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Bacterial interference with immunospecific defences

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There are many descriptions of bacterial agents that can suppress different phases of specific immunity. Bacterial agents are frequently employed as tools to modulate the immune system in experimental models or clinical therapy. Little attention has been given to the implications of such immunoregulating properties for infectious processes or for the natural role of the microbial flora in the normal regulation of the immune system. There are very few studies attempting to investigate directly the possible role of bacterial immunosuppressant factors in acute infection. Several examples of natural and experimental chronic infections have been described in which progressive uncontrolled infection is associated with a depressed cell mediated immunity, but a causal relation is unproven. This depression is usually not antigenically specific and there is some evidence that it may be initiated and maintained by persistent cell-wall components of the microorganisms. The bacteria implicated in suppression are all facultative or obligate intracellular parasites that can multiply and survive in the monocyte/macrophage. Bacterial immunosuppressants may have a crucial role in the pathogenesis of progressive chronic inflammation that occurs after infection.

1. Introduction

A variety of products of microbial origin can modulate regulation of the immune system, as well as other physiological systems of the host (Schwab 1975, 1977). These exogenous immunoregulatory agents can be derived from many species, including members of the indigenous microflora and infectious microorganisms. It is in fact probable that a microbial flora is essential for efficient functioning of the immune system (Dubos *et al.* 1963). This paper is organized on the concept that bacteria products influence the immune response by modifying the host's mechanisms of immune regulation.

1. Summary of bacteria or bacterial products reported to suppress the specific immune response, and possible sites of action

Some current concepts of cell functions and interactions in the immune response, from stem cell differentiation to effector cell expression, are summarized in figure 1. The numbers indicate possible sites or pathways where bacterial products can influence regulation.

(a) *Site 1: suppression of immature B lymphocytes in bone marrow*

Neonatal and adult B lymphocytes differentiate and develop competence in the bone marrow and spleen (Owen 1972). The immature B cells in bone marrow (defined as non-Thy 1 bearing, non-adherent cells, stimulated by the dextran sulphate mitogen) can be suppressed by a product associated with the protoplast membranes of group A streptococci (Gaumer & Schwab 1972; Toffaletti & Schwab 1979; Schwab *et al.* 1981.

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(*b*) *Site* 2: *interference with lymphocyte circulation and trapping*

The lymphocytosis promoting factor produced by *Bordetella pertussis* (Morse & Barron 1970) can interfere with T lymphocyte circulation and trapping in antigen-stimulated lymph nodes by modifying the lymphocyte membrane.

(*c*) *The monocyte/macrophage* (*sites* 3, 4, 5, 6, 7)

The monocyte/macrophage is a key cell in regulation. The term 'processing' is used to convey the idea of some kind of appropriate degradation of antigen (site 3). It has been suggested that lipopolysaccharide (LPS, endotoxin) and Mycobacteria can interfere with 'processing (Whang & Neter 1967; Hirschberg 1978), but the evidence is indirect. There is more convincing

