survival of mice infected with *Mycobacterium tuberculosis*. *Clin. Exp. Immunol.* **138,** 30–38.

Han, Y., Ulrich, M. A., and Cutler, J. E. (1999). *Candida albicans* mannan extract-protein conjugates induce a protective immune response against experimental candidiasis. *J. Infect. Dis.* **179,** 1477–1484.

Harada, Y., Muramatsu, M., Shibata, T., Honjo, T., and Kuroda, K. (2003). Unmutated immunoglobulin M can protect mice from death by influenza virus infection. *J. Exp. Med.* **197,** 1779–1785.

Hasenkrug, K. J., and Chesebro, B. (1997). Immunity to retroviral infection: The Friend virus model. *Proc. Natl. Acad. Sci. USA* **94,** 7811–7816.

Hasenkrug, K. J., Brooks, D. M., and Chesebro, B. (1995). Passive immunotherapy for retroviral disease: Influence of major histocompatibility complex type and T-cell responsiveness. *Proc. Natl. Acad. Sci. USA* **92,** 10492–10495.

Hayashi, S., Takashima, Y., and Otsuka, H. (2005). Pseudorabies virus propagated in rabbit kidney-derived RK13 cells is neutralized by natural IgM antibodies in normal swine serum which specifically lyse host cells. *J. Vet. Med. Sci.* **67,** 229–234.

Homann, D., Tishon, A., Berger, D. P., Weigle, W. O., von Herrath, M. G., and Oldstone, M. B. (1998). Evidence for an underlying CD4 helper and CD8 T-cell defect in B-cell-deficient mice: Failure to clear persistent virus infection after adoptive immunotherapy with virus-specific memory cells from muMT/muMT mice. *J. Virol.* **72,** 9208–9216.

Janeway, C. A., Travers, P., Walport, M., and Shlomchik, M. J. (2001). "Immunobiology: The Immune System in Health and Disease." Garland Publishing, New York.

Johnson, A. M., McDonald, P. J., and Neoh, S. H. (1983). Monoclonal antibodies to *Toxoplasma* cell membrane surface antigens protect mice from toxoplasmosis. *J. Protozool.* **30,** 351–356.

Johnson, C. M., Cooper, A. M., Frank, A. A., Bonorino, C. B., Wysoki, L. J., and Orme, I. M. (1997). *Mycobacterium tuberculosis* aerogenic rechallenge infections in B cell-deficient mice. *Tuber. Lung Dis.* **78,** 257–261.

Johnson, L. L., and Sayles, P. C. (2002). Deficient humoral responses underlie susceptibility to *Toxoplasma gondii* in CD4-deficient mice. *Infect. Immun.* **70,** 185–191.

Johnston, R. B., Jr., Lehmeyer, J. E., and Guthrie, L. A. (1976). Generation of superoxide anion and chemiluminescence by human monocytes during phagocytosis and on contact with surface-bound immunoglobulin G. *J. Exp. Med.* **143,** 1551–1556.

Kang, H., Remington, J. S., and Suzuki, Y. (2000). Decreased resistance of B cell-deficient mice to infection with *Toxoplasma gondii* despite unimpaired expression of IFN-gamma, TNF-alpha, and inducible nitric oxide synthase. *J. Immunol.* **164,** 2629–2634.

Kaylor, P. S., Crawford, T. B., McElwain, T. F., and Palmer, G. H. (1991). Passive transfer of antibody to *Ehrlichia risticii* protects mice from ehrlichiosis. *Infect. Immun.* **59,** 2058–2062.

Klenerman, P. (2004). Commentary: T cells get by with a little help from their friends. *Eur. J. Immunol.* **34,** 313–316.

Kozel, T. R., MacGill, R. S., Percival, A., and Zhou, Q. (2004). Biological activities of naturally occurring antibodies reactive with *Candida albicans* mannan. *Infect. Immun.* **72,** 209–218.

Kruetzmann, S., Rosado, M. M., Weber, H., Germing, U., Tournilhac, O., Peter, H. H., Berner, R., Peters, A., Boehm, T., Plebani, A., Quinti, I., and Carsetti, R. (2003). Human immunoglobulin M memory B cells controlling *Streptococcus pneumoniae* infections are generated in the spleen. *J. Exp. Med.* **197,** 939–945.

Lacroix-Desmazes, S., Bayry, J., Kaveri, S. V., Hayon-Sonsino, D., Thorenoor, N., Charpentier, J., Luyt, C. E., Mira, J. P., Nagaraja, V., Kazatchkine, M. D., Dhainaut, J. F., and Mallet, V. O. (2005). High levels of catalytic antibodies correlate with favorable outcome in sepsis. *Proc. Natl. Acad. Sci. USA* **102,** 4109–4113.

