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Immunocompetent Cells in Resistance to Bacterial Infections

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INTRODUCTION

The purpose of this review is to summarize the current status of research and ideas concerning the cells involved in resistance to bacterial infections. Recent concepts regarding cells involved in both antibody production and in cell-mediated immunity will be discussed, as well as the roles both these reactions may play in host resistance to bacterial infections. The final sections of the review discuss various mechanisms by which macrophages, thymus-derived cells, and bone marrow-derived cells may participate in these reactions. An effort has been made to reference recent review articles which, hopefully, will allow the reader to locate in-depth discussions of topics not covered in depth here.

Nonspecific Resistance to Infection

The first line of defense by mammalian hosts against monocellular parasites generally consists of phagocytosis of the offending organism

by polymorphonuclear leukocytes and mononuclear macrophages. Macrophages phagocytose foreign particles and compartmentalize them in phagosomes. Ideally, foreign organisms are then degraded by lysosomal enzymes that enter the phagosome after fusion between lysosomes and phagosomes. However, many facultative intracellular organisms are not degraded once they are encased in phagosomes and, in fact, they may multiply and divide, thus killing the macrophage (82, 357). To increase the efficiency of its nonspecific defense mechanism, the host has devised ways to activate its macrophage population. Such activated macrophages may then destroy organisms that otherwise might kill the cell and possibly even the host. Properties of these activated macrophages have been well reviewed elsewhere (33, 89, 210, 211, 244, 247, 272, 287, 313, 316).

Under ideal normal conditions, wandering macrophages encounter the foreign organism, phagocytose it, and destroy it. There are a number of means by which each of these stages can be accelerated, resulting in increases in nonspecific defense mechanisms. The first stage, interaction between phagocyte and foreign particle, can be accelerated by chemotactic factors. A variety of materials has been isolated that increase the flow of phagocytes toward a foreign particle. Chemotaxis and chemotactic factors have been well reviewed elsewhere (31, 178, 340, 342) and will be discussed briefly later.

The second event in degradation of foreign bodies by macrophages is phagocytosis itself. Phagocytosis, or opsonization, of bacteria can be enhanced by nonspecific serum components called opsonins. Immunologically specific opsonizing antibodies will be discussed later. Evidence is available suggesting that some of the nonspecific opsonins are, or are dependent upon, components of complement that may be activated either by the conventional pathway or by the alternate pathway (222, 241, 307). Other evidence demonstrates that serum immunoglobulins (Ig's) may also act as nonspecific opsonins, since phagocytosis of latex particles, bentonite, and colloidal carbon has been shown to be markedly enhanced by serum Ig's (270, 332). Although these nonspecific opsonins have been demonstrated to play an important role in phagocytosis of bacteria, particularly in phagocytosis of rough, gram-negative organisms (222), they are thought not to be nearly as efficient as immunologically specific opsonizing antibodies (223, 239).

One way to enhance nonspecific phagocytosis is by coating the organism with opsonins, as described above. Another method for enhancing phagocytosis is through direct stimulation of the phagocytic cells, resulting in increased phagocytosis and destruction of the organism. This is the result of the process called macrophage activation. A major consequence of macrophage activation is the third event in the phagocytic process, degradation of the phagocytosed material. Since properties of activated macrophages have been well reviewed elsewhere, they will not be discussed further here.

Specific Resistance to Infection

Under ideal conditions for the host, when the first line of defense cannot cope with an invader, the second line of defense is recruited. This involves specific immune responses to antigenic components of the invading organism. There are two kinds of immune responses, humoral antibody production and cell-mediated immunity. Both are important mechanisms for resisting bacterial infections.

Humoral antibodies are particularly effective in combating infections by bacteria that replicate outside of cells and are thus free in body tissues and fluids, and in neutralizing bacterial toxins. Cell-mediated immunity has been reported to be the major merchanism for destroying bacteria that replicate intracellularly and thus are protected from serum antibodies. Mechanisms involved in these types of resistance will be the major part of this review.

CELLS INVOLVED IN HUMORAL ANTIBODY PRODUCTION

To understand the cells involved in resistance to bacterial infections, one must first try to understand the cells involved in normal immune responses, including both humoral antibody production and cell-mediated immunity. This section is a discussion of current concepts concerning events involved in humoral antibody production, and a rather general model incorporating many current ideas is presented. Most events discussed below are not yet clarified and constitute areas of extremely active research. To facilitate discussion, events involved in humoral antibody formation are assigned an arbitrary order as follows. (i) Antigen is trapped and/or processed by macrophages; (ii) antigen triggers specific T cells; (iii) B cells are triggered and; (iv) B cells make antibodies.

The first event, particularly in the case of bacteria, which contain a very large number of antigenic determinants, may be trapping and/or processing of the antigen by macrophages. Experiments have shown that antigen bound to macrophage surfaces or internalized by macrophages is immunogenic and may be more immunogenic than antigen that has not been

processed by macrophages (124, 232, 325, 326). Degradation and presentation of antigen by macrophages might be a more important event when dealing with large, particulate antigens than in developing immune responses to soluble protein antigens. Considerable evidence (325) suggests that large particulate materials are more antigenic because they are readily phagocytosed, whereas small monomeric proteins that may not be taken up by macrophages are less immunogenic and, in fact, are often tolerogenic. It has been suggested that tolerance is induced to those antigens that are not filtered through macrophages but that reach lymphocytes directly (95). Macrophage processing and presentation of antigen have been reviewed recently (281, 325).

It is not clear whether all antigens must undergo processing and presentation by macrophages. In vitro evidence concerning the murine response to erythrocyte antigens has shown that the adherent cell population (rich in macrophages), which is normally required for in vitro responses (238), can be replaced by reducing agents and antioxidants such as 2-mercaptoethanol and vitamin E (59, 69, 109). However, macrophage function apparently cannot be replaced by 2-mercaptoethanol during in vitro responses to soluble antigens (109). This would suggest that large particulate antigens may not need to undergo macrophage processing to induce immune responses. It should be remembered, however, that these in vitro findings may not reflect the more physiological in vivo events.

The second event in humoral antibody formation occurs, again, with most, but not necessarily with all, antigens. Those antigens that are called "thymus-dependent antigens" cannot normally trigger bone marrow-derived cells (B cells) to synthesize antibodies in the absence of thymus-derived cells (T cells). Thymus-independent antigens, on the other hand, can apparently stimulate B cells when T cells are severely depleted or absent. T independence is particularly demonstrable for IgM antibody formation and is less so for IgG antibody formation (231, 320). T-independent antigens are generally polymeric structures of small molecules with repeating antigenic units and are often of bacterial origin. They include pneumococcal polysaccharide (162), lipopolysaccharide (LPS) of gram-negative bacteria (11), polymerized flagellin (20), polyvinylpyrrolidone (11), levan (229), MS2 coliphage (26), and various hapten-T independent carrier combinations such as trinitrophenyl-LPS and dinitrophenyl-Ficoll (163, 302).

Most evidence suggests that thymus-dependent antigens trigger immunologically specific T cells via antigen-specific surface receptors (76, 147, 176, 224, 230). The presence, but not the nature, of antigen-specific receptors on T cells is well established and is discussed in the section on T lymphocytes. Whether antigen stimulates T cells directly, or whether antigen must be presented bound to macrophages, is not yet clear. Nevertheless, suffice it to say that antigen interacts with T cells via a specific receptor. T cells then stimulate B cells, and most evidence suggests that a factor, or factors, secreted by T cells is responsible for B cell stimulation (94, 103, 132, 137, 290, 308, 347). The exact nature of the factor(s) is currently under active investigation. Some investigators suggest that it is immunologically specific (114, 321), whereas others believe that the T cell factor is nonspecific (17, 50, 103, 290). Recent evidence in the mouse indicates that T cell factors might be products coded for by the immunoregulatory Ir gene complex (177).

Another area of extremely active investigations concerns the question of whether synthesis and release of T cell factors requires interaction of T cells with macrophages or some other adherent cell. In vitro studies demonstrating immune responses when adherent cell function is replaced by a reducing agent or a macrophage supernatant (59, 69, 156) suggest that T cell-macrophage interactions may not be required for B cell stimulation. However, other more direct experiments suggest that interactions between T cells and macrophages are required for T cell activation (109, 114, 115, 279a, 282, 296, 339).

