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HOST RESISTANCE TO BACTERIAL AND PARASITIC INFECTIONS

Humans and animals are continually being exposed to a variety of infectious agents, often become infected, but generally do not develop clinical disease. There are many factors that determine whether or not an infected host becomes ill; these include the virulence of the bacterium or parasite, the ability of the host defense mechanisms to control the infection, and exogenous or environmental conditions. The need to develop sensitive and reproducible experimental host resistance models to define impaired immunologic function following exposure to environmental chemicals or drugs has been recognized during the past few years.

Numerous studies have documented the complexity of the immune system of mammalian hosts. The immune response cannot simply be divided into a humoral and a cellular arm. There are multitudes of soluble factors and cell subpopulations, each with regulatory and modulatory capabilities. The complexity results' not only from the large number of distinctive components involved, but also as a consequence of the varied cooperative events that are required to complete an immunologic process. The immune system contains extensive redundancy, in that many individual responses may contribute significantly to host resistance. In some instances, the sum of many host defense activities is needed to achieve adequate protection from an infectious agent.

Key words: *bacteria, parasite, infections resistance, animals, immune response*

A number of infectious agents have evolved sophisticated mechanisms for avoiding the consequences of the immune response of the host. The mechanisms appear to play a major role in the success of the pathogen [3]. Antigenic mimicry refers to the ability of a pathogen to display host antigens on its surface and thereby masquerade as “self.” Certain microbes cleave immunoglobulins and coat themselves with immunoglobulin fragments such as Fab [11], or bind the Fc portion of immunoglobulin and expose Fab still capable of antigen recognition [38]. This enables the microbe both to mask its antigens and to present host antigens on its surface. Antigenic depletion is achieved by shedding antigens from the surface of the pathogen or by the capping and shedding of surface antigens [9]. Antigenic variation refers, to a periodic shift in surface antigens [10]. Immunologic subversion involves immunosuppression of humoral or cell-mediated responses. The pathogen may produce substances that are toxic to lymphocytes or other immunocompetent cells [12]. *Plasmodium* [42] and *Naegleria* [35] stimulate polyclonal antibody synthesis

(nonspecific) resulting in hypergammaglobulinemia. The impact of this immunologic diversion on host resistance has not been established.

Immunologic mechanisms involved in host resistance

There are numerous humoral and cellular responses that may contribute to the capability' of a host to defend against infection. These include antibody produced by B lymphocytes, cytotoxic T lymphocytes, natural killer cells, neutrophils and macrophages. There are subsets of T lymphocytes that carry out characteristic functions; Some subsets act as netper cells, while others suppress certain immune functions. There are numerous interactions between these components in addition to these individual components of host resistance. It is rare that a single component of the immune system is solely responsible for host resistance to a bacterial pathogen or parasite. Nevertheless, some components appear to be more important in host defense than others.

A vast literature relates immune impairment with altered host resistance. Although there is general agreement that severely depressed cell-mediated immunity or humoral immunity results in altered host susceptibility to infectious agents, there is no general agreement regarding the effects of subtle or chronic immunosuppression on host resistance [8].

Innate Resistance

Physical barriers prevent infectious agents from invading the host tissues. Skin, which is composed of many layers of specialized cells, is practically impermeable to pathogenic microbes. The keratinized dead cells on the outmost layer of the skin are shed continuously. Infectious agents that colonize the skin are disposed of continuously. The ciliated epithelial cells of the respiratory tract create a steady motion, carrying mucus and particles trapped in it toward the pharynx. Coughing and sneezing increase this exit transport. Saliva flushes the oral cavity and tears wash over the conjunctiva. The acidic nature of some areas of the host's body also contributes to host defenses. The skin is slightly acidic and the stomach contents are quite acidic. Stomach acidity kills most ingested microbes. Innate immunity eneompasses those responses to infectious agents that did not involve prior exposure. Phagocytosis of bacteria by polymorphonuclear leukocytes and macrophages is an important line of innate resistance. Exogenous factors that impair these innate host defense processes may alter the susceptibility of a host [31].