Lee, E., and Rikihisa, Y. (1997). Anti-*Ehrlichia chaffeensis* antibody complexed with *E. chaffeensis* induces potent proinflammatory cytokine mRNA expresssion in human monocytes through sustained reduction of IkB-alpha and activation of NF-kappaB. *Infect. Immun.* 2890–2897.

Lendvai, N., Qu, X., Hsueh, W., and Casadevall, A. (2000). Mechanism for the isotype dependence of antibody-mediated toxicity in *Cryptococcus neoformans* infected mice. *J. Immunol.* **164,** 4367–4374.

Li, J. S., and Winslow, G. M. (2003). Survival, replication, and antibody susceptibility of *Ehrlichia chaffeensis* outside of host cells. *Infect. Immun.* **71,** 4229–4237.

Li, J. S., Yager, E., Reilly, M., Freeman, C., Reddy, G. R., Reilly, A. A., Chu, F. K., and Winslow, G. M. (2001). Outer membrane protein-specific monoclonal antibodies protect SCID mice from fatal infection by the obligate intracellular bacterial pathogen *Ehrlichia chaffeensis*. *J. Immunol.* **166,** 1855–1862.

Li, J. S., Chu, F., Reilly, A., and Winslow, G. M. (2002). Antibodies highly effective in SCID mice during infection by the intracellular bacterium *Ehrlichia chaffeensis* are of picomolar affinity and exhibit preferential epitope and isotype utilization. *J. Immunol.* **169,** 1419–1425.

Li, L., Dial, S. M., Schmelz, M., Rennels, M. A., and Ampel, N. M. (2005). Cellular immune suppressor activity resides in lymphocyte cell clusters adjacent to granulomata in human coccidioidomycosis. *Infect. Immun.* **73,** 3923–3928.

Lieberman, M. M., Frank, W. J., and Brady, A. V. (1988). Protective mechanism of the immune response to a ribosomal vaccine from *Pseudomonas aeruginosa*. II. *In vitro* bactericidal and opsonophagocytic studies with specific antiserum. *J. Surg. Res.* **44,** 251–258.

Little, S. F., Ivins, B. E., Fellows, P. F., and Friedlander, A. M. (1997). Passive protection by polyclonal antibodies against *Bacillus anthracis* infection in guinea pigs. *Infect. Immun.* **65,** 5171–5175.

Lowell, G. H., MacDermott, R. P., Summeers, P. L., Reeder, A. A., Bertovich, M. J., and Formal, S. B. (1980). Antibody-dependent cell-mediated antibacterial activity: K lymphocytes, monocytes, and granulocytes are effective against shigella. *J. Immunol.* **125,** 2778–2784.

Mack, D. G., and McLeod, R. (1992). Human *Toxoplasma gondii*-specific secretory immunoglobulin A reduces *T. gondii* infection of enterocytes *in vitro*. *J. Clin. Invest.* **90,** 2585–2592.

Mackaness, G. B. (1971). Resistance to intracellular infection. *J. Infect. Dis.* **123,** 439–445.

Mackaness, G. B. (1977). Cellular immunity and the parasite. *Adv. Exp. Med. Biol.* **93,** 65–73.

Maitta, R., Datta, K., Chang, Q., Luo, R., Subramanian, K., Witover, B., and Pirofski, L. (2004). Protective and non-protective human IgM monoclonal antibodies to *Cryptococcus neoformans* glucuronoxylomannan manifest different specificity and gene usage. *Infect. Immun.* **22,** 4062–4068.

Malik, Z. A., Denning, G. M., and Kusner, D. J. (2000). Inhibition of Ca(2+) signaling by *Mycobacterium tuberculosis* is associated with reduced phagosome-lysosome fusion and increased survival within human macrophages. *J. Exp. Med.* **191,** 287–302.

Marsh, C. B., Pope, H. A., and Wewers, M. D. (1994). Fc-gamma receptor cross-linking downregulates Il-1 receptor antagonist and induces IL-1beta in mononuclear phagocytes stimulated with endotoxin or *Staphylococcus aureus*. *J. Immunol.* **152,** 4604–4611.

Marsh, C. B., Gadek, J. E., Kindt, G. C., Moore, S. A., and Wewers, M. D. (1995). Monocyte Fc-gamma receptor cross-linking induces IL-8 production. *J. Immunol.* **155,** 3161–3167.

Marsh, C. B., Wewers, M. D., Tan, L. C., and Rovin, B. H. (1997). Fc-gamma receptor cross-linking induces peripheral blood mononuclear cell monocyte chemoattractant protein-1 expression. *J. Immunol.* **158,** 1078–1084.

