

# Evolution of virulence

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Human history cannot be understood well without understanding the causes and consequences of human disease. This fact has become amply apparent over the past few decades as the impacts of infectious diseases have been studied in the context of war, colonization, and competition [1–5]. It is much less widely appreciated that the reverse is also true. Historical studies of infectious diseases may help guide modern health sciences to recognize options for controlling diseases of the present and future. Ecologic and evolutionary perspectives are enmeshed with the historical perspective of infectious diseases, because infectious agents spread and evolve over times scales that accord with historical events. They may influence historical events and may be influenced by such events. The influence of historical events on the evolution of pathogens largely has been neglected until the past quarter century. It has become clear that activities that were undertaken for one purpose can have unforeseen effects on the evolution of important characteristics of pathogens, such as virulence (which is defined broadly here to mean the degree of harm imposed on the host). An understanding of these evolutionary effects helps in understanding why some pathogens cause more harm than others, the environmental circumstances that permit this harm, and, most importantly for the future, the human activities that can ameliorate or prevent this harm.

## **Evolutionary theory about virulence**

For most of the 20th century, the prevailing dogma was that disease organisms eventually should evolve toward benign coexistence with their hosts; harmful diseases were interpreted as a transitory state of maladaptation [6–7]. This belief has not been useful for ameliorating the suffering caused by infectious diseases, because it suggests that the occurrence of

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severe disease is bad luck and that not much can be done to control this evolutionary process. This view arose more from assumptions about the harmony of nature than from rigorous application of evolutionary principles. Specifically, it failed to cast the problem in the context of natural selection. Rather than asking whether harmful or mild variants would win out in competition with each other over the short run, the focus was on what was stable over the long run. Natural selection is powerless to favor long-term stability if the variants that win in the short term destabilize the system. Natural selection may favor the evolution of extreme harmfulness if the host exploitation that causes this harm enhances the competitive success of the harmful variants over benign variants in the short run. If predator-like variants of a pathogen population out-produce and out-transmit benign variants, benign coexistence may be precluded. Instead of generating long-term stability, the evolutionary conflict of interest between a predator-like pathogen and its host generates an evolutionary arms race in which pathogen and host each evolve characteristics that give them a leg up on the other, shifting the level of host exploitation closer to the optimum for the pathogen or that of the host.

Before the last 2 decades of the 20th century, a few authors expressed reservations about the traditional dogma [8–10], but they largely were ignored. Over the past quarter century, however, the evolution of virulence has been broadly investigated by a theoretical framework that is based on the principles of natural selection [11–15]. This framework offers explanations for the broad range of virulence found among host parasite relationships and offers possibilities for virulence management (ie, the control of diseases by controlling the evolution of virulence) [16]. The evolutionary framework also provides insight into the true scope of infectious causation of chronic disease and a sense of which diseases can be prevented or cured by developing disease-control strategies, such as vaccines and antibiotics.

### **Acute infectious diseases**

For acute infectious diseases, theory about the evolution of virulence focuses on the negative effects of virulence on transmission of pathogens between hosts. Much of the variation in these negative effects of virulence depends on whether pathogens can be transmitted from hosts that have become immobilized by the infections. Pathogens that can be transmitted readily from immobile hosts should be molded by natural selection to exploit hosts severely and to be highly virulent [5]. The reason is simple. Variants that exploit severely gain the competitive advantages of this exploitation while incurring little, if any, competitive cost from the illness that their exploitation generates, because they still can be transmitted from hosts that have the severe, immobilizing illness. Specific applications of this idea are presented.

### *Vector-borne transmission*

Parasites transmitted by biting arthropods can be transmitted effectively from immobilized hosts and therefore should evolve to a higher level of virulence than directly transmitted parasites. A comparison of viral, bacterial, and protozoal agents of human diseases showed that vector-borne pathogens are more lethal on a per-infection basis than are directly transmitted pathogens [12]. The association between vector-borne transmission and virulence explains why diseases such as malaria, yellow fever, dengue, sleeping sickness, and visceral leishmaniasis are so severe, whereas most of the respiratory-tract pathogens of humans are relatively benign.