Acquired Humoral Immunity

Acquired immunity involves those responses to infectious agents that are dependent upon processes stimulated by prior exposure. In acquired humoral immunity, antibodies are produced in response to antigenic stimulation. Some antigens, especially those with repeating subunits such as *Escherichia coli* endotoxin, can stimulate B lymphocytes directly to synthesize and release antibody [1]. Most antigens elicit antibody production only with the assistance of T lymphocytes and macrophages. The type of immunoglobulin produced is a function of the type of antigen and the time after exposure. Generally IgM is the earliest immunoglobulin produced, followed by IgG. IgA is a secretory antibody often associated with the mucosa of the gastrointestinal tract and the respiratory tract. IgE is the antibody

responsible for immediate hypersensitivity reactions such as anaphylactic shock. The purpose of antibody is to recognize foreign substances such as microbes, and to assist in their elimination from the body. Binding of antibody to a pathogen or microbial toxin may by itself prevent injury to the host. Some antibody/antigen complexes bind complement, which eventually lyses the target cell. Antigen-coated pathogens are recognized effectively by macrophages, which phagocytize the microbe and kill it intracellularly.

Acquired Cell-Mediated Immunity

Cell-mediated immunity, which is directed against foreign cells such as bacteria and parasites, is dependent upon the activity of T lymphocytes. Killer T cells kill antigen bearing cells. Other T lymphocytes produce substances known as lymphokines that attract, immobilize or otherwise modulate the functions of macrophages, B lymphocytes and granulocytes [31]. These processes result in skin reactions with a delayed time course, as seen in contact allergies. The macrophage is the other key cell type involved in cell-mediated immunity. Macrophages are active in phagocytizing, processing, and presenting antigen to T lymphocytes or B lymphocytes. The "individual cells of the immune system, that is, the B lymphocytes, T lymphocytes, and macrophages, work in concert to protect a host from pathogens. There is overlap in their function which provides some margin of safety for the host [31].

Animal models to assess altered host resistance

In applying bacterial and parasitic infections in animal models to assess the toxicity of environmental chemicals and drugs, a number of concepts about host-parasite interactions need to be considered. Ideally, the model should simulate a prevalent human disease; the animal should be infected by a natural route; a low challenge level should be used so that the host's immune system is not overwhelmed; the disease course and pathogenesis should be similar to the corresponding disease of man; and the relevant host resistance factors should be similar to those in man. All of these criteria can be achieved only rarely but a model should satisfy as many of these conditions as possible. Mice are used predominantly because of convenience, cost, and recorded experience. The mouse is a good host because of the extensive studies on its immune system. The most useful parameters are mortality, survival time, and growth of the bacterium or parasite in target organs.

Bacterial infections may be conveniently divided into acute/purulent, chronic/ granulomatous, and toxigenic. Acute/purulent infections, as exemplified by *Streptococcus pneumoniae*, are characterized by short duration, acute course and the accumulation of polymorphonuclear leukocytes at sites of entry. Opsonizing antibodies exert protective effects, and as a rule the disease subsides after polymorphonuclear leukocytes and mononuclear phagocytes have phagocytized most infecting bacteria and killed them within phagolysosomes. Bacteria that cause acute, purulent infections are categorized as extracellular pathogens [15]. Chronic, granulomatous infections, as exemplified by *Listeria monocytogenes,* are characterized by cyclic systemic disease. These bacterial pathogens are also phagocytized by polymorphonuclear leukocytes and mononuclear phagocytes.

Phagocytosis of these organisms may be enhanced by specific antibodies and complement, as is the situation for extracellular pathogens. After phagocytosis, however, these bacteria survive within polymorphonuclear leukocytes, and at least initially also in mononuclear phagocytes. Bacteria that cause chronic granulomatous infections are categorized as facultative intracellular pathogens [37]. Facultative intracel elicit delayed hypersensitivity reactions and live bacteria are required to induce protective immunity [26]. The development of immunity to facultative intracellular bacteria requires the cooperation of two host cell types: specific T lymphocytes and mononuclear phagocytes. The tasks of T lymphocytes are to recruit and assemble mononuclear phagocytes for the formation of granulomatous lesions, and to activate the phagocytes for enhanced bactericidal activity [15]. This host defense process is referred to as cell-mediated immunity [39]. Cell-mediated immunity enhances the killing efficiency of the macrophage through lymphokines such as macrophage chemotactic factor, macrophage migration-inhibition factors and macrophage activation factor. Toxigenic infections result from the production of toxins by certain bacteria and require the production of specific antitoxins for their neutralization.