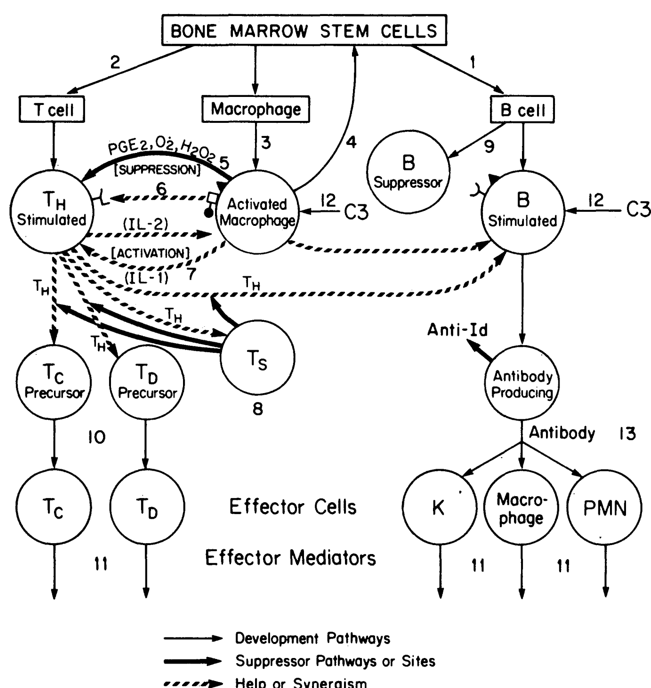

FIGURE 1. Cell interaction and regulation in the immune response. The numbers refer to possible sites, described in the text, at which bacteria might affect regulation. The K cell represents several cell types involved in antibody-dependent cell-mediated immunity. PMN cells are polymorphonuclear leucocytes. Other cells are defined as follows: T_H, T helper-inducer lymphocyte; T_D, delayed-type hypersensitivity cell; T_S, T suppressor lymphocyte; T_C, cytoxic T lymphocytes.

evidence that bacteria can influence proliferation and recruitment of monocytes/macrophages (site 4). Thus LPS, peptidoglycan or synthetic muramyl dipeptide (MDP) structures of the bacterial cell envelope can stimulate macrophages directly or through activation of the alternative complement pathway (a.c.p.) to secrete a variety of factors, including colony-stimulating factor (CSF) which will increase myeloid and lymphoid bone marrow stem cells (Moore *et al.* 1980; van den Engh & Bol 1975; Stabler *et al.* 1978; Wuest & Wachsmuth 1982). The significance of the resulting monocytosis is indicated by three examples in which adherent suppressor cell activity (probably macrophages) is associated with prolonged elevation of blood monocyte levels: human tuberculosis (Ellner 1978), rheumatoid arthritis (Seitz *et al.* 1982) and bacterial cell wall-induced arthritis in rats (Schwab 1982). Macrophages stimulated by

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bacterial products also secrete prostaglandin E_2 (PGE_2), which limits the activity of CSF (Pelus *et al.* 1979).

The macrophage, activated by numerous bacterial components, also regulates the T helper/inducer lymphocyte (T_H; murine Lyl^+, 23^-) by affecting at least three pathways. Site 5 indicates the secretion of PGE_2 or oxygen metabolites, or both, which can suppress the response of T_H cells to mitogens or antigens (Metzger *et al.* 1980; Hoffeld *et al.* 1981; Mattingly *et al.* 1979). Kato & Yamamoto (1982*a*) report that PGE_1 sereted by adherent cells stimulated with live Bacille Calmette Guerin (B.C.G.) will suppress delayed-type hypersensitivity cells (T_D). High doses of B.C.G. (10^7 viable units of Tice strains) can activate naturally occurring suppressor cells in the bone marrow and spleen of mice (Klimpel & Henney 1978; Bennett *et al.* 1978). The suppressor cells in the spleen are adherent to nylon wool, and suppression of T cell responses to mitogens is inhibited by 10^{-7} M indomethecin (Bennett *et al.* 1981). An increase in myeloid colony-forming units induced by B.C.G. (site 4) is parallel to the increase in suppressor cell activity in bone marrow and spleen, and they may be identical (Bennett & March 1980). *Propionibacterium acnes* (incorrectly called *Corynebacterium parvum*) (Scott 1972) and *Listeria monocytogenes* (Kongshavn *et al.* 1977) can also induce suppression of T cell responses through stimulation of an adherent suppressor cell.

Stobo (1977) has described the secretion of a suppressor factor by macrophages from patients with chronic fungal infections accompanied by depressed DTH skin tests to several antigens and low proliferative response to mitogens. The undefined suppressor factor did not inhibit responding T cells directly, but activated a T_S cell.

The prolonged suppression of T cell functions induced by chronic infection or high doses of killed B.C.G. or *P. acnes* may be ascribed to the accumulation of persistent structures of the microbial cell wall that the host cannot effectively degrade and eliminate. This is indicated by the observation that suppression of specific and non-specific stimulation of T cells can be induced in rats by injection of the purified peptidoglycan–polysaccharide complex (PG–APS) isolated from cell walls of group A streptococci (Hunter *et al.* 1980). Specific anergy to peptidoglycan lasts at least 90 days, and *in vitro* assays of T cell stimulation show that an adherent suppressor cell is involved (Regan *et al.* 1982). A non-specific suppression of T cell response to mitogens is also mediated by adherent cells, but this response returns to normal by about 30 days. Adherent suppressor cell activity is inhibited by catalase (10000 Sigma units), but not by 10^{-6} M indomethecin.

