Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Biological response modifiers and infectious diseases: 
Actual and potential therapeutic agents

James J. Rusthoven

Hamilton Regional Cancer Centre, Ontario Cancer Foundation, and Department of Medicine, McMaster University, 
Hamilton, Ont., Canada

(Accepted 16 September 1993)

Biological response modifiers (BRMs) are agents which can modify the immune response to cancer or invasion of the organism by infectious agents. An explosive appearance of new BRMs has resulted from the development of recombinant gene technology and the availability of monoclonal antibodies. Colony-stimulating factors first became available for the prevention of neutropenia but may also have a role in the treatment of infections. Interleukin-1 is being tested as a modulator of hematopoiesis and may be useful as a helper factor for T- and B-cell function. Immunoglobulins are being used against viral and bacterial infections while interferons can prevent viral upper respiratory infections and suppress or eradicate some viral hepatitides. Other BRMs which show promise include chemical agents and traditional herbal medicines.

Key words: Biological response modifiers; Septic shock; Interleukin-1; Colony-stimulating factors; Interferons; Immunoglobulins

Introduction

Biological response modifier (BRM) is a recent term, first coined in 1982, which connotes an agent and treatment approach whose perceived action involves the modification of an individual's own biologoical responses [1]. Prior to 1982, the term immunotherapy was used to refer to such agents and usually referred to naturally-occurring products obtained and tested at various grades of purity. Perhaps the oldest strategy of immune modification for the good of the host is the bacterial vaccine, first developed against microbes in the 19th century [2]. Antimicrobial vaccines are now a well-established part of standard medical practice while anticancer vaccines remain in the developmental stages. Some of these latter vaccines have been extracted from species used in the original vaccines of Coley and are undergoing clinical testing [3].
However, the advent of hybridoma, recombinant DNA, and gene insertion technologies have explosively widened the number of agents available for clinical testing. Agents which have been called BRMs now range from monoclonal antibodies [4], recombinant forms of interferons [5], interleukins [6], and colony-stimulating factors (CSFs) [7,8] to traditional Chinese medicines [9]. This review will focus primarily on agents whose mechanisms of action are at least partially understood and on those which are being or may soon be applied to the infectious diseases. While most such agents are products of the creative technologies mentioned above, some natural products whose properties may be unique or complementary to technologically-produced products will be discussed. A summary of these agents is presented in Table 1.

Mechanisms of inflammation

The rationale for the production and clinical application of BRMs for infectious diseases comes from our growing understanding of the inflammatory response to infectious agents. Two recent articles have reviewed this response in detail from the perspective of degrees of infection [10] and from that of the interactions between the hypothalamic-pituitary-adrenal (HPA) axis and the immune system [11]. There is evidence that infectious agents act as stressors which can adversely alter the HPA axis response to such agents and thus disrupt the normal inflammatory response [12-14]. Glucocorticosteroids play a vital role in the intensity of the immune response at several levels including gene expression, transcription, translation, post-translational processing and the secretion of proteins, and cell progenitor proliferation and differentiation. These effects are inhibitory at virtually all levels of the immune system including macrophage antigen presentation, B-cell production of antibodies, and the proliferation and differentiation of lymphocyte and granulocyte effector cells [15]. These inhibitory effects are, in turn, mediated through the inhibition of interleukins (ILs) such as IL-1, IL-2, IL-3, and IL-6 as well as the suppressor of tumour necrosis factor (TNF), gamma interferon (γIF), endogenous CSF such as granulocyte-macrophage CSF (GM-CSF) and the inhibition of proinflammatory mediators such as prostaglandins and leukotrienes. Glucocorticosteroids also suppress or inhibit the functions of effector cells such as eosinophils, mast cells, neutrophils, and mono-

| TABLE 1 | Areas for therapeutic trials of BRMs in infectious diseases |
|---------|----------------------------------------------------------|
| **Colony-stimulating factors** | Prevention of neutropenia in congenital, and cyclic neutropenic states |
| | Prevention of neutropenia during intensive anti-cancer therapy |
| | Treatment of febrile neutropenia |
| | Prevention and treatment of AIDS-related neutropenia or infection |
| | Treatment with antibiotics for infections in various immuno-compromised states (e.g. burns, asplenia, neonatal infections) |
| **Interleukin-1** | Improving hematopoiesis |
| | T-cell and B-cell helper factor |
| **Interleukin-6** | Stimulates thrombopoiesis |
| | Down-regulates IL-1 |
| | Interacts with other growth factors to amplify hematopoiesis |
| **IL-1-Antagonist** | Blocks shock-like effects of IL-1 |
| **Immunoglobulin** | (1) IVIG |
| | Kawasaki’s disease |
| | Prevention and treatment of viral disease in immuno-compromised patients |
| | Treatment of neonatal bacterial infection |
| | Treatment and prevention of infections in burn patients |
| | (2) Anti-endotoxin antibodies for prevention of sepsis |
| | (3) Anti-idiotypic antibodies as vaccines |
| **Interferons/Interferon inducers** | Intranasal prophylaxis against viral respiratory infections |
| | Treatment of hepatitis B and C |
| | Treatment of AIDS |
| **Others** | Nucleic acid analogs (isoprinosine) |
| | Thiols (diethylidithiocarbonate) |
| | Cyanoaziridine (azimexon) |
| | Herbal preparations |
cyte-macrophages. Thus, the production and inhibition of inflammation is a complex phenomenon, involving any or all of a variety of mediators whose human genes have been identified and can be produced for clinical intervention.

**Pathophysiology of inflammatory response to infectious agents**

For patients with localized infections, complete resolution with or without the aid of antibiotics is the rule in an otherwise healthy host. While these individuals may not require further exogenously-administered therapy, much can be learned about the response of endogenous mediators which could be useful in immunodeficient hosts. For example, studies have shown that alveolar macrophages produce G-CSF in response to infectious agents [16]. *In vitro*, G-CSF has been shown to improve the functional activity and survival of granulocytes against pathogens such as *Candida* sp., *Staph. aureus*, and *P. aeruginosa* [17,18].

Various factors may contribute to the host’s failure to locally contain infection. These include the disruption of local barriers to infection dissemination such as burns or trauma, advancing age, the presence of underlying disorders such as renal or cardiac failure, diabetes mellitus, hepatic cirrhosis, or asplenia, and the concomitant administration of immunosuppressive drugs. In ways that are not yet fully understood, these factors can alter the complex equilibrium between mediators which enhance inflammation and those which suppress it. The factors mentioned above may detrimentally upset this balance in several ways: by altering the capability of target cells to release mediators and by disturbing the type and quality of interdependent mediators in the local environment [10]. Inflammation is normally controlled by the counter-effects of mediators which enhance or suppress inflammation. TNFα enhances prostaglandin I₂ release while the latter down-regulates further TNFα production [19,20]. Similarly, G-CSF, αIF, and TNFα can improve neutrophil function [21,22] while products of the neutrophilic burst can neutralize the effect of leukotriines on increased vascular permeability at the inflammatory site [23]. However, some mediator interactions are self-perpetuating and can lead to infection dissemination and sepsis. Examples of this include the release of αIF by activated T-cells which then stimulates macrophages to release IL-1 [24]. The latter can then induce the release of TNFα and platelet-activating factor (PAF), with all three factors promoting the release of each other [25]. Since these three factors can induce symptoms of sepsis, much research is being directed toward understanding their relationship to states of sepsis and the development of counter-intervention which may prevent or reverse the septic state.

The importance of the vascular endothelium in the evolution of septic states is rapidly becoming evident. This defense system is not only a mechanical barrier to infection and mediator release from the local environment but is also a source of TNFα, IL-1, PAF, IL-6 [26–28], endothelin-1, endothelium-derived relaxing factor (EDRF) [29], and arachidonic acid metabolites [30]. While the limited release of TNFα, IL-1, endotoxin, etc., can induce a down-regulation of subsequent mediator release with a resultant aborption of the process of sepsis development, such down-regulation could be prevented by a shortage of down-regulating mediators or an overwhelming release of sepsis-inducing mediators. Such substances may damage the endothelium further, resulting in the release of more sepsis-promoting factors, and the eventual development of end-organ ischemia and multiple organ failure [10].

The final stage of sepsis is multiple organ failure (MOF), a well-recognized clinical syndrome associated with a wide variety of clinical events or states. While infection and shock lead the list of predisposing factors, others include mechanical, thermal, and traumatic factors and pancreatitis [31]. Several mechanisms of MOF evolution have been put forward. The so-called macrophage hypothesis supports the previously-outlined evolution of sepsis via endogenous moderators. Again, the unchecked release of IL-1, IL-6, αIF, and TNFα and the self-perpetuating interaction of these agents forms the basis of this hypothesis [32].

In summary, several endogenously produced cytokines have been implicated as important promoters of the process of sepsis. In the remainder of this review, strategies which focus on the suppression of the uncontrolled release of sepsis-promoting agents
or on the stimulation or exogenous restoration of sepsis-preventing agents will be presented. At the end, other agents or strategies which show promise but whose mechanisms of action are less clear will also be reviewed.

Colony-stimulating factors

G-CSF and GM-CSF were the first CSFs approved for clinical use in cancer patients. Effectiveness of either or both of these agents has been demonstrated in clinical situations where infection prevention is a primary concern: congenital, idiopathic chronic, and cyclic neutropenia; following standard doses of myelosuppressive chemotherapy; in conjunction with bone marrow transplantation (BMT) or peripheral blood stem cell (PBSC) reconstitution as support following myeloablative therapy; and as supportive therapy in patients with AIDS. G-CSF reduced infection, hospitalization, and febrile neutropenia rates as well as the frequency and duration of antibiotic usage in a randomized trial of patients treated with myelosuppressive therapy for small cell lung cancer [33]. Side effects were minimal. Survival was similar whether or not G-CSF was given. GM-CSF has not been tested in the setting of a randomized trial in this situation but fever and flu-like symptoms are more frequent than with G-CSF. No completed randomized trial has been published comparing prophylactic antibiotics with G-CSF or GM-CSF, nor has a trial been conducted comparing the effectiveness of G-CSF with antibiotics compared to antibiotics alone in the setting of febrile neutropenia following standard dose chemotherapy.

In patients undergoing autologous BMT, randomized trials have demonstrated accelerated neutrophil recovery and a reduced duration of antibiotic therapy and hospitalization with GM-CSF compared to placebo [34]. No such trial of G-CSF has been undertaken but non-randomized studies suggest a possible beneficial effect [35]. PBSCs can be harvested more efficiently after G-CSF or GM-CSF with or without the benefit of a post-chemotherapy rebound phase [36,37]. Whether or not post-transplantation peripheral blood cell recovery can be further improved by the addition of either factor is not yet clear. The optimal schedule for CSFs is one of several issues that remains outstanding. The supportive care of patients with chronic neutropenic diseases has made major advances due to these CSFs. Patients with congenital or idiopathic neutropenia have been treated for up to 3 years with G-CSF with associated elevations of neutrophil counts above $1.0 \times 10^9/l$ and marked reduction in infection-related symptoms [38]. Adverse events of such chronic treatment have been infrequent and generally mild except for occasional thrombocytopenia, bone pain, and hypersplenism. Treatment with GM-CSF has been less effective and also produces eosinophilia. Patients with cyclic neutropenia have regular, 14 to 28 day cycles of neutropenia resulting in recurrent fever, infections, and mucosal ulceration. Treatment with G-CSF can result in a reduced frequency of all three clinical problems coincident with an elevation of the cyclical nadir and a shortening of the cycle length [39]. Chronic therapy does not appear to result in stem cell depletion [40]. Experience with GM-CSF has been limited and has not resulted in elevations of neutrophil levels.