The third event in humoral antibody formation is the actual stimulation of B cells to form antibody and may, in fact, consist of two events rather than a single event. A huge volume of theoretical and experimental literature has been published in the last few years discussing models and mechanisms of B cell activation. The models can be divided into one-signal models and two (or more)-signal models. One-signal models propose that B cell activation results from a single signal that performs all necessary functions, whereas the two-signal models suggest that two signals, one delivered by or mimicking antigen and one delivered by or mimicking T cell function, are required. These models are discussed briefly below. Data that support or conflict with them will not be discussed here, but may be found in many of the review articles that are referenced.

One-signal models include: (i) The one-signal model of Coutinho and Möller (84, 86, 87) postulates that a B cell is activated by a single nonspecific signal delivered to the B cell through

surface molecules that are neither the Ig receptors nor the Fc receptors on B cells. Antigen, which does bind to the Ig receptors, functions only as a focusing mechanism for presentation of this nonspecific B cell-activating signal.

(ii) The one-signal model of Mitchell (230) suggests that correct antigen triggering of B cells is sufficient for B cell activation. The T cell functions, either directly or indirectly, to regulate antigen presentation to B cells, one result of which is B cell activation. A variation of this theory is the one-signal model of Hoffmann (155) which postulates that cross-linking of receptors is all that is needed for triggering of B cells but that T cell factors can prevent B cell receptors from being cross-linked.

Two-signal models include: (i) The original and modified two-signal model of Bretscher and Cohn (47–49) suggests that two specific signals must be delivered to the B cell in order for antibody formation to occur. Signal 1 is deliverd by antigen to the specific Ig receptor on the B cell; signal 2 is generated as a consequence of associative antibody (which is most likely located on, or secreted by, T cells) binding to an antigen molecule. This complex, or a mediator released as a consequence of complex formation, then provides the B cell with signal 2.

(ii) Other two-signal models suggest that the first signal a B cell receives is delivered by antigen and that the second signal is delivered by a nonspecific T cell factor. A recent expansion of these ideas is that antigen delivers the mitogenic signal to the B cell and that the T cell factor subsequently delivers the signal for B cells to differentiate into antibody-secreting cells (101, 352). Another group, however, believes that B cell division is the second signal (183). But in light of earlier observations (103a), this interpretation is probably incorrect.

(iii) Another variation of the two-signal model of Bretscher and Cohn suggests that cell-bound complement component C3 provides the second signal to B cell receptors for C3 (99, 148).

(iv) Further modifications of the two-signal theories propose that presentation of the second signal is mediated by macrophages (51, 109, 114, 115, 296). The Feldmann model for macrophage involvement suggests that T cells, activated by carrier determinants, release Ig receptors (IgT) that are cytophilic for macrophages. The macrophage then binds the carrier portion of the antigen by these newly acquired Ig determinants and thus presents the hapten portion of the antigen to the B cell which, consequently, is stimulated (109, 114, 115). This presentation need not involve cell-to-cell contact (109).

A three-signal model for B cell activation has recently been proposed (291). According to this model, the first signal a B cell receives is delivered by a hapten or T-dependent antigen and prepares it for subsequent events. The second signal stimulates B cell division and can be delivered by many T-dependent antigens. The third signal, which leads to active synthesis of antibodies, is nonspecific and provides T cell help. Thymus-independent antigens, according to this model, can deliver all three signals.

Regardless of the number of signals involved, it seems clear that a single T cell, which is the limiting cell in some, if not all, normal immune responses (58), can stimulate one or more B cells (63, 331). Thus, this single unit of immune response can contain several B cells, which can make antibodies of one or more specificities (57, 63). This evidence then suggests that once a T cell has been stimulated by antigen to secrete its nonspecific factor, this factor can activate any B cell that is in close proximity to the T cell and that also has received antigenic stimulation.

The fourth and final event in the humoral immune response is the synthesis and release of antibodies. Very little is known concerning biochemical events occurring inside the B cell which lead to antibody synthesis. Recent data suggest that activation to cell division and/or antibody formation may result from an increase in the intracellular ratios of cyclic guanosine 5′-monophosphate to cyclic adenosine 5′-monophosphate (348, 349).

It is clear that many of the above models are not entirely incompatible with each other, and many may well overlap. Taken together, the above models allow one to synthesize a common model which is, at the very least, an oversimplification but is, hopefully, a safe generalization. This model, depicted in Fig. 1, visualizes the physiological events in humoral antibody formation as follows: (i) Antigen, either processed by macrophages or not, stimulates T cells via a specific antigen receptor. (ii) The stimulated T cell secretes a factor or factors, probably nonspecific, that can trigger B cells. (iii) Any B cell that receives, either together or separately, both its specific antigenic signal via the Ig receptor and a nonspecific T cell signal, is activated. (iv) Activation of B cells via surface receptors leads to intracellular changes, possibly involving cyclic nucleotide metabolism, which result in synthesis and secretion of antibody.

CELLS INVOLVED IN CELL-MEDIATED IMMUNITY

Cell-mediated immune responses have not been shown to involve humoral antibodies, but rather are mediated directly by immunocompe-

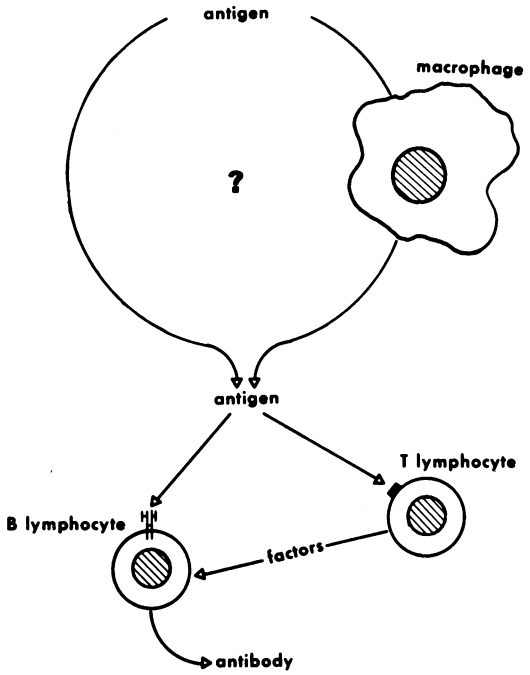

FIG. 1. *This simplified model for humoral immune responses suggests that the antigen, either processed and/or presented by macrophages or not, stimulates specific T cells. The stimulated T cell then releases a factor which, in conjunction with antigen, triggers B cells. The B cell, triggered by both antigen and by the T cell product, makes and releases antibody.*

tent cells. Immune responses in which cell-mediated immunity probably plays a major role include tumor immunity, delayed-type hypersensitivities, graft rejection, resistance to intracellular organisms, and many autoimmunities. Although these responses originally were considered due only to direct cell interactions, we now know that humoral factors may also be involved. The events occurring during cell-mediated immune reactions can be outlined as follows: (i) Antigen, either processed by macrophages or not, stimulates T cells via specific receptors. (ii) The stimulated T cell either *(a)* interacts directly with the antigen or, *(b)* secretes lymphokines that affect other cells that probably are not immunocompetent. (iii) The nonimmunocompetent cell actively attacks and neutralizes the antigen.

The first event, antigen processing by macrophages and/or polymorphonuclear leukocytes, has not been well studied for cell-mediated immunity. No compelling evidence is available to indicate that antigen processing by macrophages is necessary for triggering of T lymphocytes. However, adherent cells, presumably macrophages, apparently are required for in vitro induction of cytotoxic lymphocytes that function in cell-mediated cytotoxicity (203, 336). Again, these cells may be needed for proper culture conditions rather than for physiological induction of cytotoxic lymphocytes in vivo. Antigen triggering of T cells for cell-mediated immunity is quite likely no different from mechanisms involved in antigen triggering of T cells for antibody production, and will not be discussed further here.