Marsh, C. B., Lowe, M. P., Rovin, B. H., Parker, J. M., Liao, Z., Knoell, D. L., and Wewers, M. D. (1998). Lymphocytes produce IL-1β in response to Fcγ receptor cross-linking: Effects on parenchymal IL-8 release. *J. Immunol.* **160,** 3942–3948.

Martinez, L. R., and Casadevall, A. (2005). Specific antibody can prevent fungal biofilm formation and this effect correlates with protective efficacy. *Infect. Immun.* **73,** 6350–6362.

Martinez, L. R., Moussai, D., and Casadevall, A. (2004). Antibody to *Cryptococcus neoformans* glucuronoxylomannan inhibits the release of capsular antigen. *Infect. Immun.* **72,** 3674–3679.

Matsuzaki, G., Vordermeier, H. M., Hashimoto, A., Nomoto, K., and Ivanyi, J. (1999). The role of B cells in the establishment of T cell response in mice infected with an intracellular bacteria, *Listeria monocytogenes*. *Cell. Immunol.* **194,** 178–185.

Matter, M., Mumprecht, S., Pinschewer, D. D., Pavelic, V., Yagita, H., Krautwald, S., Borst, J., and Ochsenbein, A. F. (2005). Virus-induced polyclonal B cell activation improves protective CTL memory via retained CD27 expression on memory CTL. *Eur. J. Immunol.* **35,** 3229–3239.

Matthews, R. C., Rigg, G., Hodgetts, S., Carter, T., Chapman, C., Gregory, C., Illidge, C., and Burnie, J. (2003). Preclinical assessment of the efficacy of mycograb, a human recombinant antibody against fungal HSP90. *Antimicrob. Agents Chemother.* **47,** 2208–2216.

Maury, E., Blanchard, H. S., Chauvin, P., Guglielminotti, J., Alzieu, M., Guidet, B., and Offenstadt, G. (2003). Circulating endotoxin and antiendotoxin antibodies during severe sepsis and septic shock. *J. Crit. Care* **18,** 115–120.

Medina, E., Goldmann, O., Toppel, A. W., and Chhatwal, G. S. (2003). Survival of *Streptococcus pyogenes* within host phagocytic cells: A pathogenic mechanism for persistence and systemic invasion. *J. Infect. Dis.* **187,** 597–603.

Mehlhop, E., Whitby, K., Oliphant, T., Marri, A., Engle, M., and Diamond, M. S. (2005). Complement activation is required for induction of a protective antibody response against West Nile virus infection. *J. Virol.* **79,** 7466–7477.

Messer, R. J., Dittmer, U., Peterson, K. E., and Hasenkrug, K. J. (2004). Essential role for virus-neutralizing antibodies in sterilizing immunity against Friend retrovirus infection. *Proc. Natl. Acad. Sci. USA* **101,** 12260–12265.

Messick, J. B., and Rikihisa, Y. (1994). Inhibition of binding, entry, or intracellular proliferation of *Erhlichia risticii* in P388D1 cells by anti-*E. risticii* serum, immunoglobulin G, or Fab fragment. *Infect. Immun.* **62,** 3156–3161.

Miki, K., and Mackaness, G. B. (1964). The passive transfer of acquired resistance to *Listeria monocytogenes*. *J. Exp. Med.* **120,** 93–103.

Miles, S. A., Conrad, S. M., Alves, R. G., Jeronimo, S. M., and Mosser, D. M. (2005). A role for IgG immune complexes during infection with the intracellular pathogen *Leishmania*. *J. Exp. Med.* **201,** 747–754.

Mineo, J. R., Khan, I. A., and Kasper, L. H. (1994). *Toxoplasma gondii*: A monoclonal antibody that inhibits intracellular replication. *Exp. Parasitol.* **79,** 351–361.

Montagnoli, C., Bozza, S., Bacci, A., Gaziano, R., Mosci, P., Morschhauser, J., Pitzurra, L., Kopf, M., Cutler, J., and Romani, L. (2003). A role for antibodies in the generation of memory antifungal immunity. *Eur. J. Immunol.* **33,** 1193–1204.

Moragues, M. D., Omaetxebarria, M. J., Elguezabal, N., Sevilla, M. J., Conti, S., Polonelli, L., and Ponton, J. (2003). A monoclonal antibody directed against a *Candida albicans* cell wall mannoprotein exerts three anti-*C. albicans* activities. *Infect. Immun.* **71,** 5273–5279.

Mozaffarian, N., Berman, J. W., and Casadevall, A. (1995). Immune complexes increase nitric oxide production by interferon-gamma-stimulated murine macrophage-like J774.16 cells. *J. Leukoc. Biol.* **57,** 657–662.