Patients with AIDS may undergo primary bone marrow failure or myelosuppression due to antiviral or supportive anti-infection therapy. G-CSF has demonstrated marked improvements in neutrophil counts in patients with anemia and neutropenia also receiving erythropoietin and zidovudine [41]. Such therapy allowed further treatment with zidovudine after zidovudine-induced myelosuppression was corrected. Similar benefits were seen with GM-CSF [42]. Whereas HIV and p24 antigen levels were unchanged with G-CSF, the latter level was elevated with GM-CSF, suggesting possible enhancement of HIV proliferation. However, this was offset by an enhanced antiviral effect of zidovudine in the presence of GM-CSF as suggested in vitro [43]. In non-neutropenic states, infection may spread due to a disruption or circumvention of normal barriers (e.g., burns or intramuscular infections) or in other states where the immune deficiency is acquired (e.g., neonatal sepsis, asplenic states). Animal model studies have suggested a possible role for CSFs in these situations. Burn patients demonstrate multiple defects of neutrophil dysfunction which precede sepsis [44]. In a murine model of burns infected with *P. aeruginosa*, mice treated with G-CSF showed marked improvement in survival compared to saline-treated
controls [45]. In another study in the same model, mice receiving single dose gentamicin plus G-CSF for 7 days demonstrated improved survival compared to mice treated with G-CSF alone (P = 0.054), gentamicin alone (P = 0.007) or neither treatment (P < 0.0001) [46].

In newborns, group B streptococcus is the most common cause of neonatal sepsis. In a study of newborn rats, group B streptococcus was given subcutaneously (sc). The survival of animals at 72 h receiving both G-CSF and antibiotics (ampicillin and gentamicin) was 91%; antibiotics alone, 28%; G-CSF alone, 9%, and no treatment, 4% (P < 0.001 when compared to controls) [47].

In a murine model of intra-abdominal sepsis using cecal ligation and puncture (CLP), O'Reilly et al. showed a dose-dependent increase in survival in mice receiving 10–1000 ng of G-CSF at CLP and continued for 7 days compared to control. Those receiving G-CSF beginning 4 days prior to CLP and continued until 2 weeks post-CLP had significantly better survival at all doses tested in that range compared to control. When given with gentamicin in this setting, the two interventions together showed survival similar to gentamicin alone [48].

Splenectomy is associated with an increased incidence of encapsulated organism infections, particularly pneumococcus. In a mouse model of pulmonary infection by aerosolized Streptococcus pneumoniae, Hebert et al. reported 70% survival of splenectomized mice treated with G-CSF from 24 h prior to 3 days following infection compared to 20% survival in saline-treated, splenectomized controls (P < 0.001) [49].

Alcohol abuse can increase the risk of severe pneumonia; impairment of neutrophil migration to the infection site has been implicated as a cause [50]. In a study of rats treated with G-CSF or its vehicle for 2 days, followed by ip administration of ethanol or saline prior to intratracheal challenge with Klebsiella pneumoniae, all rats receiving ethanol without G-CSF developed bacteremia (18/18) while none receiving G-CSF prior to ethanol (0/18) became bacteremic. Furthermore, all twelve ethanol-treated controls died at 72 h whereas only 1 of 12 pretreated with G-CSF died. A study of pulmonary infection due to P. aerogenosa in the same model produced similar results [50].

Other studies have suggested a role for CSFs in parasitic or less common bacterial infections. The functional improvement in eosinophils seen with GM-CSF may suggest a role in parasitic infections such as Schistosoma mansoni, where GM-CSF can improve the adherence to and killing of these organisms by eosinophils in vitro [51]. Cheers et al. demonstrated that susceptibility to Listeria monocytogenes infection and the endogenous response of M-CSF and G-CSF levels may in part have a genetic basis, at least in mice [52]. It should be noted that GM-CSF may be associated with a more adverse outcome compared to no GM-CSF in patients with sepsis. While only a preliminary observation [53], it has been found that GM-CSF treatment is associated with a twenty-fold increase in endogenous serum TNF levels following iv endotoxin challenge in rats. No effect on TNF levels was found using G-CSF [54]. Human peripheral blood monocytes have also been found to produce TNF and IL-1 when stimulated by GM-CSF in vitro [55]. These data support the hypothesis that clinical sepsis may be initiated and exacerbated by agents which stimulate TNF production in vivo. The use of such agents in these patients must be tested carefully even if concomitant treatment with antibiotics is used.

### IL-1, IL-6, and TNF

**Understanding potential clinical consequences as they relate to the infectious diseases**

IL-1 refers to two genetically and chemically distinct polypeptides which recognize the same receptors and share most biological activities. The term ‘interleukin’ is misleading in this context. The diverse sources of IL-1 include macrophages, monocytes, neutrophils, T- and B-lymphocytes, astrocytes, endothelial cells, keratinocytes, intestinal epithelium, maternal placental cells, and others. Leukemic cells can produce IL-1. Known since the 1940s as a heat-labile protein extracted from exudative fluid, it was known as endogenous pyrogen [56]. Since then, discoveries of its wide-ranging biological properties have led to a succession of synonyms such as catabolin [57], osteoclast activating factor [58], hemopoietin-1 [59], lymphocyte proliferation promot-
ing factor of neutrophils [60], and tumour-inhibiting factor-2 [61]. These properties as well as the structural and genetic aspects of IL-1 have been eloquently reviewed previously [62,63]. This review will focus on aspects of IL-1 that apply to sepsis or other aspects of infectious diseases.

IL-1 can autostimulate its own gene expression and synthesis in monocytes and endothelial cells [64,65]. IL-1 production is induced by M-CSF, GM-CSF, and TNF [66,67], and is inhibited by γIFN [68]. IL-10, a T-helper cell product, inhibits lipopolysaccharide (LPS)-induced IL-1 production [69]. While endotoxin may be the most potent inducer of endogenous IL-1, exotoxins of Gram-positive organisms such as staphylococci and streptococci can also stimulate IL-1 as well as TNF production. Such a mechanism has been implicated in the development of toxic shock syndrome [62].

When given to patients with cancer in phase I trials, IL-1 has produced fever, arthralgias, myalgia, headache, anorexia, insomnia, and gastrointestinal upset at doses ranging from 10 to 100 ng/kg [70,71]. Such effects are more pronounced when given iv compared to sc. Increases in circulating neutrophils and platelets were seen and, with other observations, confirm the biological effects seen in animal models. Such hematopoietic effects have exciting potential for therapy. While hematopoietin-1 was eventually characterized as IL-1α, no differences in hematopoietin-1 activity have been found between IL-1α and IL-1β. In animal models, IL-1 accelerated neutrophil recovery in 5-fluorouracil-treated [59] and lethally-irradiated [72] mice. A low, prophylactic dose of IL-1 was shown to accelerate the recovery of chemotherapy-induced neutropenia in mice [73] and to protect mice infected with P. aeruginosa during cyclophosphamide-induced neutropenia whether or not gentamicin was administered as well [74]. While a direct antibacterial effect was unlikely, the mechanism of this effect is unclear. However, this paradoxical protection by an agent known to mediate sepsis is likely critically dependent on the dose given (low dose) and the time of administration. Endogenous release of G-CSF or GM-CSF from endothelial and bone marrow stromal cells has been reported and may play a role [59]. In addition, IL-1 acts directly and synergistically on the responsiveness of early progenitor stem cells to other CSFs [75]. While having no direct effect on stem cell differentiation or proliferation, IL-1 may induce stem cell factor [76]. Finally, IL-1 can regulate the cell cycle of progenitors and may allow for the protection of such cells from cytotoxic agents through such changes [77]. Short exposure is probably important to permit these effects and to avoid the induction of septic phenomena; continuous IL-1 exposure in vivo leads to TNF-mediated myelosuppression [78]. The beneficial effects of low dose IL-1 may also be mediated through the observed down-regulation of TNF and IL-1 receptors, the mediation of oxygen scavenger molecules, or the induction of corticosteroids [79,80]. The catabolic effects of IL-1 include its induction of anorexia and weight loss [81]. While these features adversely contribute to the sepsis syndromes, the most profound and serious effect is that on the vascular system. While inducible at doses below 1 μg/kg iv, hypotension is the dose-limiting effect of IL-1 at 300 ng/kg [70]. Cyclooxygenase inhibitors block this effect as well as hypotension induced by the combination of IL-1 and TNF [83].

Immunologically, IL-1 activates T-cells through IL-2 induction, although it is not clear whether or not IL-1 is a requirement for T-cell activation [84]. As with T-cells, IL-1 acts as a helper factor with other factors such as IL-6 and IL-4 in the activation of B-cells. Furthermore, most cells including B-cells that act as accessory cells to antigen recognition produce IL-1 [85], suggesting a fundamental role for IL-1 in this early step of immune recognition against foreign antigen.

The synergistic actions of IL-1 and TNF have been alluded to earlier. Like IL-1, TNF can induce shock and is more potent than IL-1 in this regard [83]. However, in rabbits and primates, antibodies to TNF can prevent endotoxin-induced shock and the associated suppression of IL-1 serum levels suggests that TNF may control IL-1 production [86]. These data suggest that monoclonal antibodies against TNF and/or the use of IL-1 receptor antagonists could be therapeutically useful in shock-like states. TNF, like IL-1, can induce CSF release in vivo and can act synergistically with TNF to protect rats from lethal irradiation [87].

IL-6 is an endogenous pyrogen and elevated
serum levels correlate with the severity of fever and sepsis in patients. However, IL-6 may serve to down-regulate IL-1 and thus counter its effects [88]. Perhaps the most important interactions of IL-6 and IL-1 involve hematopoiesis [59]. Together, these agents stimulate multilineage colony formation of murine bone marrow cells after exposure to chemotherapy in vitro [89]. However, as with IL-1, the timing of IL-6 exposure may determine whether its effects will be myeloprotective or detrimental by inducing progenitor proliferation too close to cytotoxic exposures.

Therapeutic implications of interventions which are antagonistic to IL-1, TNF, or endotoxin

The discovery of agents antagonistic to the shock-like effects of IL-1, TNF, and endotoxin may afford us the therapeutic tools to prevent or treat sepsis by directly interfering with the endogenous mediators of sepsis. IL-1ra or IL-1 inhibitor is one of several naturally-occurring inhibitors of IL-1. Others include lipids, lipoproteins, TGF-β, some neuropeptides, α-2 macroglobulin, and a form of Tamm-Horsfall protein [62]. While these latter substances also inhibit IL-6, IL-2, and other cytokines, others have been detected which specifically inhibit IL-1. Sources of such inhibitors have included endotoxin-treated volunteers [90], urinary extracts from febrile patients [91], and from patients with leukemia [92].

The substance now known as IL-1ra is a small, naturally-occurring protein which blocked the binding of IL-1 to T-cells and fibroblasts but did not bind to IL-1 [93]. A recombinant human IL-1ra (rhuIL-1ra) has been developed and its biological properties are identical to those of the natural form. In rabbits and baboons, rhuIL-1ra prevents the septic shock syndrome induced by E. coli suspensions [94]. In a rabbit inflammatory bowel disease model induced by IL-1, rhuIL-1ra prevented the immune complex-mediated disease [95]. Other potential clinical roles for rhuIL-1ra include the inhibition of ectopic IL-1 secretion by various malignancies and the reduction of any IL-1-mediated inflammation. Phase I clinical testing is underway in humans.