After T cells are stimulated, they either attack the antigen directly or they secrete lymphokines (100), which activate other cells, which in turn nonspecifically attack the antigen. The most extensive studies on direct T cell killing have utilized in vitro experimental models of cell-mediated cytotoxicity against murine alloantigens. These reactions are antigen specific, require cell-cell contact (40, 66, 185, 265), and have not yet been shown to involve any humoral factors (40, 66, 265). Antibody inhibits rather than enhances direct cytotoxicity reactions (52, 235). The immunocompetent cells involved in cell-mediated cytotoxicity seem to be T lymphocytes (39, 66, 67, 202). Some evidence suggests that macrophages may amplify the cytotoxic capabilities of these T cells (66, 111). Experiments on graft-versus-host reactions in vivo suggest that more than one type of T cell may be involved in cell-mediated cytotoxicities (64, 65). The mechanisms by which T cells kill target cells in direct T cell-mediated cytotoxicity is not well understood. Direct contact between killer and target cell membranes, via undefined receptors, apparently leads to membrane changes that cause cell lysis. Characteristics of this killing recently have been reviewed (40, 66, 265).

The second mechanism by which T cells bring about cell-mediated immune reactions is through secretion of lymphokines which in turn activate nonlymphoid cells to enhance destruction of the antigen. In the past, lymphokines have been broadly defined as factors secreted by T lymphocytes. As discussed below, it appears as if B lymphocytes can also secrete lymphokines and as if stimuli other than the specific antigen can induce lymphokine production. Lymphokines generally act on non-immunocompetent cell populations, inciting them to increased levels of normal activity. Lymphokines, listed in Table 2, are discussed in more detail later. In many cases, in the absence of lymphokines the nonspecific cell is overwhelmed by the invading cell or organism, whereas, in the presence of immunologically induced lymphokines, enhanced activity by the infecting cell will overwhelm the invader.

Figure 2 illustrates this simplified model of

cell-mediated immune responses. Activities of T cells, B cells, and macrophages will be discussed below.

HUMORAL ANTIBODIES IN RESISTANCE TO BACTERIAL INFECTION

B cells stimulated by bacterial antigens, whether through T-dependent or T-independent pathways, produce antibodies that function in a variety of different ways to diminish the pathogenic effects of the invading organisms. These antibodies, classified by their function, by the antigens that induce them, and by their antibacterial effects, are outlined in Table 1 and discussed below. It is important to emphasize that these antibodies are not necessarily structurally different from each other and, in fact, that many of them may be identical. The mechanism by which these molecules function in resisting bacterial infection is probably dependent on the nature of the antigen with which they combine rather than on the structure of the antibody itself. For instance, in theory, a single Ig molecule can induce agglutination if it combines with cell wall components of a whole bacterium, but can induce lysis if complement is present, and can promote opsonization if it blocks an antiphagocytic surface component. Functional kinds of antibacterial antibodies are discussed below.

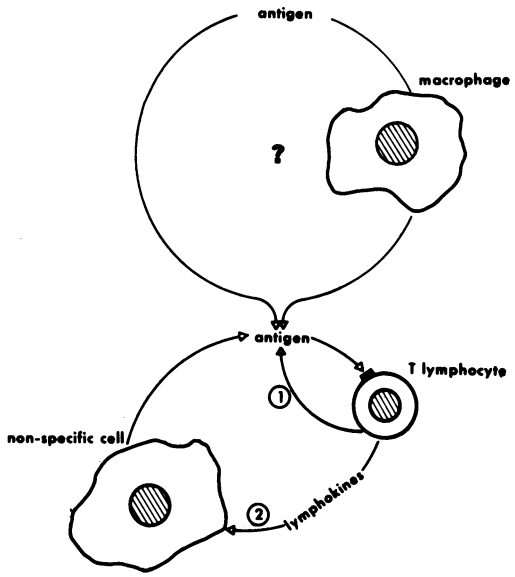

FIG. 2. *In cell-mediated immune responses, antigen, either processed and presented by macrophages or not, stimulates specific T cells. The stimulated T cell then either (i) attacks the antigen directly or (ii) releases lymphokines, which stimulate nonspecific cells to enhanced phagocytosis and destruction of the antigen.*

Agglutinins

Agglutinins are antibodies that clump, or agglutinate, large particulate antigens. When directed against antigens on intact bacteria, agglutinins combine with surface components of the organism. Antibacterial effects of agglutinins are thought to occur because the antibodies clump the bacteria, thus decreasing their motility and rendering the organisms more susceptible to phagocytosis. Clinical trials with *Bordetella pertussis* vaccines, for instance, have shown a correlation between agglutinating antibodies to the vaccine and the protective ability of the vaccine (328). In pneumococcal pneumonia, agglutination of pneumococci in the alveoli by specific antibody tends to immobilize the bacteria and slow the spread of the disease (363).

Opsonins

Opsonins are loosely defined as molecules that promote phagocytosis. There are several kinds of opsonins. Nonspecific opsonins such as components of complement have been discussed earlier (222, 241). Opsonins also may be anti-

TABLE 1. *Antibacterial activities of antibodies*

Antibodies	Function	Bacterial antigens	References
Agglutinins	Clump and immobilize organisms, facilitating phagocytosis	Surface antigens	328, 363
Opsonins	Enhance phagocytosis	Surface antigens	32, 90, 105, 222, 241, 260, 323, 332, 363, 364
Precipitins	Neutralize toxins and surface antigens	Surface antigens and exotoxins	46, 90
Bacteriolysins	Lyse bacteria in the presence of complement	Surface antigens	35, 90

TABLE 2. *Lymphokines and their relationship to resistance to bacterial infection*

Lymphokine	Target cell	Activity	References
MIF and macrophage-activating factor	Macrophage	Inhibits macrophage migration and activates macrophages	40, 121, 127, 186, 244, 245, 272, 305, 313
Macrophage chemotactic factor	Macrophage	Attracts macrophages	343, 358
Leukocyte chemotactic factor	Polymorphonuclear leukocyte	Attracts polymorphonuclear leukocytes	342, 343
Blastogenic factor	Lymphocyte	Stimulates lymphocyte blastogenesis	40, 100, 127
Transfer factor	Lymphocyte (?)	Transfers delayed skin reactions	41, 53, 180, 181, 182, 192, 193, 194, 356

bodies that are cytophilic for macrophages and bind to these cells as well as to the bacteria that are about to be phagocytosed (32, 260, 323). Finally, opsonins may be antibodies that are directed against antigens on the surface of bacteria and that enhance phagocytosis (105, 332).

Some of the most extensive studies on the roles of opsonins in resistance have been with *Diplococcus pneumoniae*, which causes pneumococcal pneumonia. This organism contains capsular polysaccharides that inhibit phagocytosis by the phagocytes of the host (90, 363, 364). Antibodies to these pneumococcal polysaccharides result in enhanced phagocytosis (90, 363). Although these antibodies promote phagocytosis and, therefore, function as opsonins, they are probably in fact precipitins, which promote phagocytosis because they neutralize the inhibiting effects of the pneumococcal polysaccharide. Similarly, although both the capsular hyaluronic acid and the M protein of streptococci are antiphagocytic, only M protein is antigenic (90, 119). Antibodies to M protein afford the only good protection against acute hemolytic streptococcal disease (90). Another class of antibodies that has been loosely defined as opsonins are those antibodies that promote killing of intracellular bacteria that might otherwise survive. For instance, a strain of virulent *Salmonella* that normally proliferates within macrophages was killed by the macrophage following pretreatment of the bacteria with a specific, non-bactericidal rabbit antiserum (167).

Precipitins

Precipitins are antibodies, usually of the IgG class, which combine with soluble antigens to form precipitates. The antibacterial activity of precipitating antibodies is generally accomplished through neutralization of bacterial components with antihost activities. Precipitins are particularly important for neutralizing bacterial exotoxins. Classic examples are the neutralization of the neurotoxic and hemolytic effects of tetanus toxins secreted by infecting *Clostridium tetani*, and neutralization of the necrotizing toxins produced by *Corynebacterium diphtheriae* (90). As discussed above, precipitins also neutralize antiphagocytic surface polysaccharides of encapsulated bacteria, thereby functioning to promote phagocytosis. Precipitins might also be the antibodies which, when combined with antigen, are chemotactic for polymorphonuclear leukocytes (46).