Mukherjee, J., Scharff, M. D., and Casadevall, A. (1992). Protective murine monoclonal antibodies to *Cryptococcus neoformans*. *Infect. Immun.* **60,** 4534–4541.

Mukherjee, J., Nussbaum, G., Scharff, M. D., and Casadevall, A. (1995). Protective and nonprotective monoclonal antibodies to *Cryptococcus neoformans* originating from one B-cell. *J. Exp. Med.* **181,** 405–409.

Murray, E. S., Charbonnet, L. T., and MacDonald, A. B. (1973). Immunity to chlamydial infections of the eye. I. The role of circulatory and secretory antibodies in resistance to reinfection with guinea pig inclusion conjunctivitis. *J. Immunol.* **110,** 1518–1525.

Nathan, C. (2002). Immunology. Catalytic antibody bridges innate and adaptive immunity. *Science* **298,** 2143–2144.

Neilson, A. R., Burchardi, H., and Schneider, H. (2005). Cost-effectiveness of immunoglobulin M-enriched immunoglobulin (pentaglobin) in the treatment of severe sepsis and septic shock. *J. Crit. Care* **20,** 239–249.

Neuwirth, R., Singhal, P., Diamond, B., Hays, R. M., Lobmeyer, L., Clay, K., and Schlondorff, D. (1988). Evidence for immunoglobulin Fc receptor-mediated prostaglandin2 and platelet-activating factor formation by cultured rat mesangial cells. *J. Clin. Invest.* **82,** 936–944.

Nie, X., Basu, S., and Cerny, J. (1997). Immunization with immune complex alters the repertoire of antigen-reactive B cells in the germinal centers. *Eur. J. Immunol.* **27,** 3517–3525.

Nimmerjahn, F., and Ravetch, J. V. (2005). Divergent immunoglobulin g subclass activity through selective Fc receptor binding. *Science* **310,** 1510–1512.

Nimmerjahn, F., Bruhns, P., Horiuchi, K., and Ravetch, J. V. (2005). FcgammaRIV: A novel FcR with distinct IgG subclass specificity. *Immunity* **23,** 41–51.

Norrby-Teglund, A., Ihendyane, N., and Darenberg, J. (2003). Intravenous immunoglobulin adjunctive therapy in sepsis, with special emphasis on severe invasive group A streptococcal infections. *Scand. J. Infect. Dis.* **35,** 683–689.

Nosanchuk, J. D., Steenbergen, J. N., Shi, L., Deepe, G. S., Jr., and Casadevall, A. (2003). Antibodies to a cell surface histone-like protein protect against *Histoplasma capsulatum*. *J. Clin. Invest.* **112,** 1164–1175.

Oli, M. W., Rhodin, N., McArthur, W. P., and Brady, L. J. (2004). Redirecting the humoral immune response against *Streptococcus mutans* antigen P1 with monoclonal antibodies. *Infect. Immun.* **72,** 6951–6960.

Ornellas, E. P., Roantree, R. J., and Steward, J. P. (1970). The specificity and importance of humoral antibody in the protection of mice against intraperitoneal challenge with complement-sensitive and complement-resistant *Salmonella*. *J. Infect. Dis.* **121,** 113–123.

Oxman, M. N., Levin, M. J., Johnson, G. R., Schmader, K. E., Straus, S. E., Gelb, L. D., Arbeit, R. D., Simberkoff, M. S., Gershon, A. A., Davis, L. E., Weinberg, A., Boardman, A., *et al*. (2005). A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N. Engl. J. Med.* **352,** 2271–2284.

Parker, S. J., Sadlon, T. A., and Gordon, D. L. (1995). Enhancement of NK cell-mediated antibody-dependent lysis of recombinant gp120-coated CD4 cells by complement. *J. Infect. Dis.* **171,** 186–189.

Paul, S., Nishiyama, Y., Planque, S., and Taguchi, H. (2006). Theory of proteolytic antibody occurrence. *Immunol. Lett.* **103,** 8–16.

Pavia, C. S., Bittker, S. J., and Curnick, K. E. (1992). Passive immunization protects guinea pigs from lethal *Toxoplasma* infection. *FEMS Microbiol. Immunol.* **4,** 97–104.

Peeling, R., Maclean, I. W., and Brunham, R. C. (1984). *In vitro* neutralization of *Chlamydia trachomatis* with monoclonal antibody to an epitope on the major outer membrane protein. *Infect. Immun.* **46,** 484–488.

Peng, Y., Kowalewski, R., Kim, S., and Elkon, K. B. (2005). The role of IgM antibodies in the recognition and clearance of apoptotic cells. *Mol. Immunol.* **42,** 781–787.