Therapeutic roles for antibody therapy

Anti-endotoxin antibody

Other strategies are evolving for the prevention and treatment of sepsis. Human polyclonal antiserum produced against endotoxin core determinants has been shown to reduce mortality in clinical trials of patients experiencing Gram-negative bacteremia [96] and to reduce the incidence of septic shock in surgical patients at high risk [97]. Suggested mechanisms by which such protection may occur include inhibition of neutrophil priming by endotoxin [98], the enhancement of endotoxin binding clearance [99,100], and inhibition of TNF production [101,102]. This antiserum was produced by injecting volunteers with a mutant E. coli known as J5; this inducer strain yielded a relatively specific immune response to lipid A and other core components. Another human polyclonal IgM produced against a Salmonella sp. Re strain protected animals from lethal challenges from several Gram-negative bacterial strains [103]. However, commercial production was hindered by toxicity in the donors, the theoretical risk of infection transmission through pooled human serum, variability of the antibody titre, and no booster response which could allow for multiple donations. However, monoclonal antibody (MOAb) technology has permitted the development of highly specific antibody against the lipid A domain of endotoxin. Using the same E. coli J5 vaccine mentioned above, a human monoclonal IgM, known as HA-1A, was found through clonal selection [104]. It binds to endotoxins among a broad range of clinical isolates of Gram-negative bacteria. This binding appears to be enhanced by concomitant presence of ceftazidine [105]. In rabbits, HA-1A can protect against septic death due to pseudomonas bacteremia [106]. HA-1A is cross-reactive with the polyclonal IgM preparation against both J5 and Re mutants. However, not all animal studies of anti-core antiserum or HA-1A have shown protection; interspecies differences, the relatively low affinity of anti-core antiserum, and variations in methods of producing or purifying the MOAb to HA-1A have been cited as possible reasons [103,107]. A recent blind, placebo-controlled, randomized trial of HA-1A in a standard canine model of endotoxic shock
showed no anti-endotoxic effect and decreased survival in the HA-1A treated group [108]. A randomized clinical trial of human IgG to E. coli J5 demonstrated no protection from Gram-negative shock but IgM may be necessary for protection [109].

HA-1A has been tested in humans in phase I and phase II trials in which safety and protection from sepsis were demonstrated [110,111]. A randomized, double-blinded, placebo-controlled trial treated 543 patients with sepsis, of whom 200 had culture-proven Gram-negative bacteremia as a cause [112]. The MOAb or placebo (human serum albumin) were administered as a single iv injection over 15 to 20 min immediately following enrolment. Other interventions such as antibiotic, corticosteroid, or cardiac and respiratory support were not controlled and patients were eligible if they developed sepsis according to a standard definition. In follow-up over 28 days for patients with culture-proven Gram-negative bacteremia, a statistically significant reduction in deaths was seen among the HA-1A treated patients (30% versus 49% for placebo, P = 0.014). No benefit was found among the other 343 patients with sepsis but without culture-proven Gram-negative bacteremia (P = 0.68). Similarly, no mortality reduction was seen when all 543 patients were analyzed (P = 0.24). While the follow-up period at this report is short, the results are provocative as is their conclusion to treat all patients with sepsis suspected but not necessarily proven to be due to Gram-negative bacteremia. However, the validity of this study has been questioned on the grounds of methodological flaws [113]. Furthermore, this criticism, and the subsequent publication of the canine model study cited above [108], has lowered the justification for using HA-1A in clinical practice until more information as to which subgroups of patients may benefit is available. Other criticisms and concerns were expressed. Wolff suggested that a non-specific IgM could have been a better control to test for the specific nature of the protection, or the polyclonal anti-J5 antiserum could have been the control [114]. However, since neither of these are used as standard treatment, the decision to use albumin was appropriate. A subsequent published response to the randomized trial suggested that patients without proven Gram-negative bacteremia who received HA-1A may have had a higher mortality rate [115].

A subsequent cost analysis of this study assessed the cost of treating all patients with sepsis as in the study versus treating only culture-proven cases, assuming the availability of a more rapid test for Gram-negative sepsis than that presently available [116]. The former strategy prevented, on average, 5.4 deaths per 100 treated patients while the cost-effectiveness was $24 100 per year of life saved. The latter strategy yielded a cost-effectiveness of $14 900 per year of life saved. Sensitivity analysis demonstrated the importance of patient selection; if, for example, only 10% of patients were proven to have Gram-negative bacteremia after all patients were treated, the cost-effectiveness would deteriorate to $65 900 per year of life saved.

Another monoclonal antibody against endotoxin, known as E5, has been tested in a multicenter, double-blind, randomized clinical trial [117]. Four-hundred-and-eighty-six hospitalized patients with signs of Gram-negative infection and sepsis were enrolled. At entry, patients received a single dose of E5 or placebo, followed by the same treatment 24 h later. Three-hundred-and-sixteen patients had Gram-negative sepsis confirmed, with bacteremia documented in 54%. While there was no survival difference among the treatment groups overall, a subgroup analysis found a significant survival advantage in patients with Gram-negative sepsis, but not in shock, who received E5 compared to those who received placebo (P = 0.01). Resolution of organ failure was more frequent in the E5 group (54% versus 30%; P = 0.05) and toxicity was infrequent and reversible. A recent study also suggests that E5 may improve the survival of ciprofloxacin-treated animals in a neutropenic rat model of Pseudomonas sepsis [118].

When the randomized, placebo-controlled trials of HA-1A [112], and E5 [117] are compared, it is clear that (1) no significant reduction in mortality was found among all patients treated with the MOAb in each trial and (2) different subsets of patients seemed to benefit in the two trials. These patients constituted a minority of all study patients. In a recent statement of guidelines from the Infectious Disease Society of America, Wenzel et al. have concluded that ‘...conclusive evidence for reduction of the mortality rate with use of endotoxin antibodies is not available.’ [119]. What is clearly needed now is
research into factors which prospectively identify patients with sepsis who would benefit the most from this exciting but somewhat costly new intervention.

**Intravenous immunoglobulin (IVIG) therapy**

Despite the availability and use of immunoglobulin in patients since 1952, a recent Consensus Development Conference Report recommended IVIG without reservation for only two non-immunodeficiency conditions: (1) acute autoimmune thrombocytopenic purpura of childhood, and (2) Kawasaki’s syndrome [120]. This is due in part to the long time required to develop a concentrated but safe preparation for iv use [121] but is also due to the relatively low levels of evidence in the literature that IVIG is clinically effective. Nine commercial preparations are available and variability in physical features and specific antibody titres exist amongst these preparations, as well as from lot to lot of the same preparation [122].

The mechanism by which IVIG may be effective is still speculative but more attention has been focused on the role of anti-idiotypic antibodies (AIA) in the preparations. Detailed reviews of the role of these antibodies in normal antibody feedback regulation are available [123,124]. In essence, IVIG may induce reticuloendothelial blockade [125], increase T-suppressor or natural killer cells [126], and/or may decrease antibody synthesis [127]. AIA within IVIG may neutralize autoantibodies [128], may block the B-cell receptor for antigen and thus block autoantibody production, or may complex with idiotypic complements to activate different T-cell subsets [129]. In animal models, AIA in IVIG have been shown to decrease autoantibody production [130]. Situations involving infectious diseases for which IVIG may be useful include the prevention and treatment of cytomegalovirus (CMV), the prevention of varicella zoster (VZ) infection, Kawasaki’s syndrome, neonates at risk for group B streptococcal infection, and possibly children with HIV infection. Patients with primary hypogammaglobulinemia also may benefit.

As mentioned above, two studies have demonstrated the efficacy of IVIG in Kawasaki’s syndrome. Two controlled trials showed fewer coronary artery abnormalities with high-dose IVIG and aspirin compared to aspirin alone [131,132]. Evidence suggests that IVIG may alter the effects of cytokines excessively produced by a bacterial toxin by blocking the effects of the toxin [133]. Alternatively, suppression of activated T-cells may play a role [134]. The next most convincing clinical situation for IVIG efficacy involving infectious diseases is in the prevention of CMV infections in immunodeficient, particularly transplant patients. Clinical trials have supported a reduction in the incidence in CMV interstitial pneumonia but not infection per se [135–137]; only one non-randomized trial suggested CMV infection could be reduced by IVIG [136]. These effects appear to depend on the evidence for previous CMV infection in the recipient or donor; a study of seronegative recipients and donors showed no benefit of IVIG above that achieved by seronegative donor blood products [138]. Benefit has also been suggested in patients with CMV infection receiving IVIG with ganciclovir [139,140]. While patients receiving either intervention had a survival rate of 13%, those receiving both had a 60% chance of survival. A recent randomized trial was designed to test the ability of IVIG to reduce the morbidity of allogeneic transplantation. Primary and secondary outcomes included graft versus host disease (GVHD) as well as infection rates [141]. Three-hundred-and-eighty-two patients received IVIG or no IVIG weekly for 90 days post-transplant, then monthly to day 360. All CMV-seropositive patients received prophylactic acyclovir, all patients received co-trimoxasole, and ganciclovir was added if CMV pneumonia developed. The 2-year survival of the two groups was identical; IVIG was, however, associated with reduced risk of GVHD, Gram-negative sepsisemia and local infection, and reduced risk of interstitial pneumonitis among CMV-seropositive patients. The data also showed a reduction in mortality other than that due to tumour relapse in the IVIG-treated group at or above age 20. Further study is required to determine the long-term effectiveness of IVIG in this setting. Renal transplant patients can also benefit and IVIG may be cost-effective; seronegative recipients had a three-fold reduction in the incidence of CMV infection [142,143]. Patients with hypogammaglobulinemia may experience fewer CMV infections when given IVIG [144]. While CMV infection is a common problem in patients with acquired immu-
nodeficiency syndrome (AIDS), the potential enthusiasm of prophylactic IVIG in this population may be tempered by the fact that CMV often results from endogenous reactivation in this setting which may reduce the effectiveness of this intervention. The same may be said for Pneumocystis carinii infections.

Two non-randomized studies suggested improved survival associated with IVIG therapy. Over a 2-year period, 2 of 14 children with AIDS who received IVIG and antibiotics as needed died compared to 14 of 28 patients treated with antibiotics alone [145]. Siegel and Oleske reported deaths in 10 of 12 untreated children with AIDS over 2 years compared to 3 of 19 patients receiving IVIG [146]. Coincident improvement in immunoregulatory function has also been reported [147]. However, a controlled trial by the National Institute of Child Health and Human Development found no improvement in mortality using IVIG compared to placebo; infection risk was only reduced in patients with CD4 counts at or above 0.2 x 10^9 per litre [148]. Unfortunately, zidovudine was not standard treatment and therefore the relevance of these results is questionable.

A randomized trial comparing IVIG and appropriate antibiotics would be helpful in this area.

IVIG has been used in the prevention or treatment of other viral illnesses. IVIG may be as effective as V-Z immune globulin in those immunocompromised children unable to take the latter for V-Z infection prevention. V-Z antibody titers are similar in appropriate doses of IVIG [149]. There is, however, evidence that IVIG does not improve the recovery of such patients with established V-Z infection [150]. IVIG did not shorten hospital time and no deaths occurred in either arm of a double-blind, randomized, placebo-controlled trial in children with respiratory syncytial virus pneumonitis [151]. No randomized trials are available for the treatment of adenovirus, influenza, or parainfluenza viruses. Uncontrolled studies suggest that IVIG may improve symptoms and/or recovery of patients with hypogammaglobulinemia and echovirus-associated polyomysitis or meningoencephalitis [152] as well as some patients with chronic Epstein-Barr virus (EBV) infection [153]. In another disease which may be related to EBV infection, authors of a double-blind, placebo-controlled trial in 49 adults with chronic fatigue syndrome reported improvement in symptoms and elevated levels of work, leisure, and social activities — information obtained by interview at 3-month follow-up [154]. An even smaller randomized trial reported no clinical benefit [155], but both studies suffered from a high type II error in the study design. IVIG has been suggested for EBV-seronegative boys with X-linked lymphoproliferative syndrome because of the frequently fatal outcome of that disease [156].