Bacteriolysins

Antibodies that combine with cell wall antigens of gram-negative bacteria can cause lysis of the bacteria in the presence of complement (35, 90). These antibodies may also effect lysis by removing a protective lypopolysaccharide (LPS) layer from the bacterial cell wall, thus allowing lysozyme to penetrate to the deeper mucopolysaccharide layer. Bacteriolysins may be important in defense against bacterial invasion of tissues and against bacteremia.

Other Antibacterial Antibodies

Another possible role for antibodies in resisting infection has been suggested by recent studies on resistance to infection by intracellular bacteria and other intracellular parasites. Resistance to these organisms has been thought to be largely by cell-mediated immune mechanisms. Some bacteria phagocytosed by normal macrophages can replicate intracellularly, whereas these same bacteria phagocytosed by activated macrophages do not divide, but are inactivated or killed. Survival of organisms in

the macrophage could be due to failure of lysosomes to fuse with the phagosome containing the organism (18, 145, 171, 172). Some recent data suggest that the organism itself is responsible for nonfusion and that humoral antibodies to components of the organism will allow fusion to occur (19, 125, 172). Other experiments suggest that stimulation of fusion by antibodies is not sufficient to result in bacterial destruction (19). Additional reports propose that antibody either has no effect or that it prevents, rather than enhances, bacterial degradation (79, 120, 129).

With this understanding of the important roles antibodies can play in resisting bacterial infections and in neutralizing many of the toxic properties and products of bacteria, it is not surprising that certain immunodeficiency diseases are acompanied by tremendous increases in bacterial infections. In fact, Bruton agammaglobulinemia, a deficiency in antibody production which results from a tremendous decrease in the number of B lymphocytes, is characterized by increased bacterial infection (135). Agammaglobulinemias often are successfully treated by frequent passive injections of antibodies.

CELL-MEDIATED IMMUNE MECHANISMS IN RESISTANCE TO BACTERIAL INFECTIONS

Cell-mediated immunity is most likely the major immune defense mechanism against infection by facultative intracellular parasites (81, 82, 89, 211, 247, 316, 357). Resistance to infection with the following bacteria is thought to be largely by cell-mediated immune mechanisms: *Mycobacterium* species (81, 82, 89, 168, 211), *Listeria monocytogenes* (207, 211, 357), *Brucella abortus* (68, 82, 168, 357), and *Salmonella* species (82, 168, 357). These organisms are capable of surviving phagocytosis and probably also of multiplying within phagocytic cells (207, 315, 357). When cell-mediated immunity develops in response to infection by these bacteria, it is manifested by immune T cells releasing lymphokines that activate macrophages (44, 186, 209, 244, 262, 292, 305). These activated macrophages then more efficiently phagocytose the bacteria and, in addition, either kill them or otherwise inactivate them (38, 44, 134, 186, 206, 209, 262, 305). Activation of macrophages is a complex series of structural and biochemical events that result in enhanced enzymatic activities. Characteristics of activated macrophages have been well reviewed (33, 89, 210, 211, 244, 247, 272, 287, 313, 316).

Recent experiments studying infection with *M. tuberculosis* and *Toxoplasma gondii* suggest that intracellular parasites are not killed by the macrophages that phagocytose them because normal fusion of lysosomes and phagosomes does not occur (18, 145, 171, 172). Activation of macrophages may promote fusion of phagosomes and lysosomes, resulting in damage to the parasite, thus killing or immobilizing it.

This immunologically mediated destruction of bacteria occurs because T cells, when stimulated by specific bacterial antigens, secrete lymphokines that appear to enhance the ability of macrophages and other nonspecifically acting cells to resist bacterial infection. When normal macrophages are incubated with lymphokines, they develop increased resistance to both mycobacteria and *Listeria* organisms (134, 186, 262). In many cases, it is not clear whether lymphokines are secreted by T cells, B cells, or both cell types. Moreover, it must be remembered that many of these mediators have been studied only in vitro and that they may have neither an in vivo correlate nor an in vivo function. Mediators that have been reported to be involved in resistance to bacterial infections and their possible modes of action are outlined in Table 2 and are discussed briefly below. References in this section are admittedly very scanty, and generally only publications relevant to bacterial infection are cited.

Migration Inhibition Factor

Since recent evidence suggests that migration inhibition factor (MIF) and macrophage-activating factor are identical molecules (245), they will be discussed together. Incubation of macrophages in an MIF-rich (and macrophage-activating factor-rich) medium leads to a number of morphological, metabolic, and functional changes. These changes include an increase in both the rate and extent of phagocytosis of dead mycobacteria and *Listeria* (186, 262, 305) and enhancement of bacteriostatic activity (121). MIF is one of the few mediators studied in vivo and apparently is required for in vivo delayed skin reactions (127). MIF is apparently not the same as blastogenic factor, lymphotoxin, mitogenic factor or, skin-reactive factor, since antibody to MIF does not inhibit function of the other four molecules (126, 127).

Macrophage Chemotactic Factor

Although macrophage chemotactic factor has not been implicated directly in resistance to bacterial infection, it might well enhance resistance by attracting macrophages to the site of infection so that they can phagocytose and

clear the invading organisms. If enough macrophages are drawn to a site of infection, even if they cannot phagocytose and destroy the infecting organisms, the tremendous influx of cells may result in granuloma formation that can wall off the organisms, thus creating a physical barrier that protects the host from invasion (357). Macrophage chemotactic factor seems to be different from MIF (343).

Chemotactic Factor for Leukocytes

Again, no direct evidence is available to prove that chemotactic factors for leukocytes are important in resistance to bacterial infection, but a number of bacterial factors have been shown to be chemotactic for leukocytes (342). Production of chemotactic factors for leukocytes is followed by increased influx of polymorphonuclear leukocytes, which are phagocytic and which can engulf and immobilize bacteria.

Blastogenic Factor for Lymphocytes

Blastogenic factor for lymphocytes, which is secreted by antigen-activated lymphocytes (40, 100), stimulates other lymphocytes to divide. This could enhance resistance by increasing the population of functional T and B lymphocytes and/or by stimulating lymphocytes to produce other lymphokines that could directly affect host resistance.

Transfer Factor

Transfer factor is a very widely studied, poorly understood molecule that was reported 20 years ago to be able to transfer delayed-type hypersensitivity reactions from skin-test-positive humans to skin-test-negative recipients (192). It is extracted from leukocytes (180, 192, 193), possibly from B lymphocytes (181), and is a low-molecular-weight molecule that generally is resistant to ribonuclease, deoxyribonuclease, and trypsin digestion (193). Transfer factor has been reported to transfer cell-mediated immunity or delayed-type hypersensitivity reactions to the following bacterial antigens: tuberculin, lepromin, tularin, diphtheria toxoid, and streptococcal antigens (194). In addition, clinical improvement has been reported in patients receiving specific transfer factor for treatment of leprosy (53) and tuberculosis (355). Transfer factor can be chemotactic for leukocytes (181). The mechanism of action of transfer factor is unknown, and there are not yet any good animal models. Current evidence suggests that transfer factor may have nonspecific properties as well as immunologically specific effects (41, 180). Some reports suggest that transfer factor can stimulate unresponsive lymphoid cells to produce lymphokines such as MIF in response to antigenic stimulation (180, 182). These molecules, in turn, may increase resistance to infection by intracellular bacteria.

Other mediators, such as interferon, skin-reactive factor, and lymphotoxin, have not been implicated in resistance to infection by intracellular bacteria.

BACTERIAL ADJUVANTS

One cannot discuss specific immune reactions to bacterial infections without considering the nonspecific enhancement of these reactions. Materials that nonspecifically enhance immune reactions are called immunological adjuvants. Many immunological adjuvants are themselves derived from bacteria and are subjects of considerable recent experimentation. This section will review bacterial adjuvants and mechanisms by which they may enhance immune responses. Table 3 lists many of these bacterial components and their suggested modes of action. Bacterial components as immunosuppressive agents recently have been well reviewed in this journal (297). Bacterial adjuvants have been studied using either whole bacteria or isolated fractions, and are discussed below.

