Annu. Rev. Public Healt

HOST-PATHOGEN INTERACTIONS IN EMER AND RE-EMERGING INFECTIOUS DISEASES: Genomic Perspective of Tuberculosis, Ma Human Immunodeficiency Virus Infectio Hepatitis B, and Cholera*

Janet M. McNicholl[1], Marie V. Downer[1], Venkatachalam Udhayakumar[2], Chester A. Alper[1] and David L. Swerdlow[3]

[1]Divisions of AIDS, STD, and TB Laboratory Research, [2]Parasitic Diseases, [3]Bacterial and Mycotic Diseases, National Center for Infectious Diseases, Disease Control, Atlanta, Georgia 30333; and [4]The Center for Blood Resear Incorporated, Boston, Massachusetts 02115; [1]e-mail:jkm7@cdc.gov

Key Words gene, polymorphism, susceptibility, resistance, vaccines

■ **Abstract** On exposure to a pathogen, a host may resist infection, beco cally infected, or progress through several stages from mild to severe infect sequelae may or may not occur. Host factors, particularly host genes, influe these stages. We have used a model of the continuum of pathogenesis of in eases to consider the effect of host genes on five pathogens of significant p burden: *Mycobacterium tuberculosis, Plasmodium* species, human immun virus, hepatitis B virus, and *Vibrio cholerae*. The relationships between thes and polymorphisms in human leukocyte antigen, cytokines, other immun or pathogen receptor genes are reviewed. We discuss gene-gene interacti effects in complex settings, such as coinfections with several pathogens. P prevention and control of these pathogens include vaccines and antimicr Research on how host genes can influence vaccine responses and the effic or other interventions, as well as further research into the relationship of h infectious disease outcomes, may lead to new strategies for prevention an

INTRODUCTION

We are rapidly nearing the completion of the Human Genome Project volves complete sequencing of ~100,000 human genes. A draft "m

*The US Government has the right to retain a nonexclusive, royalty-free lic to any copyright covering this paper.

human genome is expected by early 2000, and the complete or partial genomes of many pathogens are already available. In this review we focus on five pathogens of public health importance. Three of these [*Mycobacterium tuberculosis*, human immunodeficiency virus (HIV), and hepatitis B virus (HBV)] have complete genome sequences available, and the others (*Plasmodium falciparum* and *Vibrio cholerae*) are partially sequenced. An explosion in tools and technology to examine host-pathogen genomic interactions, ranging from microarray-based probing techniques of the pathogen and host (103) to large polymorphism databases and new epidemiologic approaches, has accompanied and facilitated these advances.

For detailed reviews of these new technologies, genetic epidemiology, and basic science as applied to infectious diseases, the reader is referred to elsewhere (1, 17, 32, 56, 89, 101, 103). In addition, databases for the human genome, Mendelian inheritance (95a), cytokine gene polymorphisms (15), other mutations or polymorphisms, and networks such as the genome epidemiology network (HuGE Net; 72) provide regularly updated information.

The Continuum of Pathogenesis in Infectious Diseases: A Model

Host-pathogen interactions in the development of infection and disease are complex and multidimensional. The role of host genes in this process can be considered along a continuum of pathogenesis (101). A simple model of this continuum is provided in Figures 1*a* and 1*b*. Although this model suggests a continuum, some patients may progress from one step to a later step without evidence of an intermediate stage. Some host genes may influence every step of this process, from exposure to development of severe disease or chronic sequelae [e.g. gene A (Figure 1*a*)]. Others may influence separate stages of the disease [e.g. genes B–E (Figure 1*a*)] or may operate at different stages of the pathogen's life cycle. Each step of the disease process may involve interactions of various kinds between genes (multigenic). For example, both genes A and B (Figure 1*a*) influence resistance to infection, but gene B has a greater effect (attributable risk) than gene A. This simplistic model does not capture the multiple other layers of host-pathogen interactions, which vary depending on factors such as the overall host/population genetic background, evolution of new pathogen variants in the host or population, and other host and nonhost factors. One example of this complexity is that certain genes may reduce risk for one infection [e.g. as hemoglobin S (HbS) heterozygosity does for malaria] while increasing risk for another infection (as HbS homozygosity and resultant sickle cell disease do for pneumococcal infections). Another complex situation arises when the host is coinfected with pathogens that exacerbate each other [e.g. with HIV and tuberculosis (TB)]. Moreover, vaccines or antimicrobial agents may alter the impact of the genes on the course of disease.

The simple model in Figure 1 can also be used to consider the phases at which host genes influence antimicrobial agents or vaccines. For example, genes that influence vaccine responsiveness or vaccine adverse events (Figure 1*b*) may include some (e.g. D or E in Figure 1*a*) that modify the natural history of the disease for