As mentioned earlier, IVIG has been used in the management of bacterially-mediated neonatal sepsis. Two uncontrolled studies reportedly demonstrated improved survival in patients suspected of neonatal sepsis who were treated with IVIG plus antibiotics versus antibiotics alone [157,158]. The benefit was particularly evident among low-birth weight, premature infants [157]. Despite these results and minimal adverse side effects, the level of evidence was considered insufficient to support its use as standard therapy by the NIH Consensus Conference [120] and randomized, comparator trials are needed. Patients with burns could also theoretically benefit from IVIG in the prevention or treatment of bacterial infection. This is based on evidence of a correlation between decreased serum immunoglobulin levels and the severity of injury in these patients [159]. However, human studies have been contradictory and flawed by inadequate study designs [160,161]. One double-blind, placebo-controlled study showed no significant improvement in mortality from infections but the high type II error and low power of the study precluded any conclusion that a real difference was not missed [162]. Again, a randomized trial with sufficient statistical power is required. Finally, patients with cystic fibrosis have been treated with IVIG but reports remain anecdotal and any perceived benefits were short-lived [163,164].

**Anti-idiotypic antibodies as vaccines**

A region on an antibody against which antibodies can be produced and which, in turn, is specifically recognized by these antibodies is known as an idioype. The existence of such regions was suggested in the early 1900s [165], confirmed in the 1960s [166], and incorporated into a network theory of antibody–antibody interaction thought to occur normally in the human immune system [167]. Ehrlich
had suggested at the turn of the century that autoimmunity against red blood cells (RBC) could be stopped or prevented by antibodies produced against the auto-antibodies to the antigen (in this case, RBC) [165]. These early pioneers suggested that these anti-antibodies had side chains which were similar to those on the RBC. This idea was further developed through the idiotypic network theory of Jerne and led to the idea that such ‘internal images’ of the antigen that exist on the anti-antibody could act as surrogate antigens within vaccines [168,169].

Over the past decade, attempts have been made to produce and test such vaccines for protection against various infectious agents [170]. While such anti-idiotypic antibodies (AIA) can afford some protection in certain models, some practical issues must be considered. The production of such a vaccine would be expensive and may outweigh the benefits. These antibodies have usually been murine in nature; therefore, adverse reactions have been a problem. Genetic engineering might allow for the introduction of human regions but this again will add to the cost. Therefore, applications of this approach are unlikely where effective native antigen-based vaccines already exist, such as in the case of hepatitis B [171,172]. However, an AIA vaccine might be useful where existing vaccines can be toxic (e.g., pertussis), or where present vaccines are ineffective; such is the case in the immunization of infants with carbohydrate antigens from Hemophilus influenzae and group B streptococci. As a protein-based preparation, an AIA vaccine may be more antigenic in such individuals. Examples of agents against which such vaccines have an AIA are being tested and include hepatitis B virus, rabies virus [173], reovirus [174], diphtheria toxin [175], polivirus [176], and of course, HIV [177]. Clearly, more work is needed before such vaccines can become commercially viable for selective indications.

Interferons: the treatment of infectious diseases

While interferons were first characterized as endogenous antiviral agents, clinical applications have been more directed toward the exploitation of their anti-neoplastic properties rather than antiviral potential. However, some applications to viral illnesses have been made and three of these areas will be reviewed here to illustrate the scope of these applications: as prophylaxis against naturally-acquired respiratory infections, as treatment against viral hepatitis, and as treatment of HIV infection.

Intranasal alpha-interferon for viral upper respiratory infection

Studies have demonstrated that prophylactic intranasally administered interferon can prevent rhinovirus and coronavirus infections in experimental models and human volunteers [178–180]. Two recent randomized trials were designed and implemented to test whether or not intranasal alpha-interferon (αIF) could reduce the incidence of colds when given to household members of individuals with established colds. Previous studies involving community-based field studies demonstrated that long-term administration of αIF was effective but nasal intolerance with nasal bleeding, stuffiness, and dryness developed after 2 weeks in up to 40% of patients [181,182]. This reduced effectiveness resulted in two randomized trials of shorter term therapy. In the study by Hayden et al., healthy family members from 60 families were randomly allocated to receive interferon intranasally at 5 x 10⁶ IU or placebo daily for 7 days, beginning with 48 h of onset of cold symptoms [183]. During the initial 8 days, the incidence of respiratory illness was significantly reduced by 39% in the interferon group (P = 0.02). Similarly, among those with culture-proven rhinovirus infections, the incidence in family members receiving interferon was reduced by 79% (P = 0.02). During the 2-week period, starting at the beginning of treatment, rhinovirus colds developed in only 1.3% of those receiving interferon versus 15.1% receiving placebo (P = 0.003). Almost twice the number of interferon users developed blood-tinged mucus or nasal bleeding (13.6% vs 7.7%; P = 0.04) but these and other symptoms were much less frequent than described in studies of longer administration. Among families who used the interferon, there was no evidence of cumulative nasal toxicity if repeated use occurred.

The second larger study was of similar design and used the same dose and duration of αIF [184]. This study demonstrated a 41% reduction in respiratory illness overall and an 86% reduction in rhinovirus
infection. Again, the rates of nasal bleeding were comparable to the previous study. No efficacy was shown involving infections or symptoms not associated with rhinoviruses. Therefore, at this time, evidence does not support the effectiveness of this approach in influenza, coronavirus, or other causes of viral upper respiratory infection. While suppression or prevention of rhinovirus infection may be cost-effective, a much greater impact may be achieved if other studies of other doses and schedules can show protection against influenza. A detailed cost analysis study of rhinovirus infection prophylaxis is also lacking and necessary.

Interferon and viral hepatitides

One of several human viral infections against which interferon was tested in the early 1970s was hepatitis B infection [185,186]. At that time, interferon was available as a relatively crude preparation from virally-stimulated human blood buffy coats [187]. In 1976, Greenberg et al. reported the first experience of treating patients with chronic active hepatitis due to hepatitis B infection with interferon [186]. This anecdotal report described a reproducible fall in Dane particle-associated DNA and DNA polymerase activity, as well as core antigen levels in three patients with high levels of circulating Dane particle markers. The suppression was dependent on the duration of interferon administration. Long-term (> 1 month) administration was also associated with e antigen elimination and surface antigen suppression. While no effect on the chronic liver disease was found, these results were encouraging, particularly in the suggestion that infectivity may be suppressed or abrogated.

With the advent of recombinant αIF, a small randomized trial was reported to show elimination of e antigen in one-third of patients treated for 4 months [188]. A subsequent randomized trial was carried out to test the efficacy of interferon alpha-2b as well as to test any added efficacy associated with a 6-week course of prednisone prior to antiviral therapy [189]. One-hundred-and-sixty-nine patients were randomly assigned to one of four treatments: (1) prednisone 60 mg daily tapering over 6 weeks followed by interferon alpha-2b 5 x 10^6 units daily for 16 weeks; (2) placebo followed by interferon as in (1); (3) placebo followed by interferon 1 x 10^6 units daily for 16 weeks; or (4) observation alone. The primary objective was to test the efficacy of interferon; and the secondary objective the efficacy of adding prednisone. No estimated sample size was given, nor were the accepted levels of type I and type II errors. However, despite a small number of patients per group, the disappearance of markers of infection (i.e., e antigen and viral DNA) was significantly more frequent in the higher dose interferon arms, with or without prednisone. Furthermore, signs of hepatitis such as periportal necrosis improved (P = 0.03) and liver function tests normalized in 87% of responding patients. In short, over one-third of patients had histological and biochemical evidence of remission from viral hepatitis B at this dose and schedule of interferon. The lower dose was not effective. Patients with lower levels of hepatitis B viral DNA in their serum had a greater likelihood of response. Longer follow-up will be needed to determine if long-term remissions can be achieved (91% of patients in this study were followed for 1 year) and whether or not the incidence of hepatocellular carcinoma is reduced. Also, better therapy is needed for those with high circulating levels of viral DNA.

Two recent randomized trials tested interferon alpha against chronic hepatitis C. In the smaller trials, Bisceglie et al. randomized 41 patients with chronic hepatitis C to receive 2 x 10^6 units subcutaneously three times per week for 6 months or placebo [190]. Samples of serum and tissue were analyzed and results were compared using a two-sample t-test and a two-sample Wilcoxon test. Significant improvements in liver function and histological tests were seen in interferon-treated compared to placebo-treated patients. Serological complete remission occurred in 48% of interferon-treated patients but by 6–12 months after therapy, only two of these ten patients still had normal liver function values. Therefore, the benefit was temporary and short-lived.

The larger trial randomized 166 patients to one of two doses of interferon alpha (3 x 10^6 units versus 1 x 10^6 units) three times weekly for 24 weeks or no treatment [191]. Thus, nearly three times as many patients were treated per arm. Primary outcomes included serological and histological evidence of remission and relapse rates. After the 6-month treat-
ment period, a significant proportion of patients receiving the high \( P < 0.001 \) or low \( P < 0.02 \) dose of interferon entered a serological complete or near complete remission compared to control patients. A higher proportion of high-dose patients had a complete remission when compared to low-dose patients \( (85\% \text{ vs } 56\%) \). Again, however, relapse occurred within 6 months of completing therapy in 51\% and 44\% of patients receiving high and low-dose interferon, respectively.

As with hepatitis B, the results are encouraging but not yet definitive. Improvements in survival and quality of life must be pursued in future trials.

The treatment of HIV infection with BRMs

The treatment of HIV infections with CSFs, antidiotypic antibodies (AIA), and IVIG has already been discussed. However, other strategies are also being tested for this devastating disease. Lane et al. randomly allocated 34 patients with asymptomatic HIV infection (CD4 counts \( < 400 \text{ cells/mm}^3 \), positive peripheral blood cultures for HIV, or p24 antigenemia) to receive \( \alpha \IF 35 \times 10^6 \) units daily for up to 12 weeks or placebo [192]. Despite this small sample size, 7 of 17 patients receiving interferon who were HIV positive became HIV negative compared to two patients (13\%) receiving placebo \( (P = 0.05) \). However, 35\% of interferon-treated patients stopped treatment due to toxicity, leaving an average daily dose of \( 17.5 \times 10^6 \) units over the study group. Granulocytopenia and elevated liver enzymes were noted in addition to the usual flu-like symptoms. Despite this, during a follow-up period ranging from 5 to 33 months, no patients receiving interferon had developed AIDS-related opportunistic infection compared to 5 placebo-treated patients \( (P = 0.02) \). These results show that interferon has activity against HIV infection but at doses not well tolerated by these patients. A similar problem is evident for the treatment of AIDS-related Kaposi's sarcoma with interferon [193]. Carter et al. have demonstrated clinical and immunologic improvement in AIDS patients using amplitgen, a double-stranded RNA interferon inducer [194]. Much more work needs to be done to find the effective dose and schedule of \( \alpha IF \), either alone or, more likely, in combination with other agents. One non-randomized trial of zidovudine and interferon \( \alpha \) suggested a greater tolerance of lower doses of interferon, depending on the dose of zidovudine, with evidence of antiviral activity [195].