Pethe, K., Alonso, S., Biet, F., Delogu, G., Brennan, M. J., and Menozzi, F. D. (2001). The heparin-binding haemagglutinin of *M. tuberculosis* is required for extrapulmonary dissemination. *Nature* **412,** 190–194.

Phalipon, A., Kaufmann, M., Michetti, P., Cavaillon, J., Huerre, M., Sansonetti, P., and Kraehenbuhl, J. (1995). Monoclonal immunoglobulin A antibody directed against serotype-specific epitope of *Shigella flexneri* lipopolysaccharide protects against murine experimental shigellosis. *J. Exp. Med.* **182,** 769–778.

Pleass, R. J., and Holder, A. A. (2005). Opinion: Antibody-based therapies for malaria. *Nat. Rev. Microbiol.* **3,** 893–899.

Polack, F. P., Auwaerter, P. G., Lee, S. H., Nousari, H. C., Valsamakis, A., Leiferman, K. M., Diwan, A., Adams, R. J., and Griffin, D. E. (1999). Production of atypical measles in rhesus macaques: Evidence for disease mediated by immune complex formation and eosinophils in the presence of fusion-inhibiting antibody. *Nat. Med.* **5,** 629–634.

Polonelli, L., De Bernardis, F., Conti, S., Boccanera, M., Magliani, W., Gerloni, M., Cantelli, C., and Cassone, A. (1996). Human natural yeast killer toxin-like candidacidal antibodies. *J. Immunol.* **156,** 1880–1885.

Pul, R., Nguyen, D., Schmitz, U., Marx, P., and Stangel, M. (2002). Comparison of intravenous immunoglobulin preparations on microglial function *in vitro*: More potent immunomodulatory capacity of an IgM/IgA-enriched preparation. *Clin. Neuropharmacol.* **25,** 254–259.

Radhakrishnan, S., Nguyen, L. T., Ciric, B., Ure, D. R., Zhou, B., Tamada, K., Dong, H., Tseng, S. Y., Shin, T., Pardoll, D. M., Chen, L., Kyle, L., *et al*. (2003). Naturally occurring human IgM antibody that binds B7-DC and potentiates T Cell stimulation by dendritic cells. *J. Immunol.* **170,** 1830–1838.

Rajan, B., Ramalingam, T., and Rajan, T. V. (2005). Critical role for IgM in host protection in experimental filarial infection. *J. Immunol.* **175,** 1827–1833.

Ramisse, F., Binder, P., Szatanik, M., and Alonso, J.-M. (1996). Passive and active immunotherapy for experimental pneumococcal pneumonia by polyvalent human immunoglobulin of F(ab') 2 fragments administered intranasally. *J. Infect. Dis.* **173,** 1123–1128.

Ramsey, K. H., Soderberg, L. S., and Rank, R. G. (1988). Resolution of chlamydial genital infection in B-cell-deficient mice and immunity to reinfection. *Infect. Immun.* **56,** 1320–1325.

Rank, R. G., and Barron, A. L. (1983). Humoral immune response in acquired immunity to chlamydial genital infection of female guinea pigs. *Infect. Immun.* **39,** 463–465.

Rank, R. G., and Batteiger, B. E. (1989). Protective role of serum antibody in immunity to chlamydial genital infection. *Infect. Immun.* **57,** 299–301.

Rank, R. G., White, H. J., and Barron, A. L. (1979). Humoral immunity in the resolution of genital infection in female guinea pigs infected with the agent of guinea pig inclusion conjunctivitis. *Infect. Immun.* **26,** 573–579.

Ravetch, J. V., and Bolland, S. (2001). IgG Fc receptors. *Annu. Rev. Immunol.* **19,** 275–290.

Ravetch, J. V., and Lanier, L. L. (2000). Immune inhibitory receptors. *Science* **290,** 84–89.

Reid, R. R., Prodeus, A. P., Khan, W., Hsu, T., Rosen, F. S., and Carroll, M. C. (1997). Endotoxin shock in antibody-deficient mice: Unraveling the role of natural antibody and complement in the clearance of lipopolysaccharide. *J. Immunol.* **159,** 970–975.

Reith, H. B., Rauchschwalbe, S. K., Mittelkotter, U., Engemann, R., Thiede, A., Arnold, A., and Lissner, R. (2004). IgM-enriched immunoglobulin (pentaglobin) positively influences the course of post-surgical intra-abdominal infections. *Eur. J. Med. Res.* **9,** 479–484.

Rhinehart-Jones, T. R., Fortier, A. H., and Elkins, K. L. (1994). Transfer of immunity against lethal murine *Francisella* infection by specific antibody depends of host gamma interferon and T cells. *Infect. Immun.* **62,** 3129–3137.