Site 6 is an even more speculative pathway of interference by bacterial products at the level of macrophage presentation of antigen to T cells. To stimulate a specific immune response, immunodeterminant structures of an antigen must be associated with an I*a* glycoprotein on the membrane of an antigen-presenting cell (Benacerraf 1981). I*a* is a product of class II genes (H2I in the mouse) of the major histocompatibility complex (m.h.c.). Yem & Parmely (1981) proposed that agents binding to I*a* on antigen-presenting cells could block the binding of a potential immunogen, and thereby interfere with stimulation of T_H cells by preventing antigen recognition. In a similar fashion, agents binding to class I m.h.c. products, or the β_2-microglobulin (Kronvall *et al.* 1978) on target cells could inhibit T_C–target cell interaction. Recently, Stewart *et al.* (1982) have shown that *Staphylococcus albus* binds to I*a* on mouse macrophages. The identity of the receptor was indicated by blocking with monoclonal anti-I*a*. Other reports indirectly supporting this concept of immune suppression by bacteria have summarized by Schwab & Toffaletti (1982).

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Site 7 indicates a very different mechanism of suppression. Secretion of interleukin 1 (IL-1) by activated macrophages promotes production of IL-2 by T lymphocytes, which functions as a T cell growth factor required for proliferation (Smith *et al.* 1980) of cytotoxic T cell precursors, delayed hypersensitivity T cell precursors and suppressor T cells (T_S). Hoffenbach *et al.* (1983) report that the anergy of T cell functions induced by *Mycobacterium leprae* infections in mice is associated with reduced production, recognition or utilization of IL-2 and this could in turn reflect defective production of IL-1 by macrophages.

(*d*) *Site* 8: *stimulation of T suppressor cells* (T_S)

It is well known that a single injection of mice with 100 μg or less of muramyl dipeptide (MDP) will enhance immune responses, and this seems to be related to a T_H cell (Sugimoto *et al.* 1978). However, repeated injection of larger doses of MDP before antigen will suppress antibody response to sheep erythrocytes (Leclerc *et al.* 1982). This suppression appears to be mediated by a non-specific suppressor T cell. Streptococcal pyrogenic exotoxin (SPE) also has been reported to modify immune responses through an effect on T_S cells (Hanna *et al.* 1982). As pointed out by Leclerc *et al.* (1982), the balance between T_H and T_S cells could be established by products of another cell, such as a macrophage (sites 5, 6, 7). In addition to an activation of adherent suppressor cells, Turcotte & Lemieux (1982) reported that *Mycobacterium bovis* (B.C.G.) infection in mice also stimulated T_S cells. In a similar study, Kato & Yamamoto (1982*b*) have reported that 10^8 heat-killed B.C.G. can induce T_S cells in mice. Turcotte and Lemieux (1982) measured T_S cells by non-specific inhibition of mitogen-induced proliferation of T lymphocytes *in vitro*, whereas Kato & Yamamoto (1982*b*) measured the suppression of specific response to purified protein derivative (PPD) (by macrophage migration inhibition) and suppressed response to *Listeria*.

Suppression by LPS given to mice before antigen has been ascribed to stimulation of a T_S cell by Uchiyama & Jacobs (1978). The studies of McGhee *et al.* (1980) also indicate that LPS induces a T_S population. Of even greater interest, this group provided evidence from genetic studies on LPS-responder and non-responder mice that LPS derived from Gram-negative bacteria of the normal microflora is responsible for the normal level of T_S cells (Michalek *et al.* 1980).

(*e*) *Site* 9: *stimulation of suppressor B cells*

Among the many other effects of LPS on regulation of the immune system is the suggested stimulation of the development of suppressor B lymphocytes (Vallera *et al.* 1980; Persson 1977; Koenig & Hoffman 1979). Whether suppression induced by LPS is due to a B or to a T suppressor population, Winchurch *et al.* (1982) have shown that the activation of suppressor cells may be mediated by cyclic AMP-mediated events. Humans vaccinated with B.C.G. develop a suppressor cell that inhibits the blastogenic response of sensitized T cells to PPD (Bona & Chedid 1976). Lymphocytes from two out of three normal immunized individuals, who remained skin-test-negative, developed a blastogenic response to PPD when the suppressor population was removed. The suppressor cell may be a B lymphocyte because it was not removed with the E-rosette-forming population nor by nylon wool. The yeast *Candida albicans* has also been shown to stimulate an Ig-bearing, adherent suppressor cell in mice (Rivas & Rogers 1983). Campa *et al.* (1980) have reported that *Pseudomonas aeruginosa* infection in mice stimulates a B suppressor cell that depresses contact sensitivity to oxazolone.