Lipopolysaccharide

The most widely characterized isolated bacterial adjuvant is the lipopolysaccharide (LPS) endotoxin of gram-negative bacteria. This material, henceforth referred to simply as LPS, is responsible for a number of diverse biological activities, including pyrogenicity, lymphocytosis, and the Swartzman reaction, which have been reviewed previously (249, 322). In addition to these physiological effects, LPS is an excellent immunological adjuvant (15, 122, 169, 243, 249, 255). LPS is a large molecule containing a core polysaccharide that is covalently linked to the glucosamine lipid, lipid A (256). The polysaccharide portion of the molecule is the O antigen (256) and is generally thought not to be responsible for, or required for, the adjuvant effect. The mitogenic and adjuvant activities of LPS have been shown to reside primarily, if not exclusively, in lipid A and not in the polysaccharide moiety (12, 72, 264, 280). However, other studies report that non-lipid A portions of LPS may also be adjuvants and mitogens. For instance, a polysaccharide-rich fraction, and not the lipid components, has been reported to stimulate mouse bone marrow colony-forming cells and to protect mice against lethal irradiation (253). An acid polysaccharide, which may

TABLE 3. *Bacterial adjuvants*

Adjuvant	Actions	References
LPS	B cell mitogen	5–7, 12, 14–16, 72, 85, 122, 130, 163, 164, 169, 170, 174, 179, 215, 219, 236, 243, 246, 247, 249, 253, 255, 256, 263, 264, 280, 285, 289, 294, 306, 322, 341, 350, 362, 365
Bordetella pertussis	Unknown	7, 96, 117, 242, 267, 327
Mycobacteria and components (PPD, BCG)	B cell mitogen (?)	3, 15, 54, 71, 82, 123, 153, 219, 225, 233, 234, 246, 251, 271, 303, 314, 357, 366, 367
Corynebacterium parvum	Unknown	4, 159, 250, 298, 299, 353, 359
Nocardia	B cell mitogen (?)	75
Listeria monocytogenes and components	B cell mitogen	61, 62, 78, 165, 191, 266, 309, 310
Other bacterial components		73, 175, 185a, 246

be part of LPS and which was prepared from *Serratia piscatorum*, is a B cell mitogen and an adjuvant (215). Yet another cell wall lipoprotein that is not LPS, but which is biologically active as a mitogen and a polyclonal activator, has been prepared from *Escherichia coli* (219). Some investigators find a direct relationship between the abilities of LPS to be a mitogen and an adjuvant (306, 350), whereas other reports suggest that mitogenesis and the ability to stimulate antibody formation can be separated (164).

The mechanism by which LPS enhances immune responses has been under investigation for many years. An early proposal was that LPS was an adjuvant because it damaged cells, which then released nucleic acids, which in turn were responsible for the adjuvant effect (220, 255). Support for this idea was provided by observations demonstrating that high doses of endotoxin in vivo could injure murine splenocytes and thymocytes, and it was suggested that the mitosis seen during recovery from this damage might be part of the adjuvant effect (285, 341).

More recently, it has been clearly shown that in the mouse LPS is a mitogen which can act directly on B cells, causing them to divide (12, 14, 15, 130, 263, 280). Concomitant with B cell division is the release, and possibly synthesis, of antibody. Hence, LPS is also a polyclonal stimulant (15, 219). In vivo experiments suggest that LPS can stimulate B cells to respond to thymus-dependent antigens when T cells are depleted or absent; thus LPS can apparently replace the requirement for T cells (170, 236, 294). In vitro experiments have confirmed this by demonstrating that haptens coupled to LPS are immunogenic when T cells are depleted or absent, again suggesting that LPS can replace the requirement for T cells (85, 163).

Although it seems clear that LPS can act directly on B cells, it is not as clear whether macrophages and/or T cells are required for, or can augment, this direct B cell effect. Several experiments suggest that one or both of these cells may be involved. Macrophages can be activated by LPS (247, 362), and may be activated to be cytotoxic to other mouse cells (6), thus demonstrating an effect of LPS on macrophages. Peritoneal exudate cells, rich in macrophages, or the reducing agent, 2-mercaptoethanol, have also been reported necessary for LPS-induced mitogenesis of B cells (174). Another study shows that high numbers of activated macrophages inhibit, whereas low numbers of macrophages enhance lymphocyte proliferation (179). Evidence has also accumulated which indicates that T cells are required for LPS to act on B cells (7, 16, 174). However, none of these experiments demonstrates a direct effect of LPS on T cells.

Since LPS can induce a population of cells which apparently contains no mature T cells to develop cells with T cell markers (289), the possibility that LPS converts null cells to T cells which then stimulate B cells must also be considered. If this can occur, then available evidence demonstrating a direct effect of LPS on B cells may in actuality represent indirect stimulation of B cells via this T cell induction pathway.

LPS has generally been assumed only to enhance humoral immune responses, which is in keeping with its purported effect on B cells. However, several reports have suggested that LPS also may be able to enhance immune responses primarily due to cell-mediated immune mechanisms (5, 246, 365). It is quite likely in these cases that LPS stimulates a nonspecific effector cell rather than an immunocompetent T or B lymphocyte.

Bordetella pertussis

The gram-negative organism *B. pertussis* is also widely studied as an immunological adju-

vant (96, 117, 267). Although it contains LPS endotoxin, it is not clear whether this material is, or is not, responsible for the reported adjuvant effect. As with LPS, no concensus has yet been reached concerning the target cell for the adjuvant effect of *B. pertussis* (7, 242, 327).

Mycobacteria and Mycobacterial Components

A variety of non-gram-negative bacteria can also function as immunological adjuvants. The earliest demonstrations of adjuvant effects utilized various strains of mycobacteria in water-in-oil emulsions (123). This material, called complete Freund adjuvant, is still widely used for inducing cell-mediated immunity and for eliciting production of large amounts of antibody or of antibody to poorly immunogenic antigens. Incomplete Freund adjuvant, which is a water-in-oil emulsion lacking mycobacteria, also enhances immune responses (123). Under some conditions, incomplete Freund adjuvant can induce tolerance, but if mycobacteria or LPS are added to this emulsion, induction of immunity occurs (54). Likewise, the whole-cell mycobacteria in complete Freund adjuvant can be replaced by the wax D component of mycobacteria (271, 303, 356), by a water-soluble extract of mycobacteria or mycobacterial culture filtrates (3), by LPS (54, 303), by *Salmonella* organisms in some laboratories (303) but not in others, by nocardiae (123), and by purified bacterial peptidoglycans (246). Other extracts of mycobacteria are also under active investigation and have been shown to have a number of immunological activities (173, 228, 233).

BCG, an attenuated strain of *Mycobacterium bovis*, has been under considerable investigation recently because of its potential clinical use as an antitumor agent. Whole BCG organisms can enhance the humoral response to sheep erythrocyte antigens (225) and can be a mitogen for T cells if macrophages are present (234). Extracts of BCG also have been reported to enhance humoral antibody production and to induce or increase antitumor immunity (153, 366; L. A. Baker, T. Sharpton, P. Minden, and P. A. Campbell, Infect. Immun., in press).

Another biologically active extract of *M. tuberculosis* is the protein isolated from culture filtrates of *M. tuberculosis* known as purified protein derivative (PPD). Widely used for inducing cutaneous hypersensitivity reactions to *M. tuberculosis*, this material has recently been shown to be a B cell mitogen (314) and a polyclonal activator (219, 251), and to stimulate production of lymphokines by B cells (367). On the other hand, some laboratories believe that PPD is not a nonspecific mitogen but, rather, that it only induces division of presensitized cells (71).