Rhodin, N. R., Van Tilburg, M. L., Oli, M. W., McArthur, W. P., and Brady, L. J. (2004). Further characterization of immunomodulation by a monoclonal antibody against *Streptococcus mutans* antigen P1. *Infect. Immun.* **72,** 13–21.

Rieben, R., Roos, A., Muizert, Y., Tinguely, C., Gerritsen, A. F., and Daha, M. R. (1999). Immunoglobulin M-enriched human intravenous immunoglobulin prevents complement activation *in vitro* and *in vivo* in a rat model of acute inflammation. *Blood* **93,** 942–951.

Rivera, J., and Casadevall, A. (2005). Mouse genetic background is a major determinant of isotype-related differences for antibody-mediated protective efficacy against *Cryptococcus neoformans*. *J. Immunol.* **174,** 8017–8026.

Rivera, J., Mukherjee, J., Weiss, L. M., and Casadevall, A. (2002). Antibody efficacy in murine pulmonary *Cryptococcus neoformans* infection: A role for nitric oxide. *J. Immunol.* **168,** 3419–3427.

Rivera, J., Zaragoza, O., and Casadevall, A. (2005). Antibody-mediated protection against *Cryptococcus neoformans* is dependent on B cells. *Infect. Immun.* **73,** 1141–1150.

Robbins, J. B., Schneerson, R., and Szu, S. C. (1995). Perspective: Hypothesis: Serum IgG antibody is sufficient to confer protection against infectious diseases by inactivating the inoculum. *J. Infect. Dis.* **171,** 1387–1398.

Robbins, J. D., and Robbins, J. B. (1984). Reexamination of the protective role of the capsular polysaccharide (Vi antigen) of *Salmonella typhi*. *J. Infect. Dis.* **150,** 436–449.

Rodriguez, A., Tjarnlund, A., Ivanji, J., Singh, M., Garcia, I., Williams, A., Marsh, P. D., Troye-Blomberg, M., and Fernandez, C. (2005). Role of IgA in the defense against respiratory infections IgA deficient mice exhibited increased susceptibility to intranasal infection with *Mycobacterium bovis* BCG. *Vaccine* **23,** 2565–2572.

Rolstad, B., and Berdal, B. P. (1981). Immune defenses against *Legionella pneumophila* in rats. *Infect. Immun.* **32,** 805–812.

Rosas, A. L., Nosanchuk, J. D., and Casadevall, A. (2001). Passive immunization with melanin-binding monoclonal antibodies prolongs survival in mice with lethal *Cryptococcus neoformans* infection. *Infect. Immun.* **69,** 3410–3412.

Sanford, J. E., Lupan, D. M., Schlagetter, A. M., and Kozel, T. R. (1990). Passive immunization against *Cryptococcus neoformans* with an isotype-switch family of monoclonal antibodies reactive with cryptococcal polysaccharide. *Infect. Immun.* **58,** 1919–1923.

Sangari, F. J., Goodman, J., Petrofsky, M., Kolonoski, P., and Bermudez, L. E. (2001). *Mycobacterium avium* invades the intestinal mucosa primarily by interacting with enterocytes. *Infect. Immun.* **69,** 1515–1520.

Savoia, D., Avanzini, C., Conti, S., Magliani, V., Frazzi, R., and Polonelli, L. (2002). *In vitro* leishmanicidal activity of a monoclonal antibody mimicking a yeast killer toxin. *J. Eukaryot. Microbiol.* **49,** 319–323.

Savoy, A. C., Lupan, D. M., Mananlo, P. B., Roberts, J. S., Schlageter, A. M., Weinhold, L. C., and Kozel, T. R. (1997). Acute lethal toxicity following passive immunization for treatment of murine cryptococcosis. *Infect. Immun.* **65,** 1800–1807.

Schwebach, J. R., Casadevall, A., Schneerson, R., Dai, Z., Wang, X., Robbins, J. B., and Glatman-Freedman, A. (2001). Expression of a *Mycobacterium tuberculosis* arabinomannan antigen *in vitro* and *in vivo*. *Infect. Immun.* **69,** 5671–5678.

Shapiro, S., Beenhouwer, D. O., Feldmesser, M., Taborda, C., Carroll, M. C., Casadevall, A., and Scharff, M. D. (2002). Immunoglobulin G monoclonal antibodies to *Cryptococcus neoformans* protect mice deficient in complement component C3. *Infect. Immun.* **70,** 2598–2604.

Shen, H., Whitmire, J. K., Fan, X., Shedlock, D. J., Kaech, S. M., and Ahmed, R. (2003). A specific role for B cells in the generation of CD8 T cell memory by recombinant *Listeria monocytogenes*. *J. Immunol.* **170,** 1443–1451.