A follow-up comparison of vector-borne pathogens indicates that this greater virulence of vector-borne pathogens is related to adaptation to the conditions of vector-borne transmission rather than to some spurious correlate of vector-borne transmission, such as injection of a pathogen below the surface of the skin. This follow-up comparison used historical data to assess the virulence of particular vector-borne pathogens in humans in relation to the degree to which the pathogen had evolved in response to vector-borne transmission between humans. Specifically, it compared the virulence of vector-borne pathogens that had just been transmitted to humans with the virulence of the same kind of vector-borne pathogen that had been cycling extensively in humans and should be better adapted to vector-borne transmission between humans. As expected from evolutionary theory, the pathogens that had been cycling in humans were more severe in humans than those that recently had been introduced to humans from some other vertebrate host [12]. The yellow fever virus, for example, was less deadly in humans just after it entered the human population than it was in outbreaks that involved extensive cycling of transmission between mosquitoes and humans.

Evolutionary management of the virulence of vector-borne diseases requires interventions that elevate the immobilization of hosts more costly to the infecting pathogens. Logic dictates that this goal can be accomplished by mosquito proofing of dwellings. People who are immobilized by illness are more likely to be at home or in a hospital than people who do not feel ill; transmission from homes and hospitals therefore should tend to involve relatively virulent variants. When such dwellings are mosquito-proof, however, vectors cannot gain access to the severely ill people who are incapacitated inside these dwellings. The vectors will instead transmit pathogens from those infected people who feel healthy enough to get up out of bed and walk outdoors. These pathogens should tend to be relatively benign. The vector proofing of dwellings therefore should favor transmission of the benign strains from people in the outside environment instead of transmission of the more virulent strains that infect the bed-ridden. This favoring of benign strains through the mosquito proofing of dwellings would be manifested as an evolutionary decline in virulence.

Though this idea has not been tested directly, geographic variations in virulence and the demonstrated effect of vector proofing of houses on disease transmission suggests that it will work [17]. Strains of malaria are mild where the potential for vector-borne transmission is low and sporadic [18–19], and mosquito proofing of houses has had a strong inhibitory effect on transmission of plasmodia [20].

#### *Water-borne transmission*

As with vector-borne pathogens, evolutionary theory predicts that water-borne pathogens should evolve to relatively high levels of virulence, because they can be transmitted from immobilized people. Reliance on the mobility of infected hosts is low for water-borne pathogens, because the waste-disposal activities of attendants and the movement of water can contaminate sources of drinking water. The lethality of diarrheal bacteria is correlated positively with the extent to which they are water borne [21]. Geographic comparisons also support the idea that the virulence of diarrheal diseases is linked to water-borne transmission; among *Shigella*, for example, severe strains have been disproportionately common where the potential for water-borne transmission is high [15].

Changes in such ratios over time support the idea that the virulence of diarrheal pathogens could be managed evolutionary by blocking water-borne transmission. Diarrheal pathogens, such as *Shigella* and *Vibrio cholerae*, evolved toward lower virulence as the water supplies were cleaned up in North America, South America, Europe, and Asia. [17,21].

#### *Attendant-borne transmission in hospitals*

Like vector-borne and water-borne pathogens, pathogens acquired while in the hospital can be transmitted from immobile hosts. In this case, the transporting is done on the hands of doctors, nurses, and other attendants and the objects they touch. Such attendant-borne transmission is the major route for most serious hospital-acquired pathogens, such as the staphylococci, streptococci, enterococci, *Pseudomonas*, and *Clostridium difficile* [15]. Attendants usually do not get infected, partly because they are less vulnerable than their patients, they wash their hands before leaving the environment, and they may have generated some immunity to the hospital organisms.

Although the evolution of virulence in hospitals has been studied only superficially, the available information supports the idea that cycling in hospitals makes pathogens more harmful. A review of all hospital outbreaks of *Escherichia coli*-related infection that occurred in the United States and United Kingdom before the effective use of antibiotics assessed whether increased attendant-borne transmission was associated with increased lethality [22]. A statistically significant association was found; strains that

had been circulating for a week rarely caused death, but strains that had circulated for many months killed about 1 in 10 infants [22].

The implications for virulence management of attendant-borne transmission in hospitals mirror the implications for vector-borne and water-borne pathogens. If the attendant-borne transmission is blocked through proper hand washing and glove use, strains circulating in hospitals increasingly are represented by strains that are brought from the outside community; such community strains depend on host mobility for transmission and tend to be less virulent than strains that have been cycling in hospital environments.