TABLE 1 Global burden of some infectious diseases

Disease	First report	Annual incidence (year of report; reference)	Prevalence (year of report; reference)	Annual morbidity (year of report; reference)	Annual mortality (reference)	Vaccine (year of introduction; efficacy)	Antimicrobial resistance
Malaria	3,000–4,000 years old	300–500 million/ year (110a)	Variable in different regions	1%–2% severe disease in African children <5 years of age (52a)	1.5–2.7 million (140)	n/a	+
HIV	1959	5.6 million (1999; 127a)	33.6 million (1999; 127a)	95% of people with HIV live in the developing world (127)	2.3 million (1999; 140)	n/a	+
TB	At least 3000–5000 BC	~8 million new cases (1997; 38a)	1.86 billion people infected with *Mycobacterium tuberculosis* (1997; 38a)	64,000 incident TB cases had HIV infection (38a)	1.87 million (1997; 38a)	Live attenuated, BCG (1921; 0%–80%)	+
Hepatitis B	~1883	200,000–300,000 new infections per year in USA (21a)	2 billion people infected with the virus (140)	350 million+ chronic carriers (1998; 138)	~1.2 million from cirrhosis of the liver and liver cancer-HBV infection associated (47)	HB surface antigen, now recombinant (1982; ~95%)	
Cholera	BC 1961: beginning of 7th pandemic in Celebes	147,425 (1997; 138)	Variable in epidemics	–	6,689 (1997; 138)	Killed parenteral and killed or live oral vaccines available or under development (partial protection; 50% or less)	Increasing resistance to tetracycline

lesions (19, 111). Of the total risk of developing smear-positive TB in some populations in South India, 29% (19) is attributable to HLA-DR2. In one study in Indonesia, 36% and 39% of the risk of developing smear-positive TB were attributed to the presence of HLA-DR2 and DQw1, respectively (18). In a Mexican study, a sixfold-increased risk of pulmonary TB was associated with DQA1*0101 and DQB1*0501, and an eightfold increase was associated with DRB1*1501 (119). In Cambodia, HLA-DQB1*0503 was associated with increased risk of clinical TB (52). The mechanism by which *HLA* genes influence disease may relate to typical functions in antigen presentation to T cells. The over-representation of HLA-DR2-positive patients in responders to the 38-kDa protein of *M. tuberculosis* in one study supports this relationship and suggests a possible role for this protein in the development of pulmonary TB (18). Some HLA-DR2-positive persons were also reported to have low levels of lysozyme, an enzyme normally elevated in persons with active pulmonary TB (110).

Cytokine genes are likely to play a role in TB severity, based on associations of IL-12 and interferon-γ (IFN-γ) polymorphisms with non-TB mycobacterial diseases (6, 34, 66, 96). The recent finding that IL-1 receptor antagonist (IL-1RA) genotypes may influence purified-protein-derivative reactivity and disease severity (132) supports this hypothesis. Other genes, such as the chromosome 10 mannose-binding protein (*MBP*) genes that influence MBP (or lectin) levels, may also play an important role. A study in one South African population found that the low-MBP-producing B allele, *G54D*, was associated with reduced risk of TB meningitis (59), whereas a study in West Africa (The Gambia) found no association of *MBP* alleles with clinical TB (14). It is interesting that *MBP* alleles may influence HIV disease course (see below), but, in HIV, low-MBP-producing alleles are associated with more severe disease rather than protection.

Tuberculosis Vaccines

The variable and less-than-optimal efficacy of the BCG vaccine (28) and the fact that it is contraindicated in immunocompromised persons highlight the need to develop improved or alternative vaccines for TB. The recent finding that worldwide BCG stocks have significant genetic variability (10) illustrates the power of pathogen genomic studies because this information provides one possible explanation for weak BCG efficacy and suggests strategies to improve the vaccine. On the host side, disseminated, sometimes fatal BCG disease has been reported in persons with sporadic or inherited mutations in the IFN-γ receptor (66). These people may also have chronic infections with weakly virulent mycobacteria, and similar infections may occur in persons with IL-12 receptor mutations (6, 34, 96), which points to the important role of the IL-12 and linked IFN-γ pathways in clearing mycobacteria. The data suggest that a correlate of TB vaccine efficacy should be the induction of these TH-1 cytokine responses; they are also reminders that BCG vaccine or similar live-vector vaccines may be contraindicated in persons with these selective cytokine receptor defects. Whereas these cases appear to be

advantage (55). Numerous studies have demonstrated that Hb variants S and I and α and β thalassemias are associated with partial protection against malari (3, 4, 44, 58, 120, 131, 133, 134). The only known host genotype that provides com plete protection against malaria infection is the Duffy negative genotype. However lack of expression of this erythrocyte chemokine receptor protects only against in fection with *P. vivax* (93), a malarial parasite causing a milder disease than th more virulent *P. falciparum*. The mechanisms of protection mediated by the H genes in the transition from exposure to clinical disease, as described in Figure 1c are not completely defined; various genes may influence early, late, or all steps i the continuum of disease.

Host gene associations with protection against severe manifestations of malari such as CM or severe anemia have been noted (Table 2). Mutations in erythrocyt structural proteins and the glucose-6-phosphate dehydrogenase (G6PD) variar associated with G6PD deficiency confer some level of protection against sever disease and death (21, 50, 79, 95, 105). In a study in The Gambia, HLA-B*530 and HLA-DRB1*1302 were independently associated with reduced risk of se vere malaria in young children (57). In a study in Kenya, HLA-DRB1*010 was associated with reduced risk of severe malaria, whereas HLA-B*5301 an HLA-DRB1*1302 were not (56). Although it is unclear why the HLA associa tions vary in these East- and West-African populations, non-MHC and nongeneti factors may play a role. A mechanistic explanation for the class I association re lates to HLA-B53-mediated induction of cytotoxic T lymphocytes to a conserve epitope of a liver stage antigen (58). Complement receptor (*CR1*) and nitric ox ide synthase gene variants have also been reported to be associated with parti protection against severe malaria in some studies (75, 104).