Shi, Y., Yamazaki, T., Okubo, Y., Uehara, Y., Sugane, K., and Agematsu, K. (2005). Regulation of aged humoral immune defense against pneumococcal bacteria by IgM memory B cell. *J. Immunol.* **175,** 3262–3267.

Silverstein, A. M. (1979). History of immunology. Cellular versus humoral immunity: Determinants and consequences of an epic 19th century battle. *Cell Immunol.* **48,** 208–221.

Song, H., Nie, X., Basu, S., Singh, M., and Cerny, J. (1999). Regulation of VH gene repertoire and somatic mutation in germinal centre B cells by passively administered antibody. *Immunology* **98,** 258–266.

Spenney, J. G., Lamb, R. N., and Cobbs, G. G. (1971). Recurrent tetanus. *South. Med. J.* **64,** 859–862.

Subramanian, K., Segal, R., Lyles, R., Rodriguez-Barradas, M. C., and Pirofski, L. (2002). HAART is associated with a qualitative change in the antibody response to HIV-infected individuals to pneumococcal capsular polysaccharide vaccination. *J. Infect. Dis.* **12,** 1168–1176.

Sullivan, N. J. (2001). Antibody-mediated enhancement of viral disease. *Curr. Top. Microbiol. Immunol.* **260,** 145–169.

Taborda, C. P., and Casadevall, A. (2001). Immunoglobulin M efficacy against *Cryptococcus neoformans*: Mechanism, dose dependence and prozone-like effects in passive protection experiments. *J. Immunol.* **66,** 2100–2107.

Taborda, C. P., Rivera, J., Zaragoza, O., and Casadevall, A. (2003). More is not necessarily better: 'Prozone-like' effects in passive immunization with immunoglobulin G. *J. Immunol.* **140,** 3621–3630.

Takeshita, S., Tsujimoto, H., and Nakatani, K. (2005). Intravenous immunoglobulin preparations promote apoptosis in lipopolysaccharide-stimulated neutrophils via an oxygen-dependent pathway *in vitro*. *APMIS* **113,** 269–277.

Tebele, N., McGuire, T. C., and Palmer, G. H. (1991). Induction of protective immunity by using Anaplasma marginale initial body membranes. *Infect. Immun.* **59,** 3199–3204.

Teitelbaum, R., Glatman-Freedman, A., Chen, B., Robbins, J. B., Unanue, E. R., Casadevall, A., and Bloom, B. R. (1998). A monoclonal antibody recognizing a surface antigen of *Mycobacterium tuberculosis* enhances host survival. *Proc. Natl. Acad. Sci. USA* **95,** 15688–15693.

Tewari, R. P., Sharma, D., Solotorovsky, M., Lafemina, R., and Balint, J. (1977). Adoptive transfer of immunity from mice immunized with ribosomes or live yeast cells of *Histoplasma capsulatum*. *Infect. Immun.* **15,** 789–795.

Toropainen, M., Saarinen, L., Wedege, E., Bolstad, K., Michaelsen, T. E., Aase, A., and Kayhty, H. (2005). Protection by natural human immunoglobulin M antibody to meningococcal serogroup B capsular polysaccharide in the infant rat protection assay is independent of complement-mediated bacterial lysis. *Infect. Immun.* **73,** 4694–4703.

Torosantucci, A., Bromuro, C., Chiani, P., De Bernardis, F., Berti, F., Galli, C., Norelli, F., Bellucci, C., Polonelli, L., Costantino, P., Rappuoli, R., and Cassone, A. (2005). A novel glyco-conjugate vaccine against fungal pathogens. *J. Exp. Med.* **202,** 597–606.

Tripp, C. S., Beckerman, K. P., and Unanue, E. R. (1995). Immune complexes inhibit antimicrobial responses through interleukin-10 production. *J. Clin. Invest.* **95,** 1628–1694.

Van Regenmortel, M. H. V. (1998). From absolute to exquisite specificity. Reflections on the fuzzy nature of species, specificity and antigenic sites. *J. Immunol. Meth.* **216,** 37–48.

van Sorge, N. M., van der Pol, W. L., and van de Winkel, J. G. (2003). FcgammaR polymorphisms: Implications for function, disease susceptibility and immunotherapy. *Tissue Antigens* **61,** 189–202.

Vasovic, L. V., Dyall, R., Clynes, R. A., Ravetch, J. V., and Nikolic-Zugic, J. (1997). Synergy between an antibody and CD8+ cells in eliminating an established tumor. *Eur. J. Immunol.* **27,** 374–382.

Vecchiarelli, A., and Casadevall, A. (1998). Antibody-mediated effects against *Cryptococcus neoformans*: Evidence for interdependency and collaboration between humoral and cellular immunity. *Res. Immunol.* **149,** 321–333.