### *Sit-and-wait pathogens*

Pathogens that are durable in the external environment also can be transmitted from very ill people, because such pathogens can reach susceptible individuals by relying on the mobility of susceptible, rather than infected, people. The high durability of smallpox, *Mycobacterium tuberculosis*, and *Corynebacterium diphtheriae* in the external environment helps explain why these pathogens have been scourges throughout history. The agent of plague, *Yersinia pestis*, can be transmitted as a durable pathogen by the respiratory route and as a vector-borne pathogen. A re-analysis of plague from evolutionary and historical perspectives suggests that both routes were important in the Black Death of the 14th century [5]. Perhaps it was this combination that led this outbreak of *Y pestis* to be so unusually destructive.

As is the case with the preceding categories, virulence management of sit-and-wait pathogens requires selective blocking of transmission from immobile individuals. In this case, however, the intervention requires selective inhibition of durable pathogens from the chain of transmission; this goal could be accomplished by requiring frequent air exchanges and decontamination of surfaces.

### **Virulence antigen vaccines**

Vaccination programs generally do not eradicate target pathogens; at the global level, only the smallpox vaccine has eradicated its target from the human population. When eradication does not occur, policymakers must consider effects of vaccination not only on the frequency of infection but also on the virulence of the pathogens that are left in the wake of the vaccination program. Vaccination programs that cause evolutionary reductions in the virulence tend to be successful because they leave behind mild variants that may circulate and protect unvaccinated individuals against virulent variants that might remain in the population, arise by mutation, or enter from other areas. The circulating, benign strains may protect unvaccinated individuals and the population as a whole against the spread of harmful strains.

This process of virulence management can be accomplished by a virulence antigen strategy. This strategy dictates that vaccines should be based on virulence antigens (ie, antigens that make mild but transmissible organisms harmful) [15,23]. The virulence antigen strategy differs from the traditional approach to vaccine development, which selects antigens on the basis of the protection conferred to study subjects regardless of whether the antigens are virulence antigens. By selectively suppressing the virulent variants, virulence antigen vaccines force the target pathogens to evolve toward benignity.

The virulence-antigen strategy is well illustrated by the diphtheria toxoid vaccine, which is based on a modified diphtheria toxin. The intact toxin liberates nutrients to the bacterium by killing nearby human cells. The immunologic response to the toxoid vaccine neutralizes the toxin and causes the toxin to be a net drain on the bacterium's nutrient budget. Toxinless *C diphtheriae* still can infect and be transmitted from people [24]; the toxin therefore qualifies as a virulence antigen, because it makes viable benign pathogens harmful. When vaccination prevents the negative effects of the toxin, the toxinless strains should have a competitive advantage over the toxigenic strains, because the toxinless strains do not waste valuable resources by producing an ineffective toxin. Toxinless strains therefore should increase in frequency relative to toxigenic-strains wherever toxoid vaccines have been administered extensively. This transition is confirmed by the historical data [25–28]. The most detailed data set came from the vaccination program administered in Romania from 1958 through 1972. As the acquired immunity rose to 97%, the percentage of isolates that produced toxin dropped from 86% to 3%, and diphtheria vanished [27].

If all of the costs of vaccine development and administration could be tallied and health benefits per dollar spent calculated, the control of diphtheria by the toxoid vaccine surely would be one of the most cost-effective vaccine programs in history. Only the smallpox vaccination program would rank higher, because it eradicated smallpox, which allowed for the abandonment of continuous vaccination.

### **Sexually transmitted diseases: a bridge between acute and chronic infectious diseases**

Theory about the evolution of virulence is fundamentally different for chronic infectious diseases than for acute infectious diseases. This difference is well illustrated by the virulence of sexually transmitted diseases, which are intermediate between acute and chronic infectious diseases. Syphilis has an acute phase that is characterized by a primary chancre, an early chronic phase that is characterized by a pervasive rash, and a late chronic phase (tertiary syphilis), which may involve mental illness, tumors, paralysis, meningitis, tremors, and cardiovascular disease. In other sexually transmitted diseases, the acute phase is inconspicuous or entirely lacking. HIV type 1 (HIV-1) causes a mild flu-like illness within about a month of the

onset of infection but is generally lethal in its chronic phase. The human T-lymphotropic virus type 1 causes asymptomatic acute infection soon after the onset of infection but causes paralysis, leukemia, or lymphoma decades later in a minority of infected people.