Corynebacterium parvum and *Nocardia*

Another bacterium that is currently being characterized as an immunological adjuvant is the gram-positive rod, *Corynebacterium parvum*. This organism has been reported to enhance both humoral and cell-mediated immune responses. It stimulates antibody formation (159, 250, 346), facilitates induction of delayed hypersensitivity (250), increases antigen uptake and presentation by macrophages (359), and increases resistance to bacterial infection (4). Again, reports in the literature suggest that the target cells for these adjuvant effects of *C. parvum* may be macrophages (159, 299, 358, 359), T cells (298, 346), or B cells (159).

Extracts of *Nocardia* species have also been reported to be adjuvants and to be B cell mitogens (75).

Listeria monocytogenes

Materials derived from the gram-positive intracellular bacterium *L. monocytogenes* are good immunological adjuvants. A monocytosis-producing extract of *L. monocytogenes* enhances the immune response to non-*Listeria* antigens (131, 157, 310). Other studies demonstrate that heat-killed *Listeria* (165), fluids from *L. monocytogenes* cultures (191), and cell wall-rich fractions of *L. monocytogenes* (61, 62; C. Schuffler and P. A. Campbell, Immunology, in press) enhance immune responses.

It has now been demonstrated that *Listeria* culture filtrates and *Listeria* cell wall fractions are B cell mitogens (78, 266) and that *Listeria* cell wall fractions can stimulate B cells directly, an effect that may be independent of both T cells and macrophages (62; C. Schuffler and P. A. Campbell, Immunology, in press). In addition, *Listeria* components can induce MIF production by sensitized rabbit lymphocytes (309).

Other Bacterial Adjuvants

A variety of miscellaneous bacterial components with adjuvant activity have also been reported (73, 175, 185a, 246).

ROLE OF MACROPHAGES

Macrophages are phagocytic cells located throughout the body in tissues and in serous fluids. Their major function is to clear the host of foreign particles. Macrophages are derived from circulating blood monocytes that originate

in hematopoietic tissues, primarily in the bone marrow (196, 247, 330). For simplicity, monocytes can be assumed to be macrophages that are not activated and are not actively phagocytic. Activation to vigorous phagocytic activity, therefore, drives inactive monocytes and macrophages to activated macrophages. Once activated, macrophages are capable of enhanced phagocytosis and killing of foreign cells and bacteria.

On their surfaces, macrophages and monocytes have receptors for a number of biologically active molecules, including Ig (32, 160, 161, 196, 201, 293) and the third component of complement, C3 (161, 195). The Fc receptors for Ig apparently mediate both attachment and phagocytosis of antibody-coated particles (34, 214), whereas the complement receptors seem to mediate attachment of Ig-coated particles, but not ingestion, unless the macrophages are activated (34, 214). "Zippering" versus "triggering" models for phagocytosis have been described recently (141a).

In this section, emphasis will be on how macrophages are stimulated to become effector cells and on how macrophages may stimulate function of other cells involved in resistance to infection. Four mechanisms by which macrophages can be stimulated to enhance resistance against bacterial infection will be considered: (i) stimulation by other cells or by factors secreted by other cells, (ii) stimulation by antibody, (iii) stimulation by bacteria and (iv) stimulation by artificial chemical means. Finally, ways in which macrophages may stimulate other cells involved in resistance, either by cell-cell interactions or by factor production, will be discussed.

Stimulation of Macrophages by Other Cells and Factors

The major mechanism for macrophage activation to enhance resistance against bacterial infection is direct stimulation by lymphokines produced by T cells responding to specific antigenic challenge. This conclusion is derived from several important observations. For instance, monolayers of normal mouse peritoneal exudate macrophages can be activated, sometimes to enhanced bactericidal activity, by the addition of sensitized lymph node or peritoneal lymphocytes plus specific antigen (197, 305). Supernatants containing mouse MIF, which can activate macrophages (237, 244, 245), can also stimulate normal peritoneal cells to enhanced bactericidal activity (121, 305). Normal macrophages incubated with supernatants from cultures of lymphoid cells stimulated in different ways exhibit enhanced resistance to *Mycobacterium tuberculosis* (262), *M. leprae murium* (134), and *L. monocytogenes* (186).

There is also evidence that in addition to activation by lymphokines from T cells, macrophages can be activated by direct interaction with other cell types. For example, normal macrophages incubated with lymphoid cells from mice immune to a lymphoma cell line became cytotoxic for the lymphoma cells (110).

Stimulation of Macrophages by Antibodies

As mentioned earlier, attachment of cytophilic antibody to macrophage surfaces by Fc receptors is thought to be responsible for opsonization. Hence, antibodies, which are factors secreted by B cells, can be considered to enhance resistance at the level of the macrophage.

Stimulation of Macrophages by Bacteria

Of considerable biological importance, materials which are, or are part of, invading bacteria have been reported to stimulate macrophages directly. For instance, LPS or its lipid A derivative can activate macrophages (6, 80). *C. parvum* organisms activate macrophages, a process that may require the presence of T cells (74). Culture filtrates from *L. monocytogenes* cultures also activate macrophages (266). BCG organisms, too, have been reported to bind to and activate macrophages to enhanced metabolic activities (33, 38, 89, 272).

Stimulation of Macrophages by Chemicals

In addition to the relatively physiological means of activating macrophages to heightened levels of resistance presented above, plant lectins and other nonspecific, nonbiological materials have been reported to stimulate macrophages. Vitamin E, or alpha-tocopherol, can enhance phagocytosis (149). Poly-L-glutamic acid (22) and synthetic polyanions (274) induce macrophage-mediated resistance to intracellular infection. Yet dextran sulfate, a good B cell adjuvant (78), has been reported to decrease macrophage-mediated resistance to infection when injected 24 h before challenge (142). Phytohemagglutinin (PHA) and concanavalin A (Con A), both T cell mitogens, activate macrophages (144). Some very interesting genetic studies indicate that glycerol trioleate can activate macrophages and, moreover, that mice can be separated genetically into "responders" or "nonresponders" to the macrophage-specific effects of this synthetic lipid emulsion (240). Physical stimulation of macrophages by low doses of irradiation activated macrophages, as evidenced by an increased number of lysosomal enzymes, but did not alter macrophage handling of a protein antigen (295).

Effects of Macrophages and Macrophage Products on Other Cells

Macrophages may themselves be actively required for function of other immunocompetent cells. In vitro immune responses by murine cells have been shown by many laboratories to require the presence of macrophages (146, 238, 279), macrophage products or factors (69, 156), or a variety of reducing agents that can replace macrophages (59, 69). A requirement for macrophages for cell cooperation during in vivo immune responses has also been reported (136).

Release of lymphokines by antigen-stimulated T cells during cell-mediated immune reactions also may require participation of macrophages as discussed below. Antigen-dependent blastogenesis by sensitized guinea pig and human lymphocytes is macrophage-dependent, and apparently requires cell-to-cell contact (8, 77, 151, 199, 281, 282, 288, 300, 339). It has been suggested that macrophages function in this system as a vehicle for antigen presentation (281, 355) and apparently must be histocompatible with the lymphocytes (282). Cluster formation between macrophages and immune lymphocytes requires the presence of antigen, with the antigenic specificity residing in the lymphocytes (355). Other studies demonstrate that antigen-independent binding can also occur between macrophages and both T and B lymphocytes (199, 304), and that this binding does not seem to involve either Ig or receptors for Ig (200). Based on these data, a model has been proposed (281) suggesting that antigen-independent binding of macrophages and lymphocytes precedes antigen-dependent and immunologically specific binding which occurs only if antigen is present and if the cells are histocompatible. These events are an obligatory prerequisite for lymphocyte activation.

In studies on another in vitro immune response, the mixed leukocyte reaction, macrophages, or a factor secreted by them, have been shown to be required for the reactions to occur (8, 23). Similarly, production of lymphokines by T cells responding to antigenic challenge, but not by B cells stimulated with mitogens, has been reported to require the presence of viable macrophages (338). It has also been suggested that macrophages are required for generation of T-helper-cell activity in vitro.

Macrophage Mediators

Several reports in the literature ascribe to macrophages the ability to produce a variety of mediators that can act on other cells or even directly on bacteria. Macrophage factors have already been described which replace the requirement for macrophages during in vitro immune responses to sheep erythrocytes (156), which are required for blastogenesis of lymphocytes (8), and which are necessary for mixed leukocyte reactions (23).