Malaria Severity Genes

Several genes have been associated with increased risk of severe malaria. Th TNF-α promoter region of the MHC has at least three single nucleotide polymo phisms located at -238, -308, and -376 from the transcriptional start site. All a substitutions of adenine (indicated by "A" in the designations) for guanine at the sites, and the -308 allele was associated with higher levels of TNF-transcriptic (73, 135). Homozygosity for TNF-308A- and TNF-376A-containing genotype was shown to be independently associated with increased susceptibility to cerebr malaria in both the Gambian and Kenyan populations (73, 84, 85). The mechanis by which these TNF-genotypic variants influence malaria severity or mortality not clear. One potential mechanism is by up-regulation of a *P. falciparum* parasi adhesion receptor such as intercellular adhesion molecule-1 on endothelial cel of blood vessels, which could lead to increased accumulation of parasites in th brain microvascular endothelial cells. This hypothesis is supported by associatio of certain genetic variants of the intercellular adhesion molecule-1 with CM ri in Kenya (43). In another population, however, intercellular adhesion molecule

TABLE 2 Host genes, impact on infectious diseases, and population frequency

Disease	Gene/genotype	Chromosome location	Impact of gene/genotype on infectious diseases[a]			Population[b] frequency
			Resistance	Severity	Disease outcome	
Tuberculosis	HLA-DR2	6p21.3		+	DR2 associated with TB severity	DRB1*1501/DRB1*1502 South African Blacks, 6.4/0.0 Black Americans, 8.6/0.8 Japanese (Wajin), 6.8/9.2 Highlanders (Papua, New Guinea), 14.7/4.5 French, 7.1/0.3 Germans, 7.8/1.1 Italians, 5.5/2.2 US Whites, 9.9/0.7 Canadians, 10.9/0.6 Indians, 12/11.9
	DRB1*1501 (serotype DR2)			+	DRB1*1501 and DRB1*1502 both associated with severity and radiographic extent of clinical TB	
	DRB1*1502 (serotype DR2)			+	DRB1*1501 and DRB1*1502 both associated with drug failure in TB treatment	
	HLA-DQB1*0503	6p21.3		+	Associated with clinical TB	Cambodians, <1%; Caucasians US, 1.7%
	NRAMP-1	2q35		+	Fourfold increased risk of TB in persons heterozygous for INTR4 and 3′UTR polymorphisms	Allelic frequency in Gambians, 3%
	IFN-γR	6q23-q24		+	Both associated with non-TB mycobacterial disease	No published data
	IL12R (IL12B1)	19p13.1		+	Only IFN-γ R is associated with adverse events post-BCG vaccination	
	HLA-DR3	6p21.3		+	DR3 associated with reduced risk of TB	DR4, ~46%; DR8, ~34% in persons of Mexican descent
	HLA-DR4/DR8			+	DR4, DR8 associated with reduced risk of PTB	

TABLE 2 (*Continued*)

Disease	Gene/genotype	Chromosome location	Impact of gene/genotype on infectious diseases[a]			Population[b] frequency
			Resistance	Severity	Disease outcome	
Malaria	β-Thalassemia	11p15	+		Partial protection against severe disease in Liberia (*P. falciparum*)	Variable frequencies in Mediterranean, Middle East, Southeast Asia, and Africa
	Melanesian ovalocytosis	17q21-q22		+	Band 3 deletion not found in patients with cerebral malaria in Papua, New Guinea; protection against severe disease	Up to 30% in aboriginal population in Southeast Asia and Pacific islands; absent in Africans
	G6PD deficiency	Xq28		+	46%–58% reduction in severe malaria for both male hemizygotes and female heterozygotes in The Gambia	Female heterozygotes in The Gambia, 13.7% in Kenya, 27.3% Male hemizygotes in The Gambia, 5.9% in Kenya, 18.8%
	HLA-B53			+	Partial protection (4%–50%) against cerebral malaria and anemia	B53 frequencies Nigerians, 40% Gambians, 25% Zambians, 21% Zimbabweans, 16% South Africans, 2% Caucasians and Asians, 0%–1%
	HLA haplotype DRB1*1302-DQB1*0501	6p21.3		+	Protection against severe malaria in The Gambia	
	HLA DRB1*0101			+	Protection against malaria anemia in Kenya	
	TNF-promoter alleles-238A, -308A, -376A	6p21.3-q21.1		+	Various effects on malaria severity in The Gambia and Kenya	TNF-308 allele frequency, Gambians, 0.16

TABLE 2 (*Continued*)

Disease	Gene/genotype	Chromosome location	Impact of gene/genotype on infectious diseases[a]			Population[b] frequency
			Resistance	Severity	Disease outcome	
Human immune-deficiency virus infection	B32CCR5	3p21		+	Heterozygosity associated with delayed progression to AIDS	Heterozygosity: Caucasians, 10%–20% African Americans, 6% Hispanics, 7% Native Americans, 13%
	CCR2-V64I	3p21		+	Delayed progression to AIDS	Caucasians, 10% Asians, 25%
	SDF1-3′A	10q11.1		+	Influence on progression	Caucasians, 21% Hispanics, 16% African Americans, 6% Asians, 26%
	TNFc	6p21.3		+	TNFc2 allele influences long-term nonprogression	Phenotype, 45.9% among Caucasians in northwest England
	RANTES-28G	17q11.2-q12		+	Delayed-progression of HIV-1 disease	Allele frequency, 17% in Japanese
Cholera	Blood group O	9q34		+	Associated with severity of clinical symptoms and vaccine nonresponsiveness	68% in Caucasians