Because infected hosts generally must be mobile to engage in sexual activity, natural selection favors benignity of sexually transmitted pathogens over the short run. To be successful in the context of natural selection, however, sexually transmitted parasites must be infectious over relatively long periods of time, because options for sexual transmission of a given infection are generally less frequent than opportunities for transmission of typical agents of acute infectious diseases—a person generally has sex with many fewer people per week than he can sneeze on. Natural selection therefore favors long-term persistence and contagiousness of sexually transmitted pathogens within each host. Accordingly, most sexually transmitted pathogens are characterized by adaptations that allow the pathogen to evade the immune system to persist in and be transmitted from the body. Although sexually transmitted pathogens are molded by natural selection to be benign over the short run, this long-term persistence within hosts raises the possibility of long-term damage, even though there is low probability of severe damage during any small period of time during the first years of infection.

According to this framework, the evolution of virulence depends on the potential for sexual transmission in the host population. If the population is characterized by a high potential for sexual transmission (high rates of partner changes and unprotected intercourse), pathogen variants that replicate to relatively high levels soon after infection tend to have a greater chance of being transmitted to new partners. If the host population is characterized by a low potential for sexual transmission, the chance of a partner change occurring soon after infection is low, and the advantages of a high shedding of pathogens soon after infection is also low. If sexual partners remain together for a long period of time, a low probability of infecting the partner per act of sexual intercourse is of little consequence to the probability of pathogen transmission between the partners, because a large number of sexual contacts will occur during the long-term relationship. The low potential for sexual transmission thus favors low levels of exploitation and low virulence. A high potential for sexual transmission should favor elevated exploitation, which should increase the chances that negative side effects eventually will occur in the long run.

This theoretical framework leads to two central predictions: The virulence of sexually transmitted pathogens (1) should be greater in populations in which the potential for sexual transmission is greater and (2) should increase within a population in response to an increase in the potential for sexual transmission. Tests of these predictions uniformly have confirmed them whenever comparisons provide clear differences in the potential for sexual transmission and the virulence of infections. These

comparisons involve HIV, human papillomavirus, human herpesvirus 2, and human T-lymphotropic viruses [29].

The confirmations suggest that the virulence of sexually transmitted pathogens could be reduced by reducing the potential for sexual transmission through interventions designed to reduce partner changes and increase the use of barrier-type contraception. Information on the virulence of sexually transmitted pathogens from restricted regions provides a sense of the potential effect of such interventions.

The evidence from Senegal is perhaps the most informative in this regard. The population in Senegal has a low potential for sexual transmission relative to populations of other countries in sub-Saharan Africa. The relatively benign HIV type 2 has not been replaced by the more virulent HIV-1 in Senegal, as it has in other areas of West Africa [30]. The HIV-1 subtype that predominates in Senegal is more benign than the HIV-1 subtypes that predominate in sub-Saharan countries with a higher potential for sexual transmission [31]. A similar difference occurs among the strains of the sexually transmitted bacterium *Chlamydia trachomatis*. The strains of *C trachomatis* that predominate in Senegal are more mild than the strains that predominate in sub-Saharan countries with a higher potential for sexual transmission [32]. These comparisons illustrate how a low potential for sexual transmission can favor benign sexually transmitted pathogens even in relatively small populations that are not isolated from surrounding populations.

### **Infectious causes of chronic diseases**

Chronic infectious diseases may seem passé relative to the acute emerging diseases that have monopolized the headlines, such as Ebola virus and severe acute respiratory syndrome. Chronic diseases, however, pose a much greater threat over the near term, and something important probably can be done to control them if their causes are examined. These two claims may seem presumptuous at first. The worst plagues of history have been acute infectious diseases that spread swiftly and lethally through human populations. The most damaging examples generally have been well adapted to transmission through human populations, either directly from person to person or indirectly through a biologic vector, such as a mosquito, or a nonbiologic vehicle, such as water. These diseases as a rule were long-adapted to humans and caused their harm when they spread through previously unexposed human populations. Measles and smallpox decimated native populations in the Americas when they were introduced during the early colonial period [1–4]. Syphilis probably caused large amounts of death in previously unexposed populations in Europe as a result of a reciprocal introduction into Europe from the New World [33–34]. These outbreaks were devastating largely because they were introduced from human populations with which they had been in evolutionary arms races into

populations that had no acquired immunity and little if any evolved resistance. Terrible new outbreaks of long-standing human diseases are unlikely to be a great threat in the future because the current high level of worldwide transportation is far greater than the level needed for global transport of well-adapted human pathogens. So far as is known, the only pathogens of humans that have not already been mixed globally by human travel are zoonotic (ie, newly introduced into humans from other species). Zoonotic diseases generally have limited potential for spread in human populations and therefore have little potential for causing devastating epidemics. AIDS is the only exception; however, even AIDS causes minor damage compared with the decimation that was caused in New World populations on contact with Old World pathogens.