In addition, macrophages appear to be able to elaborate factors that are directly bactericidal. *Listeria* cells were sterilized by products of macrophages incubated with stimulated lymphocytes (27, 221). A soluble material released from mouse macrophages immune to *L. monocytogenes* has been described that exerts antilisterial activity in vitro (301). In addition, guinea pig alveolar macrophages cultured with PPD released a cytotoxic factor (150).

ROLE OF THYMUS-DERIVED CELLS (T CELLS)

Uncommitted lymphoid cells, which migrate from normal bone marrow to the thymus, can be "influenced" by the thymus to become thymus-derived (or T) cells (see reviews 176, 224). These T cells are immunologically competent and can function in both cell-mediated and humoral immune responses and, therefore, in resistance to bacterial infection.

During humoral immune responses, T cells provide helper function for B cells to produce antibodies to bacterial antigens. These antibodies have antibacterial activity, as described earlier. In contrast, certain classes of T cells can suppress formation of humoral antibodies to so-called T-independent bacterial antigens (24). Thus, it appears that although T helper cells are not required for induction of immune responses to pneumococcal polysaccharides (162), there exists a class of suppressor T cells that can inhibit the response to this antigen (24). It should be mentioned that a recent report fails to confirm this suppressor T cell activity (345). However, a rebuttal to this report has been offered (25). Accepting for the moment the existence of suppressor or regulator T cells for immune responses to pneumococcal polysaccharide, this so-called T-independent antigen would appear not to be T independent at all.

T cells are also required for induction of cell-mediated immune responses. Immunologically mediated resistance to bacteria that can grow in the cells that have phagocytosed them appears to depend on activation of these phagocytic cells by T cells or their products. A role for T cells in this type of resistance has been confirmed, since resistance to infection by *L. monocytogenes* can be transferred from immune mice to normal mice by spleen cells, but not if the spleen cells have been treated with anti-theta (anti-Thy-1) antiserum and complement

to remove T cells (36, 37, 190, 370). Other experiments show that adult-thymectomized, lethally irradiated, bone marrow-reconstituted rats and mice develop less resistance to infection by *L. monocytogenes*, *M. leprae*, or BCG (217, 252, 273), as well as decreased levels of antituberculous immunity (317).

T cells function in immunologically mediated resistance to infection by releasing lymphokines, which stimulate macrophages to increased bacteriostatic or bactericidal activity. The rest of this section will be concerned with how T cells are activated to synthesize and release mediators and the specificity of T cell function in resistance to infection.

Stimulation of T Lymphocytes by Antigens

T cells clearly have receptors for antigen and can be stimulated by specific antigens. Evidence for this is as follows. Autoradiographic studies indicate that approximately 1 per 10^5 T cells will bind a specific antigen (56). T cells can be specifically "suicided" by antigen heavily labeled with radioisotopes (28, 30, 83, 278). It has been suggested that T cells may not be able to bind free antigen; rather, antigen may have to be presented to T cells by other cells (28). Moreover, the receptor for antigen on T cells may not be synthesized by T cells but may be passively acquired (10, 269, 329, 333, 351, 368). It is the intent of this reviewer to avoid consideration of the nature of the T cell receptor for antigen, since this is an extremely controversial topic that is widely discussed in the literature. Nevertheless, suffice it to say that T cells can be stimulated by specific antigen, and that one consequence of specific antigenic stimulation of T cells is the release of lymphokines (44, 134, 186, 187, 262, 305). As discussed earlier, these lymphokines then presumably drive macrophages to enhanced antibacterial activity.

Stimulation of T Lymphocytes by Mitogens

T cells can be stimulated to divide by nonspecific mitogens as well as by specific antigens. Materials that have been reported to be T cell mitogens include phytohemagglutinin (PHA) (15, 70, 139, 166, 311, 312, 318), pokeweed mitogen (70, 140, 166, 312), Con A (15, 70, 311), and BCG (234). Mitogens that are generally considered specific for B cells may, under certain circumstances, also stimulate T cells (108, 139). Table 4 lists some known lymphocyte mitogens and whether they stimulate T or B cells. It is interesting that both cell types seem to bind mitogens such as PHA, Con A, and LPS equally, but that only one cell type will divide (15, 140, 311). The reason for this equal binding but selective division is not clear.

Since several recent experiments demonstrate that nonimmune cells in culture can release lymphokines (138, 257, 259, 324), possibly as a consequence of cell division (324), it is not surprising that mitogens, which also cause cell division, can apparently stimulate mediator release (45, 158, 259, 275). In contrast, however, a recent publication suggests that lymphokine activity induced by Con A stimulation of cells may actually be caused by residual Con A and that MIF activity induced by PHA stimulation of cells appears to be due to a simulated effect by medium depleted of nutrients rather than by the presence of MIF (319).

Specificity of Resistance to Bacterial Infections

The observation that animals immune to *M. tuberculosis* are also resistant to infection by a wide variety of supposedly unrelated organisms suggested that resistance to infection by intracellular bacteria was nonspecific (97, 107, 133, 353). However, the recent demonstration that many of these organisms share antigens (226,

TABLE 4. *B and T cell mitogens*

Mitogen	Target lymphocyte	Species	References
PHA	T	Mouse, man	15, 70, 139, 166, 311, 312, 318
	B	Man, guinea pig, mouse	70, 108, 139
Con A	T	Mouse, man	15, 70, 311
	B	Man, guinea pig	13, 15, 70, 108
LPS	B	Mouse, guinea pig	12, 14, 15, 72, 85, 130, 164, 219, 263, 280, 306, 350
	T	Rabbit, guinea pig, mouse	108, 139
Pokeweed mitogen	T, B	Mouse, man	70, 140, 166, 312
Listeria cell wall fraction	B	Mouse	78
BCG	T	Mouse	234
Dextran sulfate	B	Mouse	91
Nocardia	B	Rabbit, mouse	75
PPD	B	Mouse, guinea pig	251, 314, 367

227) would suggest that this resistance may be, at least in part, specific. As described earlier, current models of the cell-mediated immune mechanisms responsible for resistance to infection propose that stimulation of T cells is antigen specific (82, 93, 209, 237, 244, 247, 262), but that stimulation by T cells of effector macrophages is not antigen specific (186, 208, 211, 247). Activation of macrophages can also be achieved directly in the absence of T cells, leading to nonspecific resistance (167, 208, 211, 371). Conflicting reports claim that T cell factors which stimulate macrophages are specific, rather than nonspecific (9, 112).

Nevertheless, the majority of data are consistent with the idea that immunological resistance to cell-mediated infection involves stimulation of antigen-specific T cells to release nonspecific lymphokines. The latter, in turn, activate macrophages to enhanced phagocytosis and bacteriostasis of all bacteria.

ROLE OF BONE MARROW-DERIVED CELLS

It must be emphasized at the outset that the term "bone marrow-derived cells" by definition means all cells derived from the bone marrow and, therefore, includes all hematopoietic cells. Hence, monocytes and macrophages, polymorphonuclear leukocytes, and lymphocytes are all potential candidates for events involving bone marrow cells or bone marrow-derived cells. Throughout this section, the term "B cells" refers to bone marrow-derived lymphocytes, whereas "bone marrow-derived cells" includes all hematopoietic cells.

B cells in Humoral Antibody Production

Bone marrow-derived lymphocytes (B cells) originate in the bone marrow and migrate to peripheral lymphoid organs, where they differentiate into immunocompetent B cells. B cells make humoral antibody and have on their surfaces Ig molecules of the same specificity as the antibody they will synthesize (2, 102, 213, 360, 361). These surface Ig molecules, or Ig receptors, are generally of the IgM or IgD class (188, 284, 286, 344), although IgG molecules, apparently synthesized by the B cells which bear them, have been reported to be on B cell surfaces as well (141, 189, 344). B cells, in addition to having Ig receptors that they have synthesized, can also bind cytophilic antibody, generally of the IgG class, by their Fc receptors for Ig (29, 93, 344). Hence, antigen most likely can stimulate B cells directly by binding to autochthonous Ig. Whether Ig's bound to B cells by Fc receptors can also function as receptors for antigen is not yet clear.