One vaccine strategy for HIV infection using AIA has been already mentioned. Other strategies focus on the delivery and recognition of natural or synthetic HIV-specific antigen. Early studies have found poor recognition of these antigens by the immune system when delivered alone.

Attempts to favourably modify these immune responses have included the use of whole-killed virus [196] and antigen–vaccinia constructs [197]. The latter involve the combining of vaccinia virus with HIV antigens in a vaccine in order to improve the recognition and immune response to HIV antigens. This example of biological modification is also being used as a strategy in tumour vaccine development [198]. While some primate studies have suggested that some vaccines may protect against HIV infection [199], much work is necessary before comparative human trials can be designed and implemented.

Serum with high anti-HIV titres and monoclonal antibodies are being tested as passive serotherapy. Uncontrolled trials of the former have documented remission of p24 antigenemia, symptomatic improvement, and loss of culturable HIV from blood [200,201]. Clinical trials of HIV monoclonal antibodies (MOAb) can not be done until MOAb with greater affinity and those directed against conserved epitopes can be developed in order to overcome the genetic fluctuation of HIV strains [202]. Other molecules which may be useful as passive therapy due to their ability to bind and neutralize HIV include genetically engineered CD4 protein [203] and conjugates of CD4 such as CD4–IgG constant region [204] and CD4–pseudomonas enterotoxin [205]. The former could also be used to bind to HIV-infected cells; CD4 would bind to HIV surface antigens and cell killing could be mediated by complement or antibody-mediated cytotoxicity.

Besides interferon, other immunomodulating drugs are being tested including thymic hormones, some of which have demonstrated immunorestoration but no clinical benefit thus far [206,207] and chemical immunomodulators. The latter include nucleic acid analogs (isoprinosine), thiols (diethyl-dithiocarbamate, DTC), imidazoles, and cyanoaziridine (Azimexon). Isoprinosine has demonstrated
improved cell-mediated immunity, symptomatic improvement, and fewer infections in HIV patients [208]. DTC has been tested in randomized trials with amelioration of symptoms, reduction in infections and improved survival demonstrated, among other benefits [209,210]. It appears particularly promising in patients at advanced stages of AIDS [210]. Finally, Azimexon has undergone preliminary human trials and has been associated with restoration and symptom relief [211].

Non-conventional therapies as BRMs against infections

The use of traditional Chinese treatments as BRMs has been recently reviewed [9]. There is experimental evidence that some of these preparations can reduce the symptoms of sepsis induced by LPS administration [212]. Oral administration of any of three traditional preparations for 2 weeks prior to ip instillation of \textit{P. aeruginosa} in mice resulted in improved survival, though statistical testing of the data was not reported [9]. \textit{In vitro} studies of macrophages from Shosaiko-to (a traditional preparation) - primed mice showed enhanced chemiluminescence and greater numbers of splenic macrophages compared to controls [213]. These, and other studies, have demonstrated other increases in immune responsiveness, including antibody responses and increased phagocytosis of stimulated macrophages [214]. Active components seem to be found in crude herbal components such as Bupleuri radix and Angelica radix. The former contains pharmacologically active glycosides with anti-inflammatory and immune-modulating properties similar to corticosteroids [215]. These and other preparations are being actively investigated and tested in Japan for their therapeutic potential in cancer and the infectious diseases.

References

1 Oldham RK. Biological response modifiers. J Natl Cancer Inst 1983;70:789–796.
2 Coley WB. The treatment of inoperable sarcoma with the mixed toxins of erysipelas and Bacillus prodigiosus. Immediate and final results in 140 cases. J Am Med Assoc 1898;31:389–395, 456–465.
3 Jaeckle KA, Mittelman A, Hill FH. Phase II trial of \textit{Serratia marcescens} extract in recurrent malignant astrocytoma. J Clin Oncol 1990;8:1408–1418.
4 Kohler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. Nature (Lond.) 1975;256:495–497.
5 Quesada JR, Hawkins M, Horning S et al. Cooperative phase I-II study of recombinant DNA-produced leukocyte interferon (clone A) in metastatic breast cancer, malignant lymphoma, and multiple myeloma. Am J Med 1984;77:427–432.
6 Dinarello CA. Interleukin-1 and the pathogenesis of the acute-phase response. N Engl J Med 1984;311:1413–1418.
7 Ruef C, Coleman DL. Granulocyte-macrophage colony-stimulating factor: pleotropic cytokine with potential clinical usefulness. Rev Infect Dis 1990;12:41–62.
8 Rusthoven J. The potential role of recombinant hematopoietic colony-stimulating factors in preventing infections in the immunocompromised host. Can J Infect Dis 1991;2:74–88.
9 Haranaka K. Traditional Chinese medicines as biological response modifiers. Mol Biother 1989;1:175–179.
10 Bone RC. The pathogenesis of sepsis. Ann Intern Med 1991;115:457–469.
11 Sternberg EM, moderator. The stress response and the regulation of inflammatory disease. Ann Intern Med 1992;117:854–866.
12 Dunn HA, Powell ML, Meitin C, Small PA Jr. Virus infection as a stressor: the influenza virus elevates plasma concentrations of corticosterone, and brain concentrations of MHPG and tryptophan. Physiol Behav 1989;45:591–594.
13 Edwards CK 3rd, Yunger LM, Lorence RM, Dantzer R, Kelley KW. The pituitary gland is required for protection against lethal effects of \textit{Salmonella typhimurium}. Proc Natl Acad Sci 1991;88:2274–2277.
14 Catania A, Manfredi MG, Airaghi I, Vivirito MC, Milazzo F, Zanussi C. Evidence of impairment of the immune-adrenal circuit in patients with acquired immunodeficiency syndrome. Horm Metab Res 1990;22:597–598.
15 Wilder R. Mechanisms of neuroendocrine effects on inflammation and the immune response, pp. 860, 861. In: Sternberg EM, moderator. The stress response and the regulation of inflammatory disease. Ann Intern Med 1992;117:854–866.
16 Tazi A, Nioche S, Chastre J, Smiejan JM, Hance AJ. Spontaneous release of granulocyte colony-stimulating factor (G-CSF) by alveolar macrophages in the course of bacterial pneumonia and sarcoidosis: endotoxin-dependent and exotoxin-independent G-CSF release by cells recovered by bronchoalveolar lavage. Am J Respir Cell Mol Biol 1991;4:140–147.
17 Roilides E, Walsh TJ, Pizzo PA, Rubin M. Granulocyte colony-stimulating factor enhances the phagocytic and bac-
tericidal activity of normal and defective human neutrophils. J Infect Dis 1991;163:579–583.
18. Nelson S, Bagby G, Andersen J, Shellito J, Summer W. Intratracheal granulocyte colony-stimulating factor enhances systemic and pulmonary host defenses. Am Rev Respir Dis 1991;143:S398.
19. Petrak RA, Balk RA, Bone RC. Prostaglandins, cyclo-oxygenase inhibitors, and thromboxane synthetase inhibitors in the pathogenesis of multiple systems organ failure. Crit Care Clin 1989;5:303–314.
20. Balk RA, Jacobs RF, Tryka F, Townsend JW, Walls RC, Bone RC. Effects of ibuprofen on neutrophil function and acute lung injury in canine endotoxin shock. Crit Care Clin 1988;16:1121–1127.
21. Slababy MR, Aggarwal BB, Rinderknect E, Swedersky LP, Finkle BS, Palladino MA Jr. Activation of human polymorphonuclear neutrophil functions by interferon-gamma and tumour necrosis factor. J Immunol 1985;135:2069–2073.
22. Lindemann A, Herrmann F, Oster W et al. Hematologic effects of recombinant human granulocyte colony-stimulating factor in patients with malignancy. Blood 1989;74:2644–2651.
23. Beutler B, Kronchin N, Milsark IW, Luedke C, Cerami A. Control of cachectin (tumour necrosis factor) synthesis: mechanisms of endotoxin resistance. Science 1986;232:977–980.
24. Dinarello CA, Cannon LG, Wolff SM. New concepts on the pathogenesis of fever. Rev Infect Dis 1988;10:168–189.
25. Butler LD, Luyman NK, Cain RL et al. Interleukin 1-induced pathophysiology: induction of cytokines, development of histopathologic changes, and immunopharmacologic intervention. Clin Immunol Immunopathol 1989;53:400–421.
26. Zuckerman SH, Shelhaas J, Butler LD. Differential regulation of lipopolysaccharide-induced interleukin 1 and tumour necrosis factor synthesis: the effects of endogenous glucocorticosteroids and the role of pituitary-adrenal access. Eur J Immunol 1989;19:301–305.
27. Lefer AM. Induction of tissue injury and altered cardiovascular performance by platelet-activating factor: relevance to multiple systems organ failure. Crit Care Clin 1989;5:331–351.
28. Utsuml K, Takai Y, Tada T et al. Enhanced production of IL-6 in tumour-bearing mice and determination of cells responsible for its augmented production. J Immunol 1990;145:397–403.
29. Vane JR, Anggard EE, Botting RM. Regulatory functions of the vascular endothelium. N Engl J Med 1990;323:27–36.
30. Dinerman JL, Mehta JL. Endothelial, platelet and leukocyte interactions in ischemic heart disease: insights into potential mechanisms and their clinical relevance. J Am Coll Cardiol 1990;16:207–222.
31. Deitch EA. Multiple organ failure: pathophysiology and potential future therapy. Ann Surg 1992;216:117–131.
32. Arai K, Lee F, Miyajima A et al. Cytokines: coordinators of immune and inflammatory responses. Annu Rev Biochem 1990;59:783–836.
33. Crawford J, Ozer H, Stoller R et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small cell lung cancer. N Engl J Med 1991;325:164–170.
34. Nemunaitis J, Rabinowse SN, Singer JW et al. Recombinant granulocyte-macrophage colony-stimulating factor after autologous bone marrow transplantation for lymphoid cancer. N Engl J Med 1991;324:1773–1778.
35. Sheridan WP, Morstyn G, Wolfe M et al. Granulocyte colony-stimulating factor and neutrophil recovery after high-dose chemotherapy and autologous bone marrow transplantation. Lancet 1989;2:891–895.
36. Gianni AM, Siena S, Bregni M et al. Granulocyte-macrophage colony-stimulating factor to harvest circulating hematopoietic stem cells for autotransplantation. Lancet 1989;2:580–585.
37. Sheridan WP, Begley CG, Juttner CA et al. Effective peripheral-blood progenitor cells mobilized by filgrastin (G-CSF) on platelet recovery after high-dose chemotherapy. Lancet 1992;339:640–644.
38. Dale DC, Hammond WP, Gabrilove J et al. Long-term treatment of severe chronic neutropenia with recombinant human granulocyte factor (r-metHuG-CSF). Blood 1990;76(suppl 1):139. abstract.
39. Hammond WP, Price TH, Souza LM, Dale DC. Treatment of cyclic neutropenia with granulocyte colony-stimulating factor. N Engl J Med 1989;320:1306–1311.
40. Migliaccio AR, Migliaccio G, Dale DC, Hammond WP. Hematopoietic progenitors in cyclic neutropenia: the effect of granulocyte colony-stimulating factor in vivo. Blood 1990;75:1951–1959.
41. Miles SA, Mitsuyasu RT, Morano J et al. Combined therapy with recombinant granulocyte colony-stimulating factor and erythropoietin decreases hematologic toxicity from zidovudine. Blood 1991;77:2109–2117.
42. Pluda JM, Yarchoan R, Smith PD et al. Subcutaneous recombinant granulocyte macrophage colony-stimulating factor used as a single agent and in an alternating regimen with azidothymidine in leukopenic patients with severe human immunodeficiency virus infection. Blood 1990;76:463–472.
43. Perno CF, Yarchoan R, Cooney DA et al. Replication of human immunodeficiency virus in monocytes: granulocytes/macrophage colony-stimulating factor (GM-CSF) potentiates viral production yet enhances the antiviral effect mediated by 3'azido-2',3'-dideoxythymidine (AZT) and other dideoxynucleoside congeners of thymidine. J Exp Med 1989;169:933–951.
44. Nelson S. The effects of thermal injury on systemic and pulmonary host defenses. Crit Care Rep 1991;2:241–253.
45. Mooney DP, Gamelli RL, O'Reilly M, Hebert JC. Recombinant human granulocyte colony-stimulating factor and burn Pseudomonas wound sepsis. Arch Surg 1988;123:1353–1357.
238

46 Silver GM, Gamelli RL, O'Reilly M. The beneficial effect of granulocyte colony-stimulating factor (G-CSF) in combination with gentamycin on survival after Pseudomonas burn wound infection. Surgery 1989;106:452–456.