Potentially Useful Bacterial Models

The pathogenesis and immune responses to *Streptococcus pneumoniae* infection have been extensively characterized [20]. Recovery from infection depends on the complement system, induction of opsonizing antibody, phagocytosis, and intracellular destruction of the bacteria [2, 40]. This classic infection measures the function of B lymphocytes to produce the T- lymphocyte-independent antibody to the pneumococcal polysaccharide, as well as the functional capability of granulocytic, phagocytic cells.

The pathogenesis and immune responses to *Listeria monocytogenes* infection have been extensively characterized [33]. Recovery from infection depends upon specific sensitization of T lymphocytes that then activate macrophages for enhanced nonspecific bactericidal activity.

Host resistance can be assessed by mortality or by viable colony counts of the liver and spleen, which are the major sites for replication of the bacteria. The infection primarily assesses competency of T lymphocytes and macrophages.

Virulence of *Escherichia coli* strains in intraperitoneal infection of mice correlates well V with virulence in natural infections [41]. Mouse virulence is directly related to survival and multiplication in the peritoneal cavity, supporting production of large amounts of endgtoxin [28]. Phagocytosis can be enhanced by the presence of opsonins and complement in normal serum or specific antibody to *E. coli* K antigens [18]. In the later phases of infection, survival largely depends on the host's defense against the effects of endotoxin.

Potentially Useful Parasitic Models

Plasmodium berghei, an intracellular sporozoan parasite causing malaria in a variety of rodents, is potentially useful in immunotoxicity assessments. *Plasmodium herghei* produces a lethal malaria in mice. Survival time is a reflection of immune competence, which involves B lymphocytes, T lymphocytes, and macrophages [25].

Specific immune responses to *P. berghei* infection include synthesis of antibodies to the parasite as well as generation of specific T lymphocytes. Passive transfer of immunoglobulin from immune donors affords protection of recipients from malaria, apparently by blocking invasion of erythrocytes [6]. In addition, opsonizing antibody to *P. berghei* promotes ingestion of infected erythrocytes by macrophages [13]. Similarly, transfer of spleen cells or specifically immune T lymphocytes protects mice from challenge with *Plasmodium.* The mechanism of protection by immune T lymphocytes has not been well defined. Complement does not appear to have a determinative role in murine malaria. Splenectomy in both nonimmune and immune animals markedly decreases host resistance to *Plasmodium.* The spleen appears to trap rigid, parasite-laden erythrocytes based on the altered elasticity of the erythrocyte, rather than by immunologic recognition [42].

Mice infected intranasally with *Naegleria fowleri* develop a fatal disease resembling primary amebic meningoencephalitis in man. Mice stimulated by repeated administration of sublethal doses of live amebae by the intravenous, intraperitoneal, or intranasal route develop species- specific agglutinating antibodies [14]. In spite of this marked humoral immune response, most attempts to elicit protective immunity have yielded only modest increases in host resistance [19]. It is well established, however, that complement is an important factor in host resistance in both man [16] and the mouse [35]. It has been proposed that pathogenicity of *N. fowleri* is determined more by capability to proliferate in the host and to escape host defenses than by unique virulence factors [27].

Mice infected with larvae of *Trichinella spiralis* eradicate the adults by a T-lymphocyte-mediated immune response [24]. The role of T-lymphocyte function in eliminating adult worms from the host has been confirmed by the observation that nude mice have impaired capability to eliminate adult worms [36]. Dean et al. [8] have proposed that humoral immunity may also be required for efficient expulsion. Young larvae of *T. spiralis* are susceptible to IgG dependent eosinophil-mediated damage [21]. Enzymes released by the granulocytes destroy the early stages of the parasite. In these reactions, complement may enhance the efficiency of the kill [7].

Environmental chemicals and drugs alter host resistance to bacterial and parasitic infections

The usefulness of host resistance assays for measuring immunotoxicologic effects of chemicals has been evaluated by comparing the immunosuppressive effects of exposure to dieth- ylstilbestrol (DES) with the effects of the known immunosuppressive drug cyclophosphamide (CPA). One bacterial and one parasitic model have been evaluated. Acute treatment with CPA (200 mg/kg) markedly depressed resistance to the bacterial infection with *Listeria monocytogenes,* and exposure to DES also impaired resistance in a dose-dependent manner. Cyclophosphamide and DES exposure had no marked effect on resistance *to Naegleria fowleri.* The data support the general validity of host resistance assays, particularly with models of short disease course for measuring immunosuppression. The results also accentuate the complexity of interpreting the effects of environmental

chemicals on host resistance because of the interactions between such factors as relative times of exposure to the chemical in relation to the time of infection (Table 2); the duration of the disease, the determinative host defense Y mechanisms, and the compensatory adjustments of other host defense processes [29].