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(*f*) *Sites* 10 *and* 11: *suppression of T_C or T_D effector cells or effector mediators*

There are also reports that bacterial products can suppress immunity by acting directly on effector cells (site 10) (Floersheim *et al.* 1971). *Vibrio cholerae* and *Escherichia coli* enterotoxins, and endotoxin, can stimulate adenyl cyclase to increase intracellular levels of cyclic adenosine monophosphate (Lichtenstein *et al.* 1973; H. S. Kantor, 1975; Winchurch *et al.* 1982), which suppresses the secretion of lymphokines and other soluble effector mediators (site 11).

(*g*) *Site* 12: *activation of complement immunoregulatory fragments*

Complement has many biological activities that could influence specific immune responses (Sundsmo 1982). There are specific receptors on B lymphocytes or monocytes for C3, C4, C5–9 and factor B. Complement activation on the surface of lymphocytes or monocytes can lead to either activation (Sundsmo 1982) or inhibition (Weigle *et al.* 1982) of polyclonal antibody responses *in vitro*. Regulatory roles proposed for complement include providing a second signal for B cells (Dukor & Hartmann 1973) and antigen trapping (Klaus & Humphrey 1977). Morgan *et al.* (1981) have reported that C3a can suppress the antibody response *in vitro* by human blood cells and by mouse spleen cells, against sheep erythrocytes. The response to T-independent antigens is not suppressed. The effect is manifested as a suppression of T_H cells, and this may be mediated by the activation of a T_S precursor cell (Morgan *et al.* 1981). C3a is short-lived because it is inactivated by a serum carboxypeptidase, but it could be very effective in the microenvironment of bacterial antigen interacting with T cells, B cells and macrophages (Morgan *et al.* 1981). In this way it could control the immune response to an infectious agent. Immunoregulation by complement is cogent to this discussion because of the capacity of many bacteria and bacterial components to activate the alternative complement pathway (a.c.p.). Thus the answer to the teleological question of why bacteria would evolve a system to activate host complement may be that factors such as C3a can suppress specific antibody response. In this sense, bacterial products that activate the a.c.p. could paradoxically be virulence factors. Peptidoglycan derived from the cell wall is common to all bacteria and is one of the most potent activators of complement *in vitro* (Greenblatt *et al.* 1978) and *in vivo* (Schwab *et al.* 1982). LPS (Kane *et al.* 1973) and teichoic acid (Fiedel & Jackson 1978; Winkelstein & Thomasz 1978) are also widely distributed and well-defined products of bacteria that can activate C3.

(*h*) *Site* 13: *interference with antibody expression*

An example of possible interference with antibody expression is provided by antibody-degrading enzymes. IgA_1 proteases are produced by certain pathogenic bacteria that colonize mucosal surfaces (Kornfeld & Plaut 1981), and have been described for *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, and oral streptococci with the group-specific H antigen (*Streptococcus sanguis*). The only known substrate is IgA_1. IgA_2 is not degraded because the enzymes cleave only proline–threonine or proline–serine in two octapeptides that occur only in the hinge region of IgA_1. The enzymes produced by the different bacteria are immunologically distinguishable, and each is selective for the location in the peptide of the bond that it can degrade (Kornfeld & Plaut 1981).

Although it may seem logical to presume that such an enzyme must contribute to virulence, there is no direct evidence in support of the concept. Suggestive evidence comes from the observation that commensal *Neisseria* strains and *Haemophilus parainfluenzae* do not produce the

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protease (Mulks & Plaut 1978). On the other hand, IgA_2 is resistent to degradation and presumably could function as well as IgA_1. The real problem, however, lies in understanding the functions of IgA that are relevant for resistance of mucous membranes to infection. If their role is to bind adherence structures or neutralize products secreted by bacteria, cleavage of the hinge region should have no effect (Williams & Gibbons 1972). If IgA can function to 'arm' phagocytic cells (Lawrence *et al.* 1975) and if this is a mechanism in resistance to bacterial infection, then cleavage of the Fc region of IgA_1 could depress specific immunity.