47 Cairo MS, Mauss D, Kommareddy S et al. Prophylactic or simultaneous administration of recombinant human granulocyte colony-stimulating factor in the treatment of group B streptococcal sepsis in neonatal rats. Pediatr Res 1990;27:612–616.

48 O'Reilly M, Silver GM, Greenhalgh D, Gamelli RL, Davis JH, Hebert JC. Treatment of intra-abdominal infection with granulocyte colony-stimulating factor. J Trauma 1992;33:679–682.

49 Hebert JC, O'Reilly M, Gamelli RL. Protective effect of recombinant human granulocyte colony-stimulating factor against pneumococcal infections in splenectomized mice. Arch Surg 1990;125:1075–1078.

50 Nelson S, Summer W, Bagby G et al. Granulocyte colony-stimulating factor enhances pulmonary host defences in normal and ethanol-treated rats. J Infect Dis 1991;164:901–906.

51 Silberstein DS, David JR. The regulation of human eosinophil function by cytokines. Immunol Today 1987;8:380–384.

52 Cheers C, Haigh AM, Kelso A et al. Production of colony-stimulating factors during infection: separate determinants of macrophage-, granulocyte-, granulocyte-macrophage-, and multi-CSF's. Infect Immun 1988;56:247–251.

53 Antman KS, Griffin JD, Elias A. Effect of recombinant human granulocyte-macrophage colony-stimulating factor on chemotherapy-induced myelosuppression. N Engl J Med 1988;319:593–598.

54 Nelson S, Mason C, Bagby G et al. Effect of murine recombinant granulocyte-macrophage colony-stimulating factor on lipopolysaccharide-induced tumour necrosis factor. Am Rev Respir Dis 1990;141:S:677.

55 Sisson SD, Dinarello CA. Production of interleukin-1 alpha, interleukin-1 beta, and tumour necrosis factor by human mononuclear cells stimulated with granulocyte-macrophage colony-stimulating factor. Blood 1988;72:1368–1374.

56 Atkins E. Pathogenesis of fever. Physiol Rev 1960;40:580–646.

57 Saklatvala J, Sarfield SJ, Townsend Y. Pig interleukin-1: purification of two immunologically different leukocyte proteins that cause cartilage resorption, lymphocyte activation, and fever. J Exp Med 1985;162:1208–1222.

58 Dewhirst FE, Stashenko PP, Mole JE, Tsurumachi T. Purification and partial sequence of human osteoclast-activating factor: identity with interleukin-1 beta. J Immunol 1985;135:2562–2568.

59 Moore MA, Warren DJ. Synergy of interleukin-1 and granulocyte colony-stimulating factor in vivo stimulation of stem-cell recovery and hematopoietic regeneration following 5-fluorouracil treatment of mice. Proc Natl Acad Sci USA 1987;84:7134–7138.

60 Mori S, Goto F, Goto K et al. Cloning and sequence analysis of cDNA for lymphocyte proliferation potentiating factor of rabbit neutrophils: identification as rabbit interleukin-1b. Biochem Biophys Res Comm 1988;150:1237–1243.

61 Fryling C, Dombalagian M, Burgess W et al. Purification and characterization of tumour inhibitory factor-2: its identity to interleukin-1. Cancer Res 1989;49:3333–3337.

62 Dinarello CA. Interleukin-1 and interleukin-1 antagonism. Blood 1991;77:1627–1652.

63 Fibbe WE, Schafsma R, Falkenburg JHF, Willemze R. The biological activities of interleukin-1. Blut 1989;59:147–156.

64 Dinarello CA, Ikejima T, Warner SJ et al. Interleukin-1 induces interleukin-1. Induction of circulating interleukin-1 in rabbits in vivo and in human mononuclear cells in vitro. J Immunol 1987;139:1902–1910.

65 Warner SJC, Auger KR, Libby P. Interleukin-1 induces interleukin-1. II. Interleukin-1 induces production of interleukin-1 by adult human vascular endothelial cells in vitro. J Immunol 1987;139:1911–1917.

66 Sisson SD, Dinarello CA. Production of interleukin-1 alpha, interleukin-1 beta and tumour necrosis factor by human mononuclear cells stimulated with granulocyte-macrophage colony-stimulating factor. Blood 1990;75:1895–1896.

67 Dinarello CA, Cannon JG, Wolff SM et al. Tumour necrosis factor ( cachectin) is an endogenous pyrogen and induces production of interleukin-1. J Exp Med 1986;163:1433–1450.

68 Ghezzi P, Dinarello CA. IL-1 induces IL-1. III. Specific inhibition of IL-1 production by IFN-gamma. J Immunol 1988;140:4238–4244.

69 Moore KW, Vieira P, Fiorentino DF et al. Homology of cytokine synthesis inhibitory factor (IL-10) to the Epstein-Barr virus gene BCRFI. Science 1990;248:1230–1234.

70 Smith J, Urba W, Steis R et al. Interleukin-1 alpha: results of a phase I toxicity and immunomodulatory trial. Am Soc Clin Oncol 1990;9:717.

71 Tewari A, Buhles WC Jr, Starnes HF Jr. Preliminary report: effects of interleukin-1 on platelet counts. Lancet 1990;336:712–714.

72 Neta R, Douches SD, Oppenheim JJ. Preliminary analysis of the effect of interleukin-1 on platelet counts. Lancet 1990;336:712–714.

73 Moore KW, Vieira P, Fiorentino DF et al. Homology of cytokine synthesis inhibitory factor (IL-10) to the Epstein-Barr virus gene BCRFI. Science 1990;248:1230–1234.

74 Van der Meer JWM, Barza M, Wolff SM, Dinarello CA. A low dose of recombinant interleukin-1 protects mice from lethal Gram-negative infection. Proc Natl Acad Sci USA 1988;85:1620–1623.

75 Fibbe WE, Falkenburg JHF, Schafsma MR, Willemze R. The hematopoietic activities of interleukin-1. Biotherapy 1989;1:263–271.
76 McNiece I, Langely K, Zsebo K. Recombinant human stem cell factor synergizes with CSF's and EPO to stimulate colony formulation of myeloid and erythroid cells. Blood 1990;76:154A (Abstr suppl).
77 Neta R, Sztein MB, Oppenheim JJ et al. The in vivo effects of interleukin-1. Bone marrow cells are induced to cycle after administration of interleukin-1. J Immunol 1987;139:1861–1866.
78 Gasparetto C, Laver J, Abboud M et al. Effect of interleukin-1 on hematopoietic progenitors: evidence of stimulatory and inhibitory activities in a primate model. Blood 1989;74:547–550.
79 Wallach D, Holtmann H, Engelmann H, Nophar Y. Sensitization and desensitization to lethal effects of tumour necrosis factor and IL-1. J Immunol 1988;140:2994–2999.
80 Ye K, Koch KC, Clark BD, Dinarello CA. Interleukin-1 beta down regulates gene and surface expression of interleukin-1 receptor type I by destabilizing its mRNA whereas interleukin-2 increases its expression. Immunology 1992;75:427–434.
81 Mrosovsky N, Molony LA, Conn CA, Kluger MJ. Anorectic effects of interleukin-1 in the rat. Am J Physiol 1989;257:R1315.
82 Gershenwald JE, Fong YM, Fahey TJ III et al. Interleukin-1 receptor blockade attenuates the host inflammatory response. Proc Natl Acad Sci USA 1990;87:4966–4970.
83 Okusawa S, Gelfand JA, Ikejima T et al. Interleukin-1 inhibits colony formulation of myeloid and erythroid cells. Blood 1989;76:154a (Abstr suppl).
84 Rothenberg EV, Diamond RA, Pepper KA, Yang JA. IL-2 inducibility in T cells before T cell receptor expression. J Clin Invest 1988;81:1162–1172.
85 Kurt-Jones EA, Beller DI, Mizel SB et al. Identification of a membrane-associated interleukin-1 in macrophages. Proc Natl Acad Sci USA 1985;82:1204–1208.
86 Fong Y, Tracey KJ, Moldawer LL et al. Antibodies to cachectin/tumour necrosis factor reduce interleukin-1 beta and interleukin-6 appearance during lethal bacteremia. J Exp Med 1989;170:1627–1633.
87 Neta R, Oppenheim JJ, Douches SD. Interdependence of radioprotective effects of human recombinant interleukin-1 alpha, tumour necrosis factor alpha, granulocyte colony-stimulating factor, and murine recombinant granulocyte-macrophage colony stimulating factor. J Immunol 1988;140:108–111.
88 Chantry D, Turner M, Abney E, Feldman M. Modulation of cytokine production by transforming growth factor-beta. J Immunol 1989;142:40–95.
89 Moreb J, Zucali JR, Weiner RS. The role of interleukin-3 and interleukin-6 and the protection from 4-hydroperoxy cyclophosphamide and the proliferation of early human hematopoietic progenitor cells. Exp Hematol 1989;17:1022–1027.
90 Dinarello CA, Rosenwasser LJ, Wolff SM. Demonstration of circulating suppressor factor of thymocyte proliferation during endotoxin fever in humans. J Immunol 1981;127:2517–2519.
91 Liao Z, Grimshaw RS, Rosenstreich DL. Identification of a specific interleukin-1 inhibitor in the urine of febrile patients. J Exp Med 1984;159:126–136.
92 Seekinger P, Dayer JM. Interleukin-1 inhibitors. Ann Inst Pasteur Immunol 1987;138:486–488.
93 Balavoine JF, De Rochemontez B, Williamson K et al. Prostaglandin E2 and collagenase production by fibroblasts and synovial cells is regulated by urine-derived human interleukin-1 and inhibitor(s). J Clin Invest 1986;78:1120–1124.
94 Ohlsson K, Bjork P, Bergenfeldt M et al. Interleukin-1 receptor antagonist reduces mortality from endotoxin shock. Nature 1990;348:550–552.
95 Cominelli F, Nast CC, Clark BD et al. Interleukin-1 gene expression, synthesis and effective specific IL-1 receptor blockade in rabbit immune complex colitis. J Clin Invest 1990;86:972–980.
96 Ziegler EJ, McCutchan JA, Fierer J et al. Treatment of Gram-negative bacteremia and shock with human antisera to a mutant Escherichia coli. N Engl J Med 1982;307:1225–1230.
97 Baumgartner J-D, Glauser MP, McCutchan JA et al. Prevention of Gram-negative shock and death in surgical patients by antibody to endotoxin core glycolipid. Lancet 1985;2:59–65.
98 Cornelissen JJ, Van Kessel CP, Brouwer E, Kraaijveeld CA, Verhoef J. Inhibition of lipid A-specific monoclonal antibodies by priming of human polymorphonuclear leukocytes by endotoxin. J Med Microbiol 1991;34:233–238.
99 Burd RS, Cody CS, Raymond CS, Dunn DL. Anti-endotoxin monoclonal antibodies protect by enhancing bacterial and endotoxin clearance. Arch Surg 1993;128:145–150.
100 Krieger JJ, Fletcher RC, Siegel SA et al. Human anti-endotoxin antibody HA-1A mediates complement-dependent binding of Escherichia coli L lipopolysaccharide to complement receptor type I of human erythrocytes and neutrophils. J Infect Dis 1993;167:865–875.
101 Cody CS, Burd RS, Mayoral JL, Dunn DL. Protective anti-lipopolysaccharide monoclonal antibodies inhibits tumour necrosis factor production. J Surg Res 1992;52:314–319.
102 Wortel CH, van der Mohlen MA, van Deventer SJ et al. Effectiveness of a human monoclonal anti-endotoxin antibody (HA-1A) in Gram-negative sepsis: relationship to endotoxin and cytokine levels. J Infect Dis 1992;166:1367–1374.
103 McCabe WR, De Maria A Jr, Berberich H, Johns MA. Immunization with rough mutants of Salmonella minnesota: protective activity of IgM and IgG antibody to the R595 (RE chemotype) mutant. J Infect Dis 1988;158:291–300.
104 Teng NNH, Kaplan HS, Hebert JM et al. Protection against Gram-negative bacteremia and endotoxia with human monoclonal IgM antibodies. Proc Natl Acad Sci USA 1985;82:1790–1794.
Wolff SM. Monoclonal antibodies and the treatment of Gram-negative bacteria. Infect Immun 1993;61:512–519.