Host resistance assays have also been used to measure immunotoxicologic effects of the potent carcinogen N-nitrosodimethylamine (DMN). The experimental models used were infections of female $B_6C_3F_1$, mice with *Listeria monocytogenes, Streptococcus pneumoniae, Plasmodium berghei* and *Naegleria fowleri.* Of these, DMN administered intraperitoneally at 3.0 mg/kg for 14 days prior to challenge impaired host resistance only for the *S. pneumoniae* model. These results emphasize the complexity of interpreting the effects of environmental chemicals on host resistance, because DMN does not appear to impair the capability of B lymphocytes to produce T-lymphocyte-independent antibody, nor to impair complement activity, nor to reduce phagocytic activity. The effects of DMN on host resistance t6 *S. pneumoniae* infection may reflect effects on an innate host defense factor. Exposure to DMN afforded limited protection in mice challenged with *L. monocytogenes* [17]. These results indicate that DMN somehow stimulates macrophage activity. These results did not definitively identify the site of action of DMN. but they documented the selectivity of host resistance assays for detecting the effects of environmental chemicals.

Mice treated with 200 mg Δ^9-tetrahydrocannabinol/kg showed a decrease in resistance to V *Listeria monocytogenes* infection [30]. Moreover, combinations of Δ^9-tetrahydrocannabinol *y* and endotoxin or live *Escherichia coli* cells were hyperadditively toxic for mice [5]. The doses of endotoxin and cannabinoid required to kill mice were magnitudes higher than expected exposures in man. Munson et al. [32], however, have shown that enhanced mortality in rabbits occurred with 5 fxg of endotoxin and 1 mg of cannabinoid per kg. These doses are within the range that might be encountered by man. On the other hand, mice infected with *Naegleria fowleri* and then exposed daily for 4 days to 50 mg Δ^9-tetrahydrocannabinol/kg *Y* lived somewhat longer than infected control animals [34]. Δ^9-Tetrahydrocannabinol inhibits the growth of several protozoans, including *N. fowleri.* The results illustrate that environmental chemicals and drugs may have an injurious effect on an infectious agent, as well as on host defense mechanisms.

Conclusions

There is a growing body of literature documenting evidence indicating that exposure of adult mice to various environmental chemicals and drugs can severely impair host resistance to bacteria and parasites [4, 9, 17, 25, 29]. These studies point out the sensitivity of host resistance assays. Studies aimed at evaluating the immunotoxicity of environmental chemicals or drugs may constitute useful means to dissect mechanisms of host resistance and immunocompetence. A variety of infectious models are available which involve relatively well defined target organs and host defense mechanisms [4]. The selection of useful test systems will not be easy because it is difficult to work with models concerned with chronic subclinical exposure to environmental chemicals or drugs. The difficulty is exacerbated when

there is also a requirement that effects on host resistance be assessed after sublethal challenges of pathogenic bacteria or parasites. In general terms, hosts with B-lymphocyte deficiencies are very susceptible to bacterial pathogens, but have relatively normal resistance to viral infections. Hosts with T-lymphocyte deficiency are extraordinarily susceptible to fungal, protozoan infections, and viral and show increased vulnerability to intracellular bacteria. Hosts with phagocytic dysfunction are unusually susceptible to bacterial infections, but have relatively normal resistance to protozoan and viral infections [4].

The effectiveness of host defense mechanisms is the critical determinant in the outcome of the struggle between an infectious agent and its host. The battery of immune responses mounted by the host is often matched by the evasive tactics of the pathogen. A growing body of data demonstrates that protective immunity is compromised when the host is exposed to injurious environmental chemicals and drugs. It is important, therefore, that infectious models be developed that can reliably assess immunotoxicity. It remains unresolved whether these models will have utility in predicting human risk.

References

1. Anderson B. Evidence for thymus-independent humoral antibody production in mice against polyvinylpyrrolidone and E. coli lipopolysaccharide / Anderson B. Blomgren. H. // Cell. Immunol. – 1979. – 2:411-424.