The diseases that are known to be a threat in the near future are those that currently are killing massive numbers of humans. In rich countries, these diseases are chronic diseases that have been and still widely are presumed to be caused by bad genes and harmful environments rather than by infectious agents. For most of the 20th century, the accepted wisdom has been that the scope of infectious chronic diseases is narrow, largely limited to the chronic phases of sexually transmitted diseases and a handful of other diseases, such as tuberculosis and shingles, diseases that were thought of as chronic sequelae to acute infectious diseases.

Evolutionary theory, however, suggests that many if not most of the major chronic diseases of humans are caused by infection [35]. The logic leading to this conclusion involves a simple application of natural selection. There are three general categories of disease causation: genetic, parasitic, and nonparasitic environmental. (“Parasitic” is broadly defined to include infectious causes.) Evolutionary considerations severely limit the feasibility of genetic causation for the most common severe chronic diseases, because such diseases tend to reduce any causal alleles down to a frequency that can be maintained by mutation [35]. If an allele provides some compensating benefit (as is the case with the allele for sickle cell anemia), it can be maintained, but few of the common and harmful diseases with unknown causes have characteristics that are consistent with such a scenario. Although a great amount of research effort has been spent on attempts to discover genetic causes of chronic diseases, this research generally has identified only genetic predispositions to common damaging diseases rather than direct causes. Even in the case of cancer, where mutational causes have been identified, these causes are insufficient to explain any more than a minuscule portion of human cancer without invoking other categories of causation. In no case has the research on genetic causation of chronic disease led to a practical breakthrough that decisively controls or cures any common and damaging chronic disease. In contrast to this lack of success, infectious causes of chronic diseases have been documented (Table 1), and preventive or curative interventions have been enacted (with vastly less funding). Peptic ulcers, stomach cancer, and liver cancer are recognized as being caused by

Table 1

Chronic diseases with an infectious cause (virus, bacteria or protozoan) accepted over the past quarter century

Disease	Infectious cause	Sexual transmission <sup>a</sup>
Tropical spastic paraparesis	Human T-lymphotropic virus type 1	Yes, genitally
AIDS	HIV	Yes, genitally
Reactive arthritis	<i>C trachomatis</i>	Yes, genitally
Cervical cancer	Human papillomavirus serotypes	Yes, genitally
Ramsay Hunt syndrome	Varicella zoster virus	No, respiratory
Progressive multifocal leukoencephalopathy	JC virus	No?
Subacute sclerosing panencephalitis	Measles virus	No, respiratory
Kaposi's sarcoma	Human herpes virus 8	Yes [38]
Liver cancer	Hepatitis B virus	Yes, sexual
Liver cancer	Hepatitis C virus	Yes?, sexual? [39,40]
Stomach cancer	<i>Helicobacter pylori</i>	No
Gingivitis	<i>Porphyromonas gingivalis</i>	Yes, orally
Peptic ulcers	<i>H pylori</i>	No
Infertility	<i>C trachomatis</i>	Yes
Ectopic pregnancy	<i>C trachomatis</i>	Yes
Rheumatoid arthritis	<i>Streptococcus pyogenes</i>	Mostly no (some orally)

A question mark indicates transmission route is uncertain.

<sup>a</sup> Most sexually transmitted pathogens can be transmitted by other routes. A “yes” in this column indicates that sexual transmission is considered to be an important, but not necessarily only, mode of transmission.

infection. Peptic ulcers and some stomach cancer can be cured and prevented by antibiotic treatment [36], and many cases of liver cancer have been prevented by screening the blood supply for hepatitis B and C viruses. Infectious agents have been associated with a large proportion of the most common severe chronic diseases of unknown cause, such as diabetes, Alzheimer's disease, atherosclerosis, and schizophrenia (Table 2). Because infectious causation of chronic diseases generally cannot be demonstrated with the same level of certainty as infectious causation of acute diseases (eg, Koch's postulates generally cannot be satisfied), acceptance of infectious causation is more protracted for chronic diseases [35]. The evidence for infectious causation of these diseases is steadily mounting and often is making sense of the evidence for genetic and noninfectious environmental causation.