Ziegler EJ, Teng NNH, Douglas H et al. Treatment of pseudomonas bacteremia in neutropenic rabbits with human monoclonal IgM antibody against E. coli lipid A. Clin Res 1987;35:619A. abstract.

Ziegler EJ. Protective antibody to endotoxin core: the emperor's new clothes? J Infect Dis 1988;158:286–290.

Quezado ZM, Natanson C, Alling DW et al. A controlled trial of HA-1A in a canine model of Gram-negative septic shock. JAMA 1993;269:2221–2227.

Calandra T, Glauser MP, Schellekens J, Verhoef J. Treatment of Gram-negative septic shock with human IgG antibody to Escherichia coli J5: a prospective double-blind randomized trial. J Infect Dis 1988;158:312–319.

Khazaeli MB, Wheeler R, Teng N et al. Initial evaluation of a human immunoglobulin M monoclonal antibody (HA-1A) in humans. J Biol Response Mod 1990;9:178–184.

Fisher CJ Jr., Zimmerman J, Khazaeli MB et al. Initial evaluation of human monoclonal anti-lipid A antibody (HA-1A) in patients with sepsis syndrome. Crit Care Med 1990;18:1311–1315.

Ziegler EJ, Fisher CJ, Sprung CL et al. Treatment of Gram-negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin: a randomized, double-blind, placebo-controlled trial. N Engl J Med 1991;324:429–436.

Siegel JP, Stein KE, Zoon KC. Anti-endotoxin monoclonal antibodies. N Engl J Med 1992;326:107–116.

Fehr J, Hofmann V, Kappeler U. Transient reversal of thrombocytopenia in idiopathic thrombocytopenic purpura by high-dose intravenous gammaglobulin. N Engl J Med 1982;306:1254–1258.

Delfraissy JF, Tchernia G, Laurian Y et al. Suppressor cell function after intravenous gammaglobulin treatment in adult chronic idiopathic thrombocytopenic purpura. Br J Haematol 1985;60:315–322.

Bussel J, Pahwa S, Porges A et al. Correlation of in vitro antibody synthesis with outcome of intravenous gammaglobulin treatment of chronic idiopathic thrombocytopenic purpura. J Clin Immunol 1986;50–56.

Abidou MI, Wall H, Lindsay HB et al. Network theory in autoimmunity: in vitro suppression of serum anti-DNA antibody binding to DNA by antibody-ideotypic antibody in systemic lupus erythematosus. J Clin Invest 1981;67:1297–1304.

Bijsterbosch MK, Klaus GGB. Cross-linking of surface immunoglobulin and Fc receptors on B-lymphocytes inhibits stimulation of inositol phospholipid breakdown via the antigen receptors. J Exp Med 1985;162:1825–1836.

Hahn BH, Ebling RM. Suppression of murine lupus nephritis by administration of an anti-idiotype antibody of anti-DNA, J Immunol 1984;132:187–190.

Furusho K, Kamiya T, Nakano H et al. High-dose intravenous gamma-globulin for Kawasaki disease. Lancet 1984;2:1055–1058.

Newburger JW, Takahashi M, Burns JC et al. The treatment of Kawasaki syndrome with intravenous gammaglobulin. N Engl J Med 1984;315:341–347.

Henderson JW, Takahashi M, Burns JC et al. The treatment of Kawasaki syndrome with intravenous gammaglobulin. N Engl J Med 1984;315:341–347.

Greenman RE, Schein RM, Martin MA et al. A controlled clinical trial of E5 murine monoclonal IgM antibody to endotoxin in the treatment of Gram-negative sepsis. The XOMA Sepsis Study Group. JAMA 1991;324:486–487.

Tanio CP, Feldman HI. The HA-1A monoclonal antibody for Gram-negative sepsis (letter). N Engl J Med 1991;324:280.

Siegel SA, Evans ME, Pollack M et al. Antibiotics enhanced binding by human lipid A-reactive monoclonal antibody HA-1A to smooth Gram-negative bacteria. Infect Immun 1993;61:512–519.

Dublish KM, Glick HA, Reuben H, Eisenberg JM. Cost-effectiveness of HA-1A monoclonal antibody for Gram-negative sepsis. Economic assessment of a new therapeutic agent. JAMA 1991;266:3466–3471.

Greenman RL, Schein RM, Martin MA et al. A controlled clinical trial of E5 murine monoclonal IgM antibody to endotoxin in the treatment of Gram-negative sepsis. The XOMA Sepsis Study Group. JAMA 1991;324:1097–1102.

Romulo RL, Palardy JE, Opal SM. Efficacy of anti-endotoxin monoclonal antibody E5 alone or in combination with ciprofloxacin in neutropenic rats with Pseudomonas sepsis. J Infect Dis 1993;167:126–130.

Wenzel RP, Andriole VT, Bartlett JG et al. Antiendotoxin monoclonal antibodies for Gram-negative sepsis: guidelines from the IDSA. Clin Infect Dis 1992;14:973–976.

Intravenous immunoglobulin: prevention and treatment of disease. NIH Consensus Development Conference. Consensus statement, May 21–23, 1990. Vol. 8 No. 5. Bethesda, MD: Department of Health and Human Services, 1990.
Meyers JD, Leszczynski J, Zaia JA et al. Prevention of cytomegalovirus infection by cytomegalovirus immune globulin after marrow transplantation. Ann Intern Med 1983;98:442–446.

Bowden RA, Sayers M, Flourney M et al. Cytomegalovirus immune globulin and seronegative blood products to prevent primary cytomegalovirus infection after marrow transplantation. N Engl J Med 1986;314:1006–1010.

Emanuel D, Cunningham I, Jules-Elysee K et al. Cytomegalovirus pneumonia after bone marrow transplantation successfully treated with a combination of ganciclovir and high-dose intravenous immune globulin. Ann Intern Med 1988;109:777–782.

Read EC, Bowden RA, Dandliker PS et al. Treatment of cytomegalovirus pneumonia with ganciclovir and intravenous cytomegalovirus immunoglobulin in patients with bone marrow transplants. Ann Intern Med 1988;109:783–788.

Sullivan KM, Kopecky KJ, Jocom A et al. Immunomodulatory and antimicrobial efficacy of intravenous immune globulin in bone marrow transplantation. N Engl J Med 1990;323:705–712.

Snydman DR, Werner BG, Heinz-Lacey B et al. Use of cytomegalovirus immune globulin to prevent cytomegalovirus disease in renal-transplant recipients. N Engl J Med 1987;317:1049–1054.

Graneto D, Swift C, Steinmuller DR et al. Use of intravenous immunoglobulin prophylaxis for primary cytomegalovirus (CMV) infection post-living-related donor renal transplantation (abstract 10). Abstracts of the American Society of Transplant Physicians Annual Meeting, Chicago, 1988.

Lederman HM, Winkelstein JA. X-linked agammaglobulinemia: an analysis of 96 patients. Medicine (Baltimore) 1985;64:145–156.

Calvelli DA, Rubinstein A. Intravenous gammaglobulin in infant acquired immunodeficiency syndrome. Pediatr Infect Dis 1986;5:S207.

Siegel FP, Oleske J. Management of the acquired immune deficiency syndrome: is there a role for immune globulins? In: Morell A, Nydegger UE, eds. Clinical use of intravenous immunoglobulins. New York: Academic Press, 1986:387–394.

Schaad UB. The role of IVIG in pediatric HIV infection. In: Imbach P, ed. Immunotherapy with intravenous immunoglobulins. London: Academic Press, 1991:201–209.

The National Institute of Child Health and Human Development Intravenous Immunoglobulin Study Group. Intravenous immune globulin for the prevention of bacterial infections in children with symptomatic human immunodeficiency virus infection. N Engl J Med 1991;325:73–80.

Paryani SG, Arvin AM, Koropchak CM et al. Comparison of varicella-zoster antibody titers in patients given intravenous immune serum globulin or varicella-zoster immune globulin. J Pediatr 1984;105:200–205.

Stevens DA, Merigan TC. Zoster immune globulin prophylaxis of disseminated zoster in compromised hosts. Arch Intern Med 1980;140:52.

Hemming VG, Rodriguez W, Kim HW et al. Intravenous immunoglobulin treatment of respiratory syncytial virus infections in infants and young children. Antimicrob Agents Chemother 1987;31:1882–1886.

Crennan JM, Van Scoy RE, McKenna CH, Smith TF. Echovirus polyomysis in patients with hypogammaglobulinemia. Failure of high-dose intravenous gammaglobulin therapy and review of the literature. Am J Med 1986;81:35–42.

Tobi M, Straus SE. Chronic Epstein-Barr virus disease: a workshop held by the National Institute of Allergy and Infectious Diseases. Ann Intern Med 1985;103:951–952.

Lloyd A, Hickie I, Wakefield D et al. A double-blind placebo-controlled trial of intravenous immunoglobulin therapy in patients with chronic fatigue syndrome. Am J Med 1990;89:561–566.

Peterson PK, Shepard J, Macres M et al. A controlled trial of intravenous immunoglobulin G in chronic fatigue syndrome. Am J Med 1990;89:554–560.

Ammann AJ, Hong R. Disorders of the T-cell system. In: Stichem ER, ed. Immunologic disorders in infants and children, ed 3. Philadelphia: WB Saunders Co, 1989:257–315.

Sidropoulos D, Boehme U, Von Muralt G et al. Immunoglobulin supplementation in prevention or treatment of neonatal sepsis. Pediatr Infect Dis 1986;5:S193.

Haqee KN, Zaidi MH, Bahakim H. IgM-enriched intravenous immunoglobulin therapy in neonatal sepsis. Am J Dis Child 1988;142:1293–1296.

Munster AM, Hoagland HC, Pruitt BA Jr. The effect of thermal injury on serum immunoglobulins. Ann Surg 1970;172:965–969.