Vecchiarelli, A., Retini, C., Casadevall, A., Monari, C., Pietrella, D., and Kozel, T. R. (1998a). Involvement of 1C3a and C5a in Interleukin-8 secretion by human polymorphonuclear cells in response to capsular polysaccharide material of *Cryptococcus neoformans*. *Infect. Immun.* **66,** 4324–4330.

Vecchiarelli, A., Retini, C., Monari, C., and Casadevall, A. (1998b). Specific antibody to *Cryptococcus neoformans* alters human leukocyte cytokine synthesis and promotes Tcell proliferation. *Infect. Immun.* **66,** 1244–1247.

Vecchiarelli, A., Monari, C., Retini, C., Pietrella, D., Palazzetti, B., Pitzurra, L., and Casadevall, A. (1998c). *Cryptococcus neoformans* differently regulates B7–1 (CD80) and B7–2 (CD86) expression on human monocytes. *Eur. J. Immunol.* **28,** 114–121.

Vordermeier, H. M., Venkataprasad, N., Harris, D. P., and Ivanyi, J. (1996). Increase of tuberculosis infection in the organs of B cell-deficient mice. *Clin. Exp. Immunol.* **106,** 312–316.

Walpen, A. J., Laumonier, T., Aebi, C., Mohacsi, P. J., and Rieben, R. (2004). Immunoglobulin M-enriched intravenous immunoglobulin inhibits classical pathway complement activation, but not bactericidal activity of human serum. *Xenotransplantation* **11,** 141–148.

Watson, D. C., Robbins, J. B., and Szu, S. C. (1992). Protection of mice against *Salmonella typhimurium* with an O-specific polysaccharide-protein conjugate vaccine. *Infect. Immun.* **60,** 4679–4686.

Wentworth, P., Jr., McDunn, J. E., Wentworth, A. D., Takeuchi, C., Nieva, J., Jones, T., Bautista, C., Ruedi, J. M., Gutierrez, A., Janda, K. D., Babior, B. M., Eschenmoser, B. M., *et al.* (2002).

Evidence for antibody-catalyzed ozone formation in bacterial killing and inflammation. *Science* **298,** 2195–2199.

Werwitzke, S., Trick, D., Kamino, K., Matthias, T., Kniesch, K., Schlegelberger, B., Schmidt, R. E., and Witte, T. (2005). Inhibition of lupus disease by anti-double-stranded DNA antibodies of the IgM isotype in the (NZB × NZW)F1 mouse. *Arthritis Rheum.* **52,** 3629–3638.

Williams, A., Reljic, R., Naylor, I., Clark, S. O., Falero-Diaz, G., Singh, M., Challacombe, S., Marsh, P. D., and Ivanyi, J. (2004). Passive protection with immunoglobulin A antibodies against tuberculous early infection of the lungs. *Immunology* **111,** 328–333.

Williams, D. M., Grubbs, B., and Schachter, J. (1987). Primary murine *Chlamydia trachomatis* pneumonia in B-cell-deficient mice. *Infect. Immun.* **55,** 2387–2390.

Winslow, G. M., Yager, E., Shilo, K., Volk, E., Reilly, A., and Chu, F. K. (2000). Antibody-mediated elimination of the obligate intracellular bacterial pathogen *Erhlichia chaffeensis* during active infection. *Infect. Immun.* **68,** 2187–2195.

Wright, K. E., and Buchmeier, M. J. (1991). Antiviral antibodies attenuate T-cell-mediated immunopathology following acute lymphocytic choriomeningitis virus infection. *J. Virol.* **65,** 3001–3006.

Yuan, R., Casadevall, A., Spira, G., and Scharff, M. D. (1995). Isotype switching from IgG3 to IgG1 converts a non-protective murine antibody to *C. neoformans* into a protective antibody. *J. Immunol.* **154,** 1810–1816.

Yuan, R., Casadevall, A., Oh, J., and Scharff, M. D. (1997). T cells cooperate with passive antibody to modify *Cryptococcus neoformans* infection in mice. *Proc. Natl. Acad. Sci. USA* **94,** 2483–2488.

Yuan, R., Spira, G., Oh, J., Paizi, M., Casadevall, A., and Scharff, M. D. (1998). Isotype switching increases antibody protective efficacy to *Cryptococcus neoformans* infection in mice. *Infect. Immun.* **66,** 1057–1062.

Zhang, Y. X., Stewart, S., Joseph, T., Taylor, H. R., and Caldwell, H. D. (1987). Protective monoclonal antibodies recognize epitopes located on the major outer membrane protein of *Chlamydia trachomatis*. *J. Immunol.* **138,** 575–581.