2. Cross-reactive antigens

Another intriguing mechanism by which bacteria may induce a non-specific immune dysfunction in the host is through the stimulation of autoantibodies that bind to lymphoid cells or tissue. Lyampert *et al.* (1976) reported cross-reactivity between group A streptococcal polysaccharide and epithelial cells of thymus and the skin of humans and other animals. This could be interpreted to indicate a mechanism by which maturation of T cells, and perhaps the balance of the T_H–T_S subpopulations, could be modified. So far no direct link between such autoantibodies and immune dysfunction has been established.

Grooten *et al.* (1980) present another example. Mice immunized with a *Micrococcus lysodeikticus* vaccine develop anti-bacterial antibodies that can bind to mouse lymphoid cells after the cultures have reached confluence. This antibody is not mitogenic for mouse lymphocytes but can inhibit lectin stimulation *in vitro* (DeBaetselier *et al.* 1977). It is conceivable that such cross-reactive antibodies could bind to lymphocytes *in vivo* and modify their function in immune response to infection.

3. Evidence that immunosuppressant factors produced by an infecting organism influence that infection

(*a*) *Acute infections*

With the possible exception of capsular polysaccharide produced by *S. pneumoniae*, there is little direct evidence that any of the immunosuppressant products of bacteria described above function as virulence factors in acute infections. The large quantities of polysaccharide capsules produced by certain strains of *S. pneumoniae* appear to function by binding all available antibody (Frisch *et al.* 1942). In contrast, the studies of Baker and colleagues may be interpreted to indicate that patients may succumb because of the relative numbers of T_S cells induced very early in infections by the capsular polysaccharide (SSS-III). The competitive relation of T_S and amplifier T cells (T_A) was shown in mice immunized with purified SSS-III (Taylor *et al.* 1983). T_S cells developed over the first 5–24 h in mice primed with a sub-immunogenic dose (0.005 μg) and after 24 h the balance shifted to a moderate enhancement of antibody response, reflecting the appearance of T_A cells. In mice primed with an immunogenic dose (0.5 μg), T_S cells could also be demonstrated by the removal of T_A cells, but the balance of T_A cells was much greater. One might speculate that in certain individuals (because of genetic control or some exogenous factor) this 'homeostatic control mechanism' of T_S/T_A cells is balanced too far in favour of T_S cells during the critical early response of the immune system to the capsular polysaccharide. Such a host would be at a distinct disadvantage in controlling the infection.

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In the example of SSS-III, suppression in the mouse is specific and induced by the immunogen itself, and is called tolerance. However, the distinction between non-specific immunosuppression and specific immune tolerance becomes less clear when we consider that both non-specific immunosuppression by MDP or LPS and specific tolerance may involve stimulation of T_S cells, and that the series of T_S cells, or suppressor factors, can be either specific or non-specific (Germain & Benacerraf 1981).

(*b*) *Chronic infections*

The best examples of immune suppression developing during the course of infection are provided in chronic infections involving facultative or obligate microorganisms that survive and multiply in the monocyte/macrophages. In most of these infections cell-mediated immunity involving effector T cells and macrophages, rather than antibody, is the major factor in specific immunity. Loss of the expression of cell-mediated immunity, which may occur in the presence of normal or elevated antibody response, is called anergy (F. S. Kantor 1975; Turk 1979). The bacterial infections in which specific and non-specific anergy have been shown include leprosy, tuberculosis, syphilis, brucellosis and streptococcal diseases. These are examples of suppression by bacterial products and several mechanisms have been described. Ellner (1978) has demonstrated adherent suppressor cells in human tuberculosis. Hoffenbach *et al.* (1983) ascribed the depressed T cell response in lepromatous leprosy to reduced IL2 production, which could, in turn, reflect an imparied production of IL1 by macrophages. Suppression induced by experimental infection of mice with large doses of *Mycobacterium bovis* (*B.C.G.*) has been ascribed to high levels of PGE_1 production by adherent cells (Kato & Yamamoto 1982*b*), and in addition by cell contact of responding T lymphocytes with adherent suppressor cells or T_S cells, or both (Turcotte & Lemieux 1982). Experimental infection of mice with *M. lepraemurium* also induced a suppression measured by plaque-forming cells synthesizing antibody against sheep erythrocytes (Bullock *et al.* 1978). The suppression was evident over the period of 4–10 weeks of infection and was associated with a splenic adherent cell; but from 11 weeks on through the life of the mouse a T_S population was present in the spleen, and the appearance of this cell corresponded with the detection of anergy and an increase in the number of bacteria in the spleen (Bullock 1979).