Wesley J, Fisher A, Fisher MW. Immunization against Pseudomonas in infection after thermal injury. J Infect Dis 1974;130:S152–S158.

Stone HH, Graber CD, Martin JD Jr., Kolb L. Evaluation of a gamma globulin for prophylaxis against burn sepsis. Surgery 1965;58:810–814.

Munster AM, Moran KT, Thupari J et al. Prophylactic intravenous immunoglobulin replacement in high-risk burn patients. J Burn Care Rehabil 1987;8:376–380.

Winnie JB, Cowan RG, Wade NA. Intravenous immune globulin treatment of pulmonary exacerbations in cystic fibrosis. J Pediatr 1989;114:309–314.

Van Wye JE, Collins MS, Baylor M et al. Pseudomonas hyperimmune globulin passive immunotherapy for pulmonary exacerbations of cystic fibrosis. Pediatr Pulmonol 1990;9:7–18.

Silverstein A. History of immunology. Antibodies and idiotypic regulation, 1899–1904. Cell Immunol 1986;99:507.

Kunkel HG, Mannik M, Williams RC. Individual antigenic specificity of isolated antibodies. Science 1963;140:1218–1219.
167 Jerne NK. Towards a network theory of the immune system. Ann Immunol (Paris) 1974;125C:373–389.

168 Nisonoff A, Lamoy E. Implications of the presence of an internal image of the antigen in anti-idiotypic antibodies; possible application to vaccine production. Clin Immunol Immunopathol 1981;21:397–406.

169 Roitt IM, Male DK, Guarnotta LD et al. Idiotypic networks and their possible exploitation for manipulation of the immune response. Lancet 1981;1:1041–1045.

170 Nisonoff A. Idiotypes: concepts and applications. J Immunol 1991;147:2429–2438.

171 Kennedy RC, Eichberg JW, Lanford RE, Dreismann JR. Anti-idiotypic antibody vaccine for type-B viral hepatitis in chimpanzees. Science 1986;232:220–223.

172 Thanavala YM, Roitt IM. Monoclonal anti-idiotypic antibodies as surrogates for hepatitis B surface antigen. Int Rev Immunol 1986;1:27–39.

173 Reagan KJ, Wunner WH, Wiktor TJ, Koprowski H. Anti-idiotypic antibodies induce neutralizing antibodies to rabies virus glycoprotein. J Virol 1983;48:660–666.

174 Gaulton GM, Greene MI. Idiotypic mimicry of viral receptors. Annu Rev Immunol 1986;4:253–280.

175 Rolf JM, Gauden HM, Tirrell SM, MacDonald AB, Eidels L. Anti-idiotypic antibodies that protect cells against the action of diphtheria toxin. Proc Natl Acad Sci USA 1989;86:2036.

176 Rimmelzwaan GF, Bunschoten EJ, Uytdehaag FG, Osterhaus AD. Monoclonal anti-idiotypic antibody vaccines against poliovirus, canine parvovirus and rabies virus. Methods Enzymol 1989;178:375–390.

177 Zaghrouni H, Goldstein D, Shah H et al. Induction of antibodies to the envelope protein of the human immundeficiency virus by immunization with monoclonal anti-idiotypes. Proc Natl Acad Sci USA 1991;88:5645–5649.

178 Merigan TC, Reed SE, Hall TS, Tyrrell DAJ. Inhibition of respiratory virus infection by locally applied interferon. Lancet 1973;1:563–567.

179 Scott GM, Phillips RJ, Wallace J, Guacci CL, Greiner J, Tyrrell DA. Prevention of rhinovirus colds by human interferon-alpha, from Escherichia coli. Lancet 1982;2:186–188.

180 Higgins PG, Phillips RJ, Scott GM, Wallace J, Bernhardt LL, Tyrrell DAJ. Intranasal interferon as protection against experimental respiratory Coronavirus virus infection in volunteers. Antimicrob Agents Chemother 1983;24:713–715.

181 Douglas RM, Albrecht JK, Miles HB et al. Intranasal interferon alpha-2 prophylaxis of natural respiratory infection. J Infect Dis 1985;151:731–736.

182 Hayden FG, Gwaltney JM Jr, Johns EM. Prophylactic efficacy and tolerance of low-dose intranasal interferon-alpha2 in natural respiratory viral infections. Antiviral Res 1985;5:111–116.

183 Hayden FG, Albrecht JK, Kaiser DL, Gwaltney JM Jr. Prevention of natural colds by contact prophylaxis with intranasal alpha2-interferon. N Engl J Med 1986;314:71–75.

184 Douglas RM, Moore BW, Miles HB et al. Prophylactic effi-
cacy of intranasal alpha2-interferon against rhinovirus in-
fecions in the family setting. N Engl J Med 1986;314:65–70.

185 Merigan TC, Jordan GW, Fried RP. Clinical utilization of exogenous human interferon. Antiviral Mechanisms (Perspectives in Virology. Vol 9). Edited by M Pollard. New York: Academic Press, 1975:249–264.

186 Greenberg HB, Pollard RB, Lutwick LI, Gregory PB, Robinson WS, Merigan TC. Effect of human leukocyte interferon on hepatitis B virus infection in patients with chronic active hepatitis. N Engl J Med 1976;295:517–522.

187 Jordan GW, Fried RP, Merigan TC. Administration of human leukocyte interferon in herpes zoster I safety circulating antiviral activity, and host responses to infection. J Infect Dis 1974;130:56–62.

188 Hoofnagle JH, Peters M, Mullen KD et al. Randomized, controlled trial of recombinant human alpha-interferon in patients with chronic hepatitis B. Gastroenterology 1988;95:1318–1325.

189 Perrillo RP, Schiff ER, Davis GL et al. A randomized, controlled trial of interferon alpha-2b alone and after prednisone withdrawal for the treatment of chronic hepatitis B. N Engl J Med 1990;323:295–301.

190 Bisceglie AM, Martin P, Kassianides C et al. Recombinant interferon alpha therapy for chronic hepatitis C. A randomized, double-blind, placebo-controlled trial. N Engl J Med 1989;321:1506–1510.

191 Davis GL, Balart LA, Schiff ER et al. Treatment of chronic hepatitis C with recombinant interferon alpha. A multicentre randomized, controlled trial. N Engl J Med 1989;321:1501–1506.

192 Lane HC, Davey V, Kovacs JA et al. Interferon-alpha in patients with asymptomatic human immundeficiency virus (HIV) infection. A randomized, placebo-controlled trial. Ann Intern Med 1990;112:805–811.

193 Krown SE, Gold JWM, Niedzwiecki D et al. Interferon-alpha with zidovudine: safety, tolerance, and clinical and virologic effects in patients with Kaposi's sarcoma associated with acquired immundeficiency syndrome (AIDS). Ann Intern Med 1990;112:812–821.

194 Carter WA, Brodsky I, Pellegrino MG et al. Clinical, immunological, and virological effects of ampligen, a mismatched double-stranded RNA, in patients with AIDS or AIDS-related complex. Lancet 1987;7:1286–1292.

195 Kovacs JA, Dayton L, Davey R et al. Combined zidovudine and interferon-alpha therapy in patients with Kaposi's sarcoma and acquired immundeficiency syndrome (AIDS). Ann Intern Med 1989;111:280–287.

196 Zagury D, Bernard J, Cheynier R et al. A group specific anamnestic immune reactive against AIDS. Nature 1988;332:728–734.

197 Zarling J, Morton W, Moran PA, McClure J, Kosowski SG, Hu SL. T-cell responses to human AIDS virus in macaques immunized with recombinant vaccinia virus. Nature 1986;323:344–346.

198 Furukawa K, Lotzova E, Freedman RS, Bowen JB, Edwards CL, Wharton JT. Effect of virus-modified tumour
cell extracts, autologous mononuclear cell infusions and interleukin-2 on oncolytic activity of effector cells of patients with advanced ovarian cancer. Cancer Immunol Immunother 1989;30:126–132.

199 Berman PW, Gregory TJ, Riddle L et al. Protection of chimpanzees from infection by HIV-1 after vaccination with recombinant glycoprotein gp 120 but not gp 160. Nature 1990;345:622–625.

200 Jackson GG, Rubenis M, Knigge M et al. Passive immunoneutralization of human immunodeficiency virus in patients with advanced AIDS. Lancet 1988;9:647–652.

201 Zolla-Pazner S, Pinter A, Mizuma H. Potential use of serotherapy in the prevention and treatment of infection with the human immunodeficiency virus. J Virol Meth 1987;17:45–53.

202 Javaherian K, Langlois AJ, McDanal C et al. Principle neutralizing domain of the human immunodeficiency virus type 1 envelope protein. Proc Natl Acad Sci USA 1989;86:6768–6772.

203 Smith DH, Bryn RA, Marsters SA, Gregory T, Groopman JE, Capon DJ. Blocking of HIV-1 infectivity by a soluble, secreted form of CD4 antigen. Science 1987;238:1704–1707.

204 Bryn RA, Mordenti J, Lucas C et al. Biological properties of a CD4 immunoadhesin. Nature 1990;344:667–670.

205 Ashorn P, Moss B, Weinstein JN et al. Elimination of infectious human immunodeficiency virus from human T-cell cultures, by synergistic action of CD4 pseudomonas exotoxin and reverse transcriptase inhibitors. Proc Natl Acad Sci USA 1990;87:1–5.

206 Barcellini W, Meroni PL, Frasca D et al. Effect of subcutaneous thymopentin treatment in drug addicts with persistent generalized lymphadenopathy. Clin Exp Immun 1987;67:537–543.

207 Silvestris F, Gernone A, Frassanito M, Dammacco F. Immunologic effect of long-term thymopentin treatment in patients with HIV-induced lymphadenopathy syndrome. J Lab Clin Med 1989;113:139–144.

208 Pedersen C, Sandstrom E, Petersen CS et al. The efficacy of inosine pranobex in preventing the acquired immunodeficiency syndrome in patients with human immunodeficiency virus infection. N Engl J Med 1990;322:1757–1763.

209 Reisinger EC, Kern P, Ernst M et al. Inhibition of HIV progression by ditiocarb. Lancet 1990;335:679–682.

210 Hersh EM, Brewton G, Abrams D et al. Ditiocarb sodium (diethyldithiocarbamate) therapy in patients with symptomatic HIV infection and AIDS. A randomized double-blind placebo-controlled multicentre study. J Am Med Assoc 1991;265:1538–1544.

211 Patt YZ, Hersh EM, Reuben JM, Claghorn L, Mavligit GM. A phase I study of intravenous azimexon therapy in human cancer. J Biol Resp Mod 1986;5:313–318.

212 Haranaka K, Satomi N, Sakurai A et al. Anti-tumor activities and tumor necrosis factor producibility of traditional Chinese medicines in crude drugs. Cancer Immunol Immunother 1985;20:1–5.

213 Satomi N, Sakurai A, Haranaka R, Haranaka K. Traditional Chinese medicines and drugs in relation to the host-defense mechanism. In: The influence of antibiotics on the host–parasite relationship. Berlin: Springer-Verlag 1988;77–86.

214 Kono H, Ohara M, Odajima S, Yamaguchi N. The effect of Saikosaponin on immune response. J Med Pharmacol Soc Wakan-Yaka 1985;2:85–89.

215 Iwama H, Amagaya, Ogihara Y. Studies of the combined use of steroid and Shosaiko-to, one of the Kanpohozai (Chinese traditional medicine), on pituitary adrenal cortical space axis function and immune responses. J Pharmacobiodyn 1986;9:189–196.