HUMAN IMMUNODEFICIENCY VIRUS INFECTION/ ACQUIRED IMMUNODEFICIENCY SYNDROME

Burden and Natural History

HIV-1 is a sexually, perinatally, and parenterally transmitted infection that, in the absence of antiretroviral therapy, usually causes acquired immunodeficiency syndrome (AIDS). Median survival in the absence of treatment is 11 years. Today >33 million persons worldwide are reported to be infected with HIV-1, a doubling since 1990 (127a). More than 16,000 new infections occur daily. The highest prevalence and incidence are in Africa and Asia. In parts of sub-Saharan Africa, ≤50% of women attending antenatal clinics are HIV infected. No preventive vaccine is available for HIV. The prohibitive cost of antiretroviral therapies will severely limit their use in economically depressed parts of the world. Moreover, resistance to many of these drugs is already developing.

Human Immunodeficiency Virus Resistance Genes

Homozygosity for the HIV-coreceptor gene deletion variant *Δ32CCR5* has been found to be associated with resistance to HIV-1 in sexual, blood-borne, and mother-infant transmission settings (64, 98, 109; reviewed in 87, 90, 97). The absence of this *CCR5* variant in most African and Asian populations and its low prevalence (~5%) in African Americans suggest that its protective effect against HIV transmission may be limited to Caucasians. *HLA* class I genes are also important, because HLA discordance was found to reduce vertical HIV transmission by one third in one mother-infant study in Kenya (80). Blood group types, such as Lewis antigen, may influence transmission through mucosal routes (16).

Human Immunodeficiency Virus Severity Genes

HLA class I and II alleles have been shown to influence HIV progression in many studies (20, 69). Several studies have reported associations of the HLA A1-B8-DR3 haplotype, HLA-B35, or HLA-Cw4 with rapid progression to AIDS and associations of HLA-B57 and HLA-B27 with slow progression. The effect of *HLA* class II genes is less consistent, and *HLA* class I effects may be modified by other genes on chromosome 6, such as *TAP* (67). An HLA-risk profile can be constructed to predict HIV disease outcomes (68); this profile influences early viral load set point, which may be the key determining factor of later disease course (106). Homozygosity for *HLA* class I alleles speeds progression to AIDS, probably by limiting the diversity of the cytotoxic-T-cell responses that control early virus load set point (20, 118). *CCR5* and *CCR5* promoter genotypes also strongly influence HIV disease progression; individuals having one copy of *Δ32 CCR5* have a delayed progression to AIDS, whereas those with certain promotor haplotypes (e.g. *P1*) have more rapid disease progression (83). The *CCR2* gene is also polymorphic and on the same chromosome (3p21) as *CCR5*. Through careful dissection of the role of the

role of the host genes coding for enzymes that metabolize or excrete these drugs might lead to modified dosing schedules and greater efficacy, better compliance, or reduced drug resistance.

CHOLERA

Burden and Natural History

Cholera is a severe diarrheal illness caused by strains of *V. cholerae* serogroup O1 or serogroup O139, which produce a potent enterotoxin. Most infected patients have no symptoms or only mild diarrhea; however, patients with severe watery diarrhea and vomiting (cholera gravis) can die within a few hours of onset owing to massive loss of water and electrolytes. The toxin consists of two subunits; the B subunit attaches to specific receptors on intestinal epithelial cells, whereas the A subunit activates adenylate cyclase. Increased levels of cyclic adenosine monophosphate in the intestinal cells lead to an outpouring of fluid into the lumen. Proper treatment with oral and intravenous fluids can reduce death rates in severe cases from 50% to <1% (117). The organism is spread through contaminated drinking water and a variety of foods and has likely caused illness on the Indian subcontinent for thousands of years. Beginning in 1817, pandemic waves of cholera spread from the Ganges River delta to much of the rest of the world. During the 20th century, cholera was confined to southern Asia until 1961, when the seventh pandemic began in the Celebes Islands of Indonesia. Since then, this pandemic has spread throughout Asia and into Africa, Europe, Oceania, and recently South America. In 1997, ~150,000 cases and ≤7000 deaths were reported to the World Health Organization from 65 countries (138). Reported cases likely represent only a small fraction of the actual number of cases that occur.

Cholera Resistance Genes

The proportion of infected people who develop severe cholera is determined by several factors, including the infecting dose, gastric acidity, and immunity conferred by previous infection (116). In addition, blood group O has been associated with severe cholera in Calcutta (25, 112), the Philippines (9), Bangladesh (27, 51), Peru (116), and among North American volunteers (76). The prevalence of blood group O varies considerably among different human populations. It is lowest in people living near the Ganges River delta, among whom 12%–20% have blood group O. The low prevalence of blood group O in this population has been attributed to selective pressure exerted by cholera over many generations. The high prevalence of blood group O among populations in Latin America (≤90%) may have intensified the cholera epidemic in that region (116).

Another possible mechanism of resistance to cholera is through mutations in the cystic fibrosis gene. Mutations that affect the cystic fibrosis transmembrane conductance regulator decrease chloride permeability of apical epithelial cells,

Antimicrobial Agents/Pharmacogenetics

Although the mainstay of treatment for cholera is rehydration therapy, antibiotic treatment will decrease the duration of illness, the requirements for fluid replacement, and the period of *Vibrio* excretion (117). It is unknown whether host genetic factors influence drug efficacy.