B cells have several other cell surface receptors whose functions are not entirely understood. For instance, B cells have receptors for complement components (98, 128, 254) and can apparently bind C3b, C3d, and C4 (43, 283). An hypothesis has been presented suggesting a role for complement receptors in B cell activation (99, 116, 148, 254).

B cells, like T cells, can be activated by a variety of mitogens. As well as stimulating B cell blastogenesis and division, mitogens stimulate B cells to synthesize and release antibodies and are thus polyclonal stimulators (87, 140, 218). B cell mitogens (Table 4) include LPS mice and guinea pigs, but probably not in man (12, 14, 15, 87, 130, 140, 218, 263, 280); PPD in mice and guinea pigs (251, 314, 367); pokeweed mitogen in man and mouse (70, 140, 166, 312); *Listeria* cell wall fraction in the mouse but not in man (78); and polyanions such as dextran sulfate (91). Although PHA and Con A are generally considered only to be T cell mitogens, evidence has been provided demonstrating a stimulatory effect of these lectins on B cells (13, 15, 70, 108).

Bone Marrow-Derived Cells in Cell-Mediated Immunity

Until recently, bone marrow-derived cells were thought not to be involved in cell-mediated immunity at all. However, it now appears that they may participate in these reactions at several levels. We will discuss bone marrow-derived cells as nonspecific mediators of cell-mediated immune reactions, as producers of lymphokines, and as possible active participants in resistance to infection.

It is perfectly clear that monocytes and their differentiated progeny, macrophages, are required as nonspecific effector cells for most, if not all, cell-mediated immune responses. Polymorphonuclear leukocytes may also participate in many of these reactions. Labeling studies demonstrated that approximately 80 to 90% of the cells seen in delayed-type skin reaction sites are nonspecific mononuclear cells, probably macrophages (216). Lubaroff and Waksman showed that delayed-type skin reactions require the presence of bone marrow-derived cells as nonspecific effector cells (204, 205). Other studies demonstrated that both thymus and bone marrow-derived cells are required to reconstitute animals for cell-mediated immune responses (106, 152, 370), and that expression of delayed hypersensitivity requires both a specific and a nonspecific cell (369). In many spe-

cies, the predominant cells seen in delayed-type skin lesions are mononuclear cells, although polymorphonuclear cells are very prevalent in some reactions, for instance in murine skin reactions to polysaccharide antigens (88, 184). In vitro evidence reviewed earlier demonstrates that macrophages and polymorphonuclear leukocytes can be target cells for lymphokines produced by lymphocytes. It is obvious from these and other studies (1, 21, 113, 334) that macrophages, which are bone marrow derived, are required as a nonspecific component of many cell-mediated immune reactions.

It is possible that bone marrow-derived lymphocytes may participate in cell-mediated immune reactions by releasing lymphokines, which in turn stimulate macrophages. Recent evidence demonstrates that B cells can produce lymphokines. For instance, purified B lymphocytes from unsensitized guinea pigs can be stimulated by PPD and by LPS, both B cell mitogens, to release MIF and to mediate the macrophage disappearance reaction (367). These observations have been confirmed, using human B cell lines (118). In addition, sensitized human B lymphocytes release MIF in response to antigen stimulation (277). Many other reports also demonstrate production of lymphokines by human, guinea pig, and murine B cells (42, 154, 212, 261, 337, 362). Although, as one group cautions (42), it is always possible that a very small number of residual T cells may be required for, or be responsible for, lymphokine production by these purified B cell populations. Other data show that nonlymphoid cells as well as lymphoid cells can produce MIF and suggest that the stimulus for this lymphokine production is cell division (251, 258, 324). In contrast, however, it has been shown that prevention of lymphocyte division by bromodeoxyuridine and light does not inhibit MIF production (276), and B cells need not divide to produce MIF. But T cell MIF production does require cell division (277). Thus, it seems established that B cells as well as T cells can produce lymphokines which, in turn, might stimulate resistance to infection by intracellular parasites.

In vivo evidence also implicates B cells in resistance to intracellular infections. Experiments in vivo demonstrate that, contrary to expectation, mice severely depleted of T cells nevertheless have some capacities for developing this kind of resistance. We originally reported that lethally irradiated mice injected with normal, isologous bone marrow cells could resist challenge by *L. monocytogenes* (60). It did not matter whether or not these mice had been thymectomized prior to irradiation and cell transfer (P. A. Campbell, unpublished observations). Experiments in which resistance to *Salmonella* and *M. bovis* infections were examined in T-depleted mice also showed evidence of resistance in the absence of T cells (82). The demonstration of significant resistance to infection by these organisms in severely T-depleted mice has been confirmed (68, 143). Although data from earlier investigations likewise showed that adult-thymectomized and adult-thymectomized, irradiated, bone marrow-reconstituted mice and rats could develop some resistance to *Listeria* (37, 198, 217, 252, 372), authors of these reports either did not comment on these findings or interpreted these mice as being unable to develop resistance, since better resistance was generally seen when T cells were also present. Our data were unable to confirm this need for T cells since lethally irradiated mice injected with bone marrow cells developed good resistance, and mice injected with both bone marrow and thymus cells did not consistently develop better resistance than did mice injected with bone marrow cells alone (60). However, this resistance was presumably largely, if not entirely, nonspecific, since neither donors nor recipients were immunized. The most likely interpretation of these experiments is that injected bone marrow monocytes, stimulated by the irradiated environment, developed into activated macrophages that were able to resist challenge. But if this were the only event responsible for induction of resistance, then probably sufficient numbers of injected splenocytes and certainly injected normal peritoneal cells, should also be able to induce resistance by providing macrophages for activation. Since we (60; P. A. Campbell, unpublished observations) and others (143, 205) have not been able to induce resistance or reconstitute skin reactivity with either peritoneal cells, peritoneal exudate cells, or spleen cells, it seems that (i) macrophages were either already maximally activated, phagocytosing debris from irradiation, and could not handle the additional listeria load or (ii) a bone marrow-derived cell in addition to the monocyte or macrophage might be required for induction of resistance under these experimental conditions.

In other in vivo and in vitro examples of cell-mediated immune reactions, requirements for B cells also have been shown. For instance, recent studies on delayed-type hypersensitivity reactions have suggested the existence of a bone marrow-derived suppressor cell that may regulate a T cell in the expression of the skin reaction (248), and other laboratories report that a non-T cell, non-macrophage population is one of two synergizing cell populations re-

quired for generation of cytotoxic activity (337). Mixed leukocyte reactions do not occur between allogeneic thymus cells unless bone marrow-derived cells are present (104). And finally, as mentioned earlier, activation of macrophages by LPS, and perhaps all macrophage activation by nonspecific mediators, requires the presence of B cells (362).

SUMMARY

In summary, evidence suggests that macrophages, thymus-derived cells, and bone marrow-derived cells can function in resisting bacterial infections as follows.

Macrophages

(i) Macrophages, as a first line of defense, phagocytose bacteria. (ii) Macrophages may process and present antigen to T and/or B cells for induction of both humoral and cell-mediated immune responses to bacteria, and may be required for immune function of one or both of these cells. (iii) Macrophages, activated by lymphokines secreted by immunologically specific T cells stimulated with antigen, phagocytose and inhibit growth of intracellular bacteria.

T Lymphocytes

(i) When the bacterial antigen is T dependent, T lymphocytes interact with B cells so the B cells may make antibodies. (ii) T lymphocytes may suppress function of B lymphocytes during humoral immune responses to bacterial antigens. (iii) Specific T lymphocytes, when stimulated by specific antigen, secrete lymphokines which in turn act on macrophages and other nonspecific cells to enhance bacterial resistance during cell-mediated immune responses. Nonspecific stimulation of T cells may also cause lymphokine release.

B Cells

(i) B cells make agglutinating, precipitating, opsonizing, and lytic antibodies, all of which probably have antibacterial properties. (ii) B cells apparently can secrete lymphokines that may activate macrophages to enhance resistance to infections.

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