2. Baker P.J. Regulation of the anti-body response to pneumococcal polysaccharide by thymus-derived cells / Baker, P.J., Amsbaugh, D.F. Stashak, P.W. et al. // Rev. Infect. Dis. – 1981. – 3:332-341.

3. Bloom B.R. Games parasites play: How parasites evade immune surveillance / Bloom B.R. // Nature. – 1999. – 279:21-26.

4. Bradley S.G. Approaches to assessing host resistance / Bradley S.G., Morahan, P.S. // Environ. Health Perspect. – 1982. – 43:61-69.

5. Bradley S.G. Enhanced susceptibility of mice to combinations of combinations of Δ^9-tetrahydrocannabinol and live or killed Gram-negative bacteria / Bradley S.G., Munson, A.E., Dewey W.L. // Infect. Immun. – 1977. – 17:325-329.

6. Butcher G.A. Antibody mediated mechanisms of immunity to malaria induced by vaccination with Plasmodium knowlesi merozoites / Bradley S.G., Munson, A.E., Dewey W.L. // Immunology. – 1978. – 34:77-86.

7. Chandra R.K. Immune responses in parasitic diseases. Part B. Mechanisms / Chandra R.K. // Rev. Infect. Dis. – 1982. – 4:756-762.

8. Dean J.H. Application of tumor, bacterial and parasite susceptibility assays to study immune alterations induced by environmental chemicals / Dean, J.H., Luster, M.I , Boorman, G.A. // Environ. Health Perspect. – 1982. – 43:81-88.

9. Doyle J.J. Antibody induced movement of membrane components of Leishmania enrietti / Doyle J.J., Behin R., Mauel J. // J. Exp. Med – 1974 – 139:1061-1069.

10. Doyle J. Antigenic variation in clones of animal-infective Trypanosoma brucei derived and maintained in vitro / Doyle J., Hirumi H., Hirumi K. // Parasitology. – 1980. – 80:359-369.

11. Eisen H. Tetrahymena pyriformis recovers from antibody immobilisation by producing univalent antibody fragments / Eisen, H., Tallan, I. // Nature. – 1977. – 270:514-515.

12. Goose J. Possible role of excretory/secretory products in evasion of host defenses by Fasciola hepatica / Goose J. // Nature. – 1978. – 275:216-217.

13. Green T.J. Demonstration of the role of cytophilic antibody in resistance to malaria parasites (Plasmodium berghei) in rats / Green T.J., Kreir .J.P. // Infect. Immun. – 1978. – 19:138-145.

14. Haggerty R.M. Serum agglutination and immunoglobulin levels of mice infected with Naegleria fowleri / Haggerty R.M., John, D.T. // J. Protozool. – 1982. – 29:117—122.

15. Hahn H. The role of cell-mediated immunity in bacterial infections / Hahn H., Kaufmann S.H.E. // Rev. Infect. Dis. – 1981. – 3:1221-1250.

16. Holbrook T.W. Activation of the alternative complement pathway by Naegleria fowleri / Holbrook T.W., Boackle R.J., Parker B.W. // Infect. Immun. – 1980. – 30:58-61.

17. Holsapple M.P. Effects ofW-nitrosodimethylamine on cell-mediated immunity / Holsapple M.P. Віск P.H., Duke S.S. // J. Leukocyte Biol. – 1985. – 37:367-381.

18. Howard C.J. The virulence for mice of strains of Escherichia coli related to, the effects of K antigens on their resistance to phagocytosis and killing by complement. / Howard C.J., Glynn A.A. // Immunol. – 1971. – 20:767-777,

19. John, D.T. Primary amebic meningoencephalitis and the biology of Naegleria fowleri / John, D.T. // Ann. Rev. Microbiol. – 1985. – 36:101-123.

20. Johnston R.B. The host response to invasion by Streptococcus pneumoniae: Protection and pathogenesis of tissue damage / Johnston R.B. // Rev. Infect. Dis. – 1981. – 3:282-288.

21. Kazura J.W. Stage-specific antibody dependent eosinophil-mediated destruc-tion of Trichinella spiralis / Kazura J.W., Grove. D.I. // Nature. – 1998. – 274:588-589.

22. Kern E.R. Use of viral infections in animal models to assess changes in the immune system / Kern E.R. // Environ. Health Perspect. 2008. – 43:71-79.