Priorities for the Future

The discovery that cholera was associated with contaminated municipal water supplies spurred the "sanitary revolution" of the 19th century, leading to modern water and sewage treatment systems. Like many emerging infections, cholera is associated with the inadequate or decaying sanitation infrastructures found in many parts of the world. Prevention of cholera will require improvements in sanitation, water quality, and food safety. Vaccines have not yet been accepted as a means of preventing cholera on a population basis because of cost, efficacy, and duration of effect. In the future, decisions to use cholera vaccine and preparedness for epidemics should take into account the prevalence of blood group O among affected populations.

HEPATITIS B

Burden and Natural History

HB is one of the most prevalent infectious diseases worldwide and is responsible for enormous morbidity and mortality, particularly in less developed countries. Worldwide, >350 million people are chronically infected (140), and >1.2 million die each year of acute or chronic HB (47). HBV is blood-borne and can be transmitted by transfusion, intravenous drug abuse, or sexual activity, as well as perinatally from mothers to infants. Most HBV infections (~60%) are asymptomatic. In symptomatic cases, HB is usually an acute disease lasting 2–4 months with fever, disturbed liver function, and jaundice. However, in perhaps 10% of patients, chronic, long-lasting, and recurrent infection may supervene. HBV replicates in hepatocytes but is not directly cytotoxic; the pathologic changes are mediated by the host's immune response. Of patients with chronic HBV infection, 25% develop chronic liver disease, which can be associated with hepatoma in some cases.

Hepatitis B Resistance Genes

In studies of European Caucasian (60) and Gambian (124) patients and controls, HLA-DR13 was negatively associated with chronic HB. In The Gambia, this association was true in separate studies of children and adults, so it was not age-related. This suggests that carriers of HLA-DR13 are protected from chronic HB. In keeping with these findings, the same authors showed in experiments in vitro (37) that

were prospectively immunized with HBsAg, the antibody response in the homozygotes was minimal or zero and far lower than that in the heterozygotes (5). However, occasional homozygotes do respond, suggesting that non-MHC genes are also involved. Both the antibody and T-cell responses to HBsAg form a continuous spectrum and are subject to (complex) genetic control. The picture is further complicated by the fact that some antibody nonresponders to the standard course of immunization become responders (albeit usually weak responders) after multiple booster injections.

The cellular basis for HBsAg nonresponsiveness is unknown. The connection between nonresponse and MHC genes is also unclear. It is of interest that patients with symptomatic or asymptomatic chronic HBV infection do not have an increase in markers for either of the haplotypes associated with HBsAg nonresponsiveness (125). Anecdotally, a nonresponder to the vaccine who contracted HBV infection became symptomatic and recovered. Anti-HBs was not detected after this natural infection.

Adverse events (including arthritis, multiple sclerosis, and other autoimmune disease) after administration of the HB vaccine have been reported to the U.S. Vaccine Adverse Effects Reporting System (54) and have been published in case reports and retrospective series (53, 55a, 100). Some patient advocates have suggested that some persons are genetically at risk for these adverse effects. The available data can neither confirm or exclude a true association, but some countries (e.g. France) have taken the precaution of not administering the HBV vaccine in school settings but in physicians' offices, where parents and their offspring can discuss the benefit and risks with a medical professional.

Antimicrobial Agents/Pharmacogenetics

Until recently, the treatment of chronic HB has been a daunting challenge with little hope of success. This has changed markedly with the introduction of IFN and a series of nucleoside analogs, including lamivudine, lobucavir, and adefovir, as reverse transcriptase inhibitors. IFN treatment results in marked reduction in viral load, loss of markers of HBV replication, such as the HBe antigen (HBe antigenemia), and improvement in immunologic abnormalities in nearly 40% of patients (82). The nucleoside analogs are well-tolerated and result in clinical improvements (36) as well as histologic improvement (62) in >40% of patients. Although escape by viral mutation has been observed in some lamivudine-treated patients (63), the significance of these variants in influencing disease course or transmissibility is unknown.

Priorities for the Future

The most important challenges in preventing the spread of HBV infection are (*a*) to develop more effective ways to eradicate HBV in all of those with chronic HBV infection and (*b*) to develop ways to interrupt maternal-fetal transmission

about host genes and infectious diseases will strengthen our ability to control and prevent infectious diseases. It allows us to construct multigenic and multidimensional perspectives of host-pathogen interactions and provides opportunities to examine in detail the complex role of genes and other factors. However, a great challenge continues to exist—to integrate this knowledge into clinical and public health practice and programs to control and prevent infectious disease in ways that provide greatest benefit and least harm at reasonable cost.