Little attention has been given to the bacterial components that may be responsible for these modifications of the host's immune regulator systems. Ellner & Daniel (1978) have reported that an arabanomannan polysaccharide isolated from the cell wall of *M. tuberculosis* can suppress the antigen-stimulated proliferation of human lymphocytes. They showed that specific responses of sensitized lymphocytes to PPD, streptokinase–streptodornase, and *Candida* were suppressed *in vitro*, but not mitogenic stimulation by phytohaemagglutinin. We propose (Schwab 1982) that the specific and non-specific immune suppression associated with massive accumulation of bacteria in the infected host (as described by Bullock (1979) and Turk (1979)) is the result of the bacterial cell walls, which are poorly biodegradable by mammalian enzymes. This is based upon our studies in rats injected with purified peptidoglycan–polysaccharide complexes isolated from cell walls of group A streptococci (see § 5).

The question of whether suppression of cell-mediated immunity demonstrated in these infections is the cause or result of progressive, uncontrolled infection is still unclear. Ellner (1978) points out that the group of tuberculosis patients with anergy and circulating adherent suppressor monocytes was clinically indistinguishable from tuberculin-responding patients. The

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classical studiesof Mackeness (1969), however, imply that any interference with function of the delayed hypersensitivity T cell subpopulation must affect killing of phagocytosed bacteria by macrophages.

4. Evidence that immunosuppression induced by a microorganism influences infection by an unrelated organism

Petit *et al.* (1982) have shown that crude preparations of *Pseudomonas aeruginosa* (culture supernatant, viable bacteria or heat-killed bacteria) can suppress the resistence of mice to infection by *Listeria monocytogenes*. In these studies *P. aeruginosa* was injected intravenously before immunization with *L. monocytogenes* or sheep red blood cells (s.r.b.c.). Resistance to a challenge dose of *L. monocytogenes* was reduced and delayed-type hypersensitivity (d.t.h.) to s.r.b.c. was suppressed. They concluded that a macrophage-like suppressor cell was induced by an undefined component of *P. aeruginosa*. Other workers (Campa *et al.* 1980) have ascribed suppression of d.t.h. by *P. aeruginosa* to a suppressor B cell. Large doses of LPS will also suppress d.t.h. responses to s.r.b.c. (Gill & Liew 1979) and *L. monocytogenes* (Newborg & North 1979). In another study, however, resistance to infection with this organism was increased by pretreatment with LPS, but d.t.h. was suppressed (Galleli *et al.* 1981). Petit *et al.* (1982) calculate that the dose of LPS in their preparations of *P. aeruginosa* was too low to account for the suppression induced, so the identity of that suppressive component remains unknown.

'*C. parvum*' vaccines (Wing & Kresefsky-Friedman 1980) have also been reported to suppress resistance to *L. monocytogenes*. The mechanism of suppression was described in site 5 (figure 1). The depression of d.t.h. by B.C.G. has been discussed in §1.

Mankiewicz & Liivak (1960) demonstrated that *Candida albicans* or a polysaccharide fraction of this yeast suppressed the resistance of guinea pigs to *M. tuberculosis*. *Candida albicans* also enhanced the infection of mice by *Staphylococcus aureus*, *Serratia marcescens*, and *Streptococci faecalis* (Carlson 1983). Injection of a mixture of 10^8 *C. albicans* colony-forming units (c.f.u.) with 500 *S. aureus* c.f.u. produced a lethal *S. aureus* infection. This interference with immunity could be another example of non-specific impedins. It is conceivable that this non-specific enhancement is related to suppression of immunity by the stimulation of suppressor cells reported by Rivas & Rogers (1983). A summary of this activity of *C. albicans* has been included in a review by Rogers & Balish (1980). The problem in all of these studies is distinguishing whether the reduced immunity is due to the activation of suppressor mechanisms of the specific immune system or depression of phagocytic cell function, or some other interruption of innate immunity.