23. Keusch G.T. Immune responses in parasitic diseases Part A. General concepts / Keusch G.T. // Rev. Infect.Dis. – 2002. – 4:751-755,

24. Larsh J.E.Jr. Studies on delayed (cellular) hypersensitivity in mice infected with Trichinella spiralis. VIII. Serologic and histopathologic responses of recipients injected with spleen cells from donors suppressed with ATS / Larsh J.E.Jr., Race G J., Martin J.H. et al. // J. Parasiio. – 2004. – 60:99-109.

25. Loose L.D. Macrophage induction of T-suppressor cells in pesticide-exposed and protozoan-infected mice / Loose L.D. // Environ. Health Perspect. – 1982. – 43:89-97.

26. Mackaness G.B. Cellular resistance to infection / Loose L.D. // J. Exp. Med. – 1982. – 116:381-406.

27.Marciano-Cabral F. Cytopathogenicity of Naegleria % fowleri and

Naegleria gruheri for established mammalian cell cultures / Marciano-Cabral F., Patterson M., John D.T. et.al. // J. Parasitol. – 2002 – 22 68:1110-1116.

28. Medearis D.N. Cell wall composition and virulence in Escherichia coli / Medearis D.N., Camitta B.M., Heath E.C. // J. Exp. Med. – 2008. – 128:399-414,

29. Morahan P.S. Immunotoxic effects of diethylstilbestrol on host resistance: Comparison with cyclophosphamide / Morahan P.S., Bradley S.G., Munson A.E. // J. Leukocyte Biol. – 2003. – 35:329-341.

30. Morahan P.S. Effects of cannabinoids on host resistance to Listeria monocytogenes and herpes simplex virus / Morahan P.S., Klykken. P.C., Smith S.H. // Infect. Immun. – 2009. – 23:670-674.

31. Munson A.E. Immunological effects of Cannabis. In: Adverse Health and Behavioral Consequences of Cannabis Use / Munson A.E., Fehr K.O'Brien // Working Papers for the ARS/WHO Scientific Meeting, Toronto – 1981. – edited by K.O. Fehr and H. Kalant. pp. 257-353. Addiction Research Foundation, Toronto.

32. Munson A.E. Lethal intefaction of bacterial lipopolysaccharide and naturally occurring cannabinoids / Munson A.E., Sanders V.M., Bradley S.G.et.al. // J. Reticuloendothel. Soc. – 1998. – 24:647- 655.

33. North R.J. Importance of thymus-derived lymphocytes in cell-mediated immunity to infection / North R.J. // Cell. Immunol. – 2003. – 7:166-176.

34. Pringle H.L. Susceptibility of Naegleria fowleri to $Д^9$-tetrahydrocannabinol / Pringle H.L., Bradley S.G., Harris L.S. // Antimicrob. Agt. Chemother. – 1999. – 16:674-679.

35. Reilly M.F. Host resistance of mice to Naegleria fowleri infections / Reilly M.F., White K.L., Bradley S.G. // Infect. Immun. – 2003. – 42:645-652.

36. Ruitenberg E.J. Trichinella spiralis infection in congenitally athymic (nude) mice. Parasitological studies with observations on intestinal pathology / Ruitenberg E.J., Elgerma A., Kruizinga W. // Immunol. – 1997. – 33:581-586.

37. Suter E. Interaction between phagocytes and pathogenic microorganisms / Suter E. // Bacteriol.Rev. – 1997. – 20:94-132.

38. Torpier G. Receptor for IgG(F_c) and human (3_2-microglobulin on S. mansoni schistosomula / Torpier G., Capron A., Ouaissi M.A. // Nature. – 1998. – 278:447-449.

39. Turk J.L. Delayed hypersensitivity: Specific cell-mediated immunity / Turk J.L. // Br. Med. Bull. – 1996. – 23:1-97.

40. Winkelstein J. A. The roleof complement in host's defense against Streptococcus pneumonia / Winkelstein J. A. // Rev. Infect. Dis. – 2003. – 3:289-298.

41. Wolberg G. Mouse virulence of K(L) antigen-containing strains of Escherichia coli / Wolberg G., DeWitt C.W. // J. Bacteriol. – 1999. – 100:730-737.

42. Wyler D. Malaria: Host-pathogen biology / Wyler D. // Rev Infect. Dis. – 1998. – 4:785-797.

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