Visit the Annual Reviews home page at www.AnnualReviews.org

LITERATURE CITED

1. Abel L, Dessein AJ. 1998. Genetic epidemiology of infectious diseases in humans: design of population-based studies. *Emerg. Infect. Dis.* 4:593–603
2. Deleted in proof
3. Allen SJ, O'Donnell A, Alexander ND, Alpers MP, Peto TEA, et al. 1997. Alpha$^+$-thalassemia protects children against disease caused by other infections as well as malaria. *Proc. Natl. Acad. Sci. USA* 94:14, 736–41
4. Allison AC. 1954. Protection afforded by sickle cell trait against subtertian malarial infection. *Br. Med. J.* 1:190
5. Alper CA, Kruskall MS, Marcus-Bagley D, Craven DE, Katz AJ, et al. 1989. Genetic prediction of nonresponse to hepatitis B vaccine. *N. Engl. J. Med.* 321:708–12
6. Altare F, Durandy A, Lammas D, Emile JF, Lamhamedi S, Le Deist F. 1998. Impairment of mycobacterial immunity in human interleukin-12 receptor deficiency. *Science* 280:1432–35
7. Anzala AO, Ball TB, Rostron T, O'Brien SJ, Plummer FA, et al. 1998. CCR2-64I allele and genotype associations with delayed AIDS progression in African women. *Lancet* 351:1632–33
8. Baggiolini M, Moser B. 1997. Blocking chemokine receptors. *J. Exp. Med.* 186:1189–91
9. Barua D, Paguio AS. 1997. ABO blood groups and cholera. *Ann. Hum. Biol.* 4:489–92
10. Behr M, Wilson M, Gill W, Salamon H, Schoolnik G, et al. 1999. Comparative genomics of BCG vaccines by whole-genome DNA microarray. *Science* 284:1520–23

10a. Bellamy R, Hill AVS. 1999. A bi-allelic tetranucleotide repeat in the promoter of the human inducible nitric oxide synthase gene. *Clin. Genet.* 52:192–93

11. Bellamy R, Kwiatkowski D, Hill A. 1998. Absence of an association between intercellular adhesion molecule 1, complement receptor 1, and interleukin 1 receptor antagonist gene polymorphisms and severe malaria in a West African population. *Trans. R. Soc. Trop. Med. Hyg.* 92:312–16
12. Bellamy R, Ruwende C, Corrah T, McAdam KPWJ, Thursz M, et al. 1999. Tuberculosis and chronic hepatitis B virus infection in Africans and variation in the vitamin D receptor gene. *J. Infect. Dis.* 179:721–24
13. Bellamy R, Ruwende C, Corrah T, McAdam KPWJ, Whittle HC, Hill AVS. 1998. Variations in the *NRAMP1* gene and susceptibility to tuberculosis in West Africans. *N. Engl. J. Med.* 338:640–44
14. Bellamy R, Ruwende C, McAdam KPWJ, Thursz M, Sumiya M, et al. 1998. Mannose binding protein deficiency is not associated with malaria, hepatitis B carriage nor tuberculosis in Africans. *Q. J. Med.* 91:13–18

hepatitis B virus. *Mt. Sinai J. Med.* 66: 84–90

34. de Jong R, Altare F, Haagen IA, Elferink DG, de Boer T, van Breda Vriesman PJC. 1998. Severe mycobacterial and *Salmonella* infections in interleukin-12 receptor-deficient patients. *Science* 280:1435–38
35. Desombere I, Hauser P, Rossau R, Paradijs J, Leroux-Roels G. 1995. Non-responders to hepatitis B vaccine can present envelope particles to T lymphocytes. *J. Immunol.* 154:520–29
36. Dienstag JL, Perrillo RP, Schiff ER, Bartholomew M, Vicary C, Rubin M. 1995. A preliminary trial of lamivudine for chronic hepatitis B virus infection. *N. Engl. J. Med.* 333:1657–61
37. Diepolder HM, Jung MC, Keller E, Schraut W, Gerlach JT, et al. 1998. A vigorous virus-specific CD4+ T cell response may contribute to the association of HLA-DR13 with viral clearance in hepatitis B. *Clin. Exp. Immunol.* 113:244–51
38. Dolin PJ, Raviglione MC, Kochi A. 1994. Global tuberculosis incidence and mortality during 1990–2000. *Bull. World Health Organ.* 70:213–20

38a. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. 1999. Consensus statement. Global burden of tuberculosis: estimated incidence and mortality by country. WHO Global Surveillance and Monitoring Project. *J. Am. Med. Assoc.* 282:677–86

39. Egea E, Iglesias A, Salazar M, Morimoto C, Kruskall MS, et al. 1991. The cellular basis for lack of antibody response to hepatitis B vaccine in humans. *J. Exp. Med.* 173:531–38
40. Ellard GA. 1976. Variations between individuals and populations in the acetylation of isoniazid and its significance for the treatment of pulmonary tuberculosis. *Clin. Pharmacol. Ther.* 19:610–25
41. Evans D. 1993. Genetics factors in drug therapy: clinical and molecular pharmacogenetics. Cambridge, UK: Cambridg Univ. Press. 211 pp.
42. Farmer P, Kim JY. 1998. Communi based approaches to the control of mu tidrug resistant tuberculosis: introducin "DOTS-plus." *Br. Med. J.* 317:671–74
43. Fernandez-Reyes D, Craig AG, Kyes S Peshu N, Snow RW, et al. 1997. A hig frequency African coding polymorphis in the N-terminal domain of ICAM-1 pr disposing to cerebral malaria. *Hum. Mo Genet.* 6:1357–60
44. Flatz G, Pik C, Sundharagiati B. 196 Malaria and haemoglobin E in Thailan *Lancet* 2:385
45. Fontelo P. 1995. Protection again cholera. *Science* 267:440
46. Gabriel SE, Brigman KN, Koller BH Boucher RC, Stutts MJ. 1994. Cystic fi brosis heterozygote resistance to choler toxin in the cystic fibrosis mouse mode *Science* 266:107–9
47. Ganem D. 1998. Towards a rationa therapy for hepatitis B. *J. Clin. Inves* 102:867–68
48. Garred P, Madson HO, Balslev U, Hof mann B, Gerstoft J, Svejgaard A. 1997 Susceptibility to HIV infection and pro gression of AIDS in relation to variant al leles of mannose-binding lectin. *Lance* 349:236–40
49. Gayle HD. 1999. Director's forum. *CDC NCHSTP News Notes* 1:2
50. Genton B, Al-Yaman F, Mgone CS Alexander N, Paniu MM, et al. 1995 Ovalocytosis and cerebral malaria. *Nature* 378:564–65