This coalescence of perspectives is well illustrated by the  $\epsilon 4$  allele-associated diseases: atherosclerosis, stroke, Alzheimer's disease, rheumatoid arthritis, and multiple sclerosis. The  $\epsilon 4$  allele is maintained at frequencies that range from about 5% to 50% in different human populations. Its frequency is lowest in populations that have been living in high densities for the past few thousand years. The frequency is higher in populations that have been relatively small and isolated during this time, and it is highest in people who have been hunter-gatherers into the 20th century. Even the

Table 2  
Chronic diseases with suspected infectious causes

Disease	Suspected pathogens	Reference
Amyotrophic lateral sclerosis	Echovirus (n)	[41,42]
Alzheimer's disease (sporadic)	<i>C Pneumoniae</i> (n), human herpes simplex type 1 (s-o)	[43,44]
Multiple sclerosis	<i>C Pneumoniae</i> (n), EBV (s-o)	[45–47]
Schizophrenia	<i>Toxoplasma gondii</i> (n?), human herpes simplex type 2 (s), bornavirus (n?)	[48–54]
Bipolar disorder	Bornavirus (n?)	[55]
Juvenile onset obsessive compulsive disorder	<i>Streptococcus pyogenes</i> (n, but some s-o)	[56]
Systemic lupus erythematosus	EBV (s-o), <i>T. gondii</i> (n?)	[57,58]
Atherosclerosis and stroke	<i>C pneumoniae</i> (n), cytomegalovirus (s-o,s-g), <i>Porphyromonas gingivalis</i> (s-o)	[59–63]
Childhood leukemia	EBV (s-o)	[64]
Head and neck cancers	Human papiloma virus (s-g)	[65]
Breast cancer	Mouse mammary tumor-like virus (n?), EBV (s-o)	[66,67]
Colon cancer	JC virus (n?)	[68,69]
Type 2 diabetes	Hepatitis C virus (s?)	[70]
Crohn's disease	<i>Mycobacterium paratuberculosis</i> (n)	[71]

A question mark indicates transmission route is uncertain.

*Abbreviations:* EBV, Epstein-Barr virus; n, nonsexually transmitted; s-o, sexually transmitted by oral contact; s-g, sexually transmitted by genital contact.

lowest frequency of the  $\epsilon 4$  allele is too great to be maintained simply by mutation. The  $\epsilon 4$  allele is the primary allelic form of the apolipoprotein E gene in other primates and cannot be considered a defective allele. One possible explanation is that the  $\epsilon 4$  allele increases vulnerability to at least one infectious cause of the  $\epsilon 4$  allele-associated diseases. Although many pathogens have been associated with these diseases (Table 2), one pathogen, *Chlamydia pneumoniae*, has been associated with all of them. This finding raises the possibility that the  $\epsilon 4$  allele increases vulnerability to *C pneumoniae* infection. As a respiratory-tract pathogen, *C pneumoniae* undoubtedly inflicts a heavier cost on dense human populations than on sparse populations. If so, the longer that a particular ethnic group has lived in high-density populations, the greater the cumulative selective pressure against the  $\epsilon 4$  allele. In accordance with this scenario, individuals who are infected with *C pneumoniae* are about four times as likely to have the  $\epsilon 4$  allele as are individuals from the general population [37]. *C pneumoniae* apparently has evolved to take advantage of people who have the  $\epsilon 4$  allele and has driven down the frequency of  $\epsilon 4$  allele over time.

The theoretical framework for understanding the evolution of virulence of sexually transmitted pathogens provides clues about which infectious agents are the most likely causes of these illnesses. The primary requirement for infectious causation of chronic disease is persistent infection, and this

theoretical framework proposes that sexual transmission favors persistent infections more than any other mode of transmission. One caveat applies. Pathogens transmitted by sexual oral contact should be selected to be persistent for the same reason that pathogens transmitted by sexual genital contact are selected to be persistent (ie, because sexual oral contact occurs rarely relative to contact through coughing or sneezing). If sexual transmission is defined broadly to include transmission through sexual oral and genital contact, sexually transmitted pathogens over the past quarter century have been responsible for a disproportionately large fraction of the chronic diseases that have been accepted as being caused by infection; about 20% of all human pathogens are sexually transmitted by this definition, but about half of the pathogens that cause these chronic diseases are sexually transmitted (see [Table 1](#)). They are also candidate causes of the chronic diseases for which infectious causation strongly is implicated but not yet accepted (see [Table 2](#)). To identify infectious causes of chronic diseases, one should look closely at the sexually transmitted pathogens.

### **Acknowledgments**

I thank Gregory M. Cochran and Levi G. Ledgerwood for contributing to the development of the ideas presented in this article.

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