Palmer & Zaman (1979) investigated d.t.h. responses in cholera patients skin tested after fluids and electrolytes were corrected. Reactions elicited with PPD, streptokinase–streptodornase (SK–SD) and *Candida* were significantly less frequent in cholera patients than in controls of comparable age and malnourishment. It is not known whether this suppression of cell-mediated immunity is related to the severity of the *Vibrio cholerae* infection or to an increased susceptibility to unrelated infections. It is also uncertain if this suppression in human infection involves the same mechanism of suppression induced experimentally with cholera enterotoxin (H. S. Kantor 1975).

Studies attempting to related bacterial infection of human infants to a prolonged suppression of cell-mediated immunity were reported by Dutz *et al.* (1976). They observed that infants under 6 months old who suffered from severe, repeated, presumably bacterial enteric infections,

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developed thymic atrophy and suppressed capacity to develop d.t.h. reactions to 2,4-dinitrochlorobenzene. Respiratory infection at any age, or intestinal infections after 6 months, did not lead to reduced d.t.h. The controls from these studies were from a totally different population, and it is impossible to distinguish effects of malnutrition and stress due to infection, but it is interesting to speculate that this may be an extreme example in humans of an influence of severe bacterial infection on susceptibility to unrelated agents through a prolonged suppression of cell-mediated immunity.

5. Evidence that bacterial immunomodulating factors can influence pathogenesis subsequent to active infection

This section is concerned with that phase of disease that develops after all bacteria composing the infection have been killed (or contained) but pathogenesis progresses. This occurs because of either processes initiated by the microorganism but not requiring its continued presence (e.g. autoimmunity) or a pathology dependent upon the continuing presence of the toxic, immunogenic debris from the bacterial cells, which the host can not effectively degrade or eliminate. The development or progress of this stage of disease could be greatly influenced by modulation of the immune system (Schwab 1982).

The pathogenesis of infection can extend well beyond the period of bacterial multiplication or metabolism. Long after the microorganisms have been killed the host must deal with the consequences of the infection in the form of persistent phlogistic debris. Examples of this may be rheumatic fever subsequent to group A streptococcal infection; enteritis-related arthritises associated with *Yersinia*, *Salmonella* or *Shigella;* and rheumatoid arthritis. We have proposed that rheumatic fever and inflammatory arthritis could be caused by the accumulation of toxic, immunogenic cell wall debris in the tissues of genetically susceptible hosts (Schwab *et al.* 1959; Cromartie 1981; Schwab 1979). These diseases are frequently accompanied by impaired lymphocyte stimulation by antigens or mitogens (Francis & Oppenheim 1970; Gray *et al.* 1981; Silverman *et al.* 1976; Seitz *et al.* 1982; Wolinsky *et al.* 1980), or anergy to skin-test antigens (Andrianakos *et al.* 1977; Waxman *et al.* 1973). We hypothesize that immune deficiency (perhaps only subtly altered) is a necessary part of the pathogenesis of chronic, recurrent inflammatory disease, and that the impairment is induced by bacterial immunosuppressant factors. Suppression of T cell functions or antibody response could affect the distribution, degradation and persistence of bacterial debris. This concept is based upon our studies of an experimental model of progressive, erosive arthritis induced in the rat by the systemic injection of aqueous suspensions of peptidoglycan–polysaccharide polymers isolated from bacterial cell wall fragments (Cromartie *et al.* 1977; Eisenberg *et al.* 1982). The development of this chronic, recurrent disease is accompanied by several types of immune dysfunction, which were briefly described in §1*c*: (1) specific anergy to peptidoglycan (Hunter *et al.* 1980); (2) transient, non-specific suppression of T cell function; (3) prolonged monocytosis (Schwab 1982); (4) depression of complement levels followed by recurrence of elevated levels in serum (Schwab *et al.* 1982); (5) depressed antibody response to secondary injection of cell wall antigens (R. Esser & J. H. Schwab, unpublished).

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