50a. Gjertson DW, Terasaki PL, eds. 1998 *HLA 1998.* Lenexa, KS: Am. Soc. Histocompat. Immunogenet. 468 pp.

51. Glass RI, Holmgren J, Haley CE, Khan MR, Svennerholm AM, et al. 1985. Predisposition for cholera of individuals with O blood group: possible evolutionary significance. *Am. J. Epidemiol.* 121:791–96
52. Goldfeld AE, Delgado JC, Thim S, Bozon

its manifestations. *Proc. Assoc. Am. Phys.* 111:299–307

70. Khomenko AG, Litvinov VI, Chukanova VP, Pospelov LE. 1990. Tuberculosis in patients with various HLA phenotypes. *Tubercle* 71:187–92
71. Khoo SH, Pepper L, Snowden N, Hajeer AH, Vallely P, et al. Tumor necrosis factor c2 microsatellite allele is associated with the rate of HIV disease progression. *AIDS* 11:423–28
72. Khoury MJ, Dorman JS. 1998. Editorial: the human genome epidemiology network. *Am. J. Epidemiol.* 148:1–3
73. Knight J, Udalova I, Hill A, Greenwood B, Peshu N, et al. 1999. A polymorphism that affects OCT-1 binding to the TNF promoter region is associated with severe malaria. *Nat. Genet.* 22:145–50
74. Knuchel MC, Spira TJ, Neumann AU, Xiao L, Rudolph DL, et al. 1998. Analysis of a biallelic polymorphism in the tumor necrosis factor α promoter and HIV type 1 disease progression. *AIDS Res. Hum. Retroviruses* 14:305–9
75. Kun JFJ, Mordmuller B, Bertrand L, Lehman LG, Luckner D, Kremsner PG. 1998. Polymorphism in promoter region of inducible nitric oxide synthase gene and protection against malaria. *Lancet* 351:265–66
76. Levne MM, Nalin DR, Rennels MB. 1979. Genetic susceptibility to cholera. *Ann. Hum. Biol.* 6:369–74
77. Li K, Leung NW, Poon AS, Wong KC, Chan TH, Lai KN. 1995. Molecular genetics of major histocompatibility complex class II genes in hepatocellular carcinoma. *Dig. Dis. Sci.* 40:1542–46

77a. Lipscombe RJ, Sumiya M, Hill AV, Lau YL, Levinsky RJ, et al. 1992. High frequencies in African and non-African populations of independent mutations in the mannose binding protein gene. *Hum. Mol. Genet.* 1:709-15

78. Liu H, Chao D, Nakayama E, Taguchi H, Goto M, et al. 1999. Polymorphism in RANTES chemokine promoter affects HIV-1 disease progression. *Proc. Natl. Acad. Sci. USA* 96:4581–85
79. Luzzatto L, Usanga EA, Reddy S. 1969. Glucose-6-phosphate dehydrogenase deficient red cells: resistance to infection by malarial parasites. *Science* 164:939
80. MacDonald KS, Embree J, Njenga S, Nagelkerke NJD, Ndinya-Achola J, et al. 1998. Mother-child class I HLA concordance increases perinatal human immunodeficiency virus type I transmission. *J. Infect. Dis.* 177:551–56

80a. Madsen HO, Garred P, Kurtzhals JA, Lamm LU, Ryder LP, et al. 1994. A new frequent allele is the missing link in the structural polymorphism of the human mannan-binding protein. *Immunogenetics* 40:37–44

81. Magierowska M, Theodorou I, Debre P, Sanson F, Autran B, et al. 1999. Combined genotypes of CCR5, CCR2, SDF1, and HLA genes can predict the long-term nonprogressor status in human immunodeficiency virus-1-infected individuals. *Blood* 93:936–41
82. Main J, McCarron B, Thomas HC. 1998. Treatment of chronic viral hepatitis. *Antiviral Chem. Chemo.* 9:449–60
83. Martin MP, Dean M, Smith MW, Winkler C, Gerrard B, et al. 1998. Genetic acceleration of AIDS progression by a promoter variant of CCR5. *Science* 282:1907–11
84. Mcguire W, Hill AVS, Allsopp CEM, Greenwood BM, Kwiatkowski D. 1994. Variation in the TNF-α promoter region associated with susceptibility to cerebral malaria. *Nature* 371:508–11
85. McGuire W, Knight JC, Hill AVS, Allsopp CEM, Greenwood BM, Kwiatkowski D. 1999. Severe malaria anemia and cerebral malaria are associated with different tumor necrosis factor promoter alleles. *J. Infect. Dis.* 179:287–90

104a. Roy S, Frodsham A, Saha B, Hazra SK, Mascie-Taylor CGN, Hill AVS. 1999. Association of vitamin D receptor genotype with leprosy type. *J. Infect. Dis.* 179: 187–91

105. Ruwende C, Khoo SC, Snow RW, Yates SN, Kwiatkowski D, et al. 1995. Natural selection of hemi- and heterozygotes for G6PD deficiency in Africa by resistance to severe malaria. *Nature* 376:246–49

106. Saah AJ, Hoover DR, Weng S. 1998. Association of HLA profiles with early plasma viral load, $CD4^+$ cell count and rate of progression to AIDS following acute HIV-1 infection. *AIDS* 12:2107–13

107. Deleted in proof

108. Salazar MH, Deulofeut H, Granja C, Deulofeut R, Yunis DE, et al. 1995. Normal HBsAg presentation and T-cell defect in the immune response to nonresponders. *Immunogenetics* 41:366–74

109. Samson M, Libert F, Doranz BJ, Rucker J, Liesnard C, et al. 1996. Resistance to HIV-1 infection in Caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. *Nature* 382:722–25

110. Selvaraj P, Kannapiran M, Reetha A, Uma H, Xavier T, Narayanan P. 1997. HLA-DR2 phenotype and plasma lysozyme, beta-glucuronidase and acid phosphatase levels in pulmonary tuberculosis. *Int. J. Tuberc. Lung Dis.* 1:265–69

110a. Sherman IW. 1998. A brief history of malaria and discovery of the parasite's life cycle. In *Malaria Parasite Biology, Pathogenesis, and Protection*, ed. IW Sherman. Washington, DC: ASM Press, pp. 3–10

111. Singh S, Mehra N, Dingley H, Pande J, Vaidya M. 1983. Human leukocyte antigen (HLA)-linked control of susceptibility to pulmonary tuberculosis and association with HLA-DR types. *J. Infect. Dis.* 148:676–81

112. Sircar BK, Dutta P, De SP, Sikdar SN, Deb BC, Pal SC. 1981. ABO blood group distributions in diarrhoea cases including cholera in Calcutta. *Ann. Hum. Biol.* 8:289–91

113. Smith MW, Dean M, Carrington M, Winkler C, Huttley GA, et al. 1997. Contrasting genetic influence of CCR2 and CCR5 variants on HIV-1 infection and disease progression. *Science* 277:959–65

114. Stead WW. 1997. A molecular approach to tuberculosis control—an idea that might work. *J. Infect. Dis.* 176:547–48

115. Stead WW, Senner JW, Reddick WT, Lofgren JP. 1990. Racial differences in susceptibility to infection by *Mycobacterium tuberculosis*. *N. Engl. J. Med.* 322:422–27

116. Swerdlow DL, Mintz ED, Rodriguez M, Tejada E, Ocampo C, et al. 1994. Severe life-threatening cholera associated with blood group O in Peru: implications for the Latin American epidemic. *J. Infect. Dis.* 170:468–72

117. Swerdlow DL, Ries AA. 1992. Cholera in the Americas: guidelines for the clinician. *J. Am. Med. Assoc.* 267:1495–99

118. Tang J, Costello C, Keet IPM, Rivers C, Leblanc S, et al. 1999. HLA class I homozygosity accelerates disease progression in human immunodeficiency virus type 1 infection. *AIDS Res. Hum. Retroviruses* 15:317–24

119. Teran-Escandon D, Teran-Ortiz L, Camarena-Olvera A, Gonzalez-Avila G, Vaca-Marin MA, et al. 1999. Human leukocyte antigen-associated susceptibility to pulmonary tuberculosis: molecular analysis of class II alleles by DNA amplification and oligonucleotide hybridization in Mexican patients. *Chest* 115:428–33

120. Terrenato L, Shrestha S, Dixit KA,

malaria situation in 1991, part I. *Wkly. Epidemiol. Rec.* 68:245–52
138. World Health Organization. 1998. Cholera in 1997. *Wkly. Epidemiol. Rec.* 27:201
139. World Health Organization. 1998. Fifty facts from the World Health Report. Geneva: WHO. http://www.WHO.ORG/whr/1998/factse.htm
140. World Health Organization. 1998. Hepatitis B Fact Sheet WHO/204. http://www.who.int/inf-fs/en/fact204. html
141. Zavaglia C, Bortolon C, Ferrioloi G, Rho A, Mondazzi L, et al. 1996. HLA typing in chronic type B, D, and C hepatitis. *J. Hepatol.* 24:658–65

NUTRITION, GEN

Cheryl L. Rock[1],
Ruth E. Patterson
[1]*Department of Family an*
Program, University of Ca
e-mail: clrock@ucsd.edu
[2]*Cancer Prevention Resea*
Seattle, Washington 98109

Key Words genetic m
diet

■ **Abstract** Dietary p
components of the enviro
study of interactions betw
of research. This review
study and types of relation
examples of specific diet-
sis on implications for ca
the genes for the activatin
of metabolizing enzyme
tion of a carcinogen or th
relationship between the
is an example of a diet-g
metabolism gene; and th
cancer and folate require
to the observed inter-indiv
nutritional factors that ha
into mechanisms by whic
provided by knowledge o
knowledge in this area wi
with diet interventions tar
susceptible and responsiv

Investigating the cellu
and important area of ba
pability of examining b
and progression of chro
study these factors in cl
ronmental factors can al

0163-7527/00/0510-0047$14.00