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Interactive Influence of Infectious Disease and Genetic Diversity in Natural Populations

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The importance of infectious disease in the survival and adaptation of animal populations is rapidly becoming apparent. Throughout evolution, animal species have been continually afflicted with devastating disease outbreaks which have influenced the demographic and genetic status of the populations. Some general population consequences of such epidemics include selection for disease resistance, the occasional alteration of host gene frequencies by a genetic 'founder effect' after an outbreak, and genetic adaptation of parasites to abrogate host defense mechanisms. A wide variety of host cellular genes which are polymorphic within species and which confer a regulatory effect on the outcome of infectious diseases has recently been discovered. The critical importance of maintaining genetic diversity with respect to disease defense genes in natural populations is indicated by certain populations which have reduced genetic variability and apparent increased vulnerability to infectious disease.

A fundamental goal of evolutionary biology is the identification and understanding of specific ecological components that influence whether a species (or a population) flourishes, survives, stumbles or becomes extinct. The regulatory contribution of infectious disease to population dynamics was recognized by Darwin[1], who suggested that epidemics provided 'a limiting check' on geometric expansion of populations, but were, he speculated, 'independent of the struggle for life'. A century later, the geneticist and theoretician J.B.S. Haldane[2] introduced the concept that parasitic diseases must also be considered as a key part of the 'struggle for life' because of the intense selective pressures exerted by these agents on the afflicted populations. It has now become generally accepted that the microbial/parasitic environment of natural populations plays a critical role in species persistence and adaptation[3]. In our own species, epidemics have influenced the outcome of major wars, stimulated migrations, and generally have been a primary determinant in mankinds demographic history[4].

Recent advances in molecular biology have revealed an elaborate organization of immunogenetic defense mechanisms in mammals. These include such interactive systems as the major histocompatibility complex, a somatic recombination of immunoglobulin and T-cell receptor gene segments, and an exquisitely programmed development of hematopoietic cell lineages[5,6]. The genomic complexities in vertebrate immune defense systems can only be interpreted in the context of previous selective host–pathogen interaction[7]. These historic epidemics have driven the co-evolution of both host and pathogen genomes, which today are punctuated with the molecular footprints of these outbreaks. We present here a number of examples from natural populations to illustrate the general principles that characterize the co-evolutionary processes of hosts and their parasites.

The consequence of disease outbreaks on populations

Evidence is accumulating that parasites (defined to include pathogenic viruses, bacteria, protozoans, helminths and arthropods[8]) play a role equal to that of predators in determining the success of natural populations. Introduction of parasites can be fatal, debilitating, or benign to a population, depending on a series of ecological parameters that influence the spread, pathology, and progression of parasitic diseases. May, Anderson and their associates have developed highly useful mathematical models which dissect the critical components of disease outbreaks in animal epizootics and human epidemics[3,8–10]. Epidemic models serve to track disease progression over time; but more importantly, they permit the definition of critical parameters which influence population dynamics of infectious disease. Paramount in these equations is the dual importance of pathogen virulence and the transmission rate of the agent in host populations.

The public health and zoological literature have provided numerous examples of disease episodes which have had a devastating effect upon the demographic structure of a population. Avian pathogens introduced by European settlers to Hawaii caused extinction of nearly one half of the endemic land bird species[11]. Several epidemics of man have been documented, but perhaps the most extensive was the bubonic plague, caused by an insect vector-borne bacterium, *Yersinia pestis*, which killed nearly 20 000 000 Europeans in the 14th century[12]. The devastating rinderpest epizootic eliminated 95% of the great wildebeest and cape buffalo herds in East Africa in the 1890s. The ecological ramifications of an ecosystem tied to the migration of diseased herds were enormous[13].

If a population or species is fortunate enough to survive an acute epidemic, there are several potential consequences of evolutionary significance. First, an epidemic will select for individuals that are genetically more resistant to the parasite than their ancestors. This selection to resistance has been nicely documented in the cases of a myxoma (poxvirus) epizootic of rabbits in Australia in the early 1950s[14] and of avian malaria in Hawaii[15,16]. In both examples, the survivors of the epizootics expressed significantly greater resistance to the pathogens than did their unexposed predecessors. Second, intense selective pressure will alter the allele frequencies of other loci that are genetically linked to loci affecting resistance. This would result in a change in gene frequencies for an array of linked polymorphic loci which are themselves unrelated to disease resistance.

Finally, when a disease outbreak is particularly severe, a large population may be reduced to a very small number of individual sur-

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vivors. This remnant population may result from the chance isolation of a few individuals who escaped exposure, or the survivors may carry resistance genes that are suddenly adaptive. Regardless of why a population survived, animals recovering from a severe contraction acquire two new ecological burdens which can contribute to population vulnerability. The first is the real prospect of demographic crashes which occur when small numbers of individuals comprise a population. The next generation may not reproduce simply because of chance or stochastic effects (e.g. accidents, altered sex ratio, prey demise, predator success, poaching, etc.). A second concern is that despite instinctive (and evolutionary adaptive) tendencies to avoid inbreeding[17], small populations must mate with close relatives to survive. The genetic and ecological consequences of such a population 'bottleneck' (Fig. 1) can be highly significant.

The impact of bottlenecks on populations and on subsequent parasite outbreaks.

Populations occasionally experience a near extinction event due to one or more of a variety of ecological pressures (climate, predation, loss of prey, drought, flood, epidemics, etc.). Demographic crashes can cause a genetic bottleneck whereby subsequent generations trace back to a few ancestors or founders. When the bottleneck is severe (say, fewer than four to eight founders) and inbreeding occurs (especially when demographic recovery is slow), chance effects result in loss of allelic variation of genes which were polymorphic before the crash[18]. Some recent population contractions have been documented by direct observation (e.g. California condors, black-footed ferrets, African wildebeest), but others are inferred by observing their genetic consequences. For instance, electrophoretic surveys of cellular enzymes have been performed in over 1000 different species since the introduction of the technique in the mid-1960s[19]. Most species retain a high level of allelic enzyme (allozyme) variability, with between 15–50% of allozyme loci being polymorphic and having average heterozygosities of 1–15% (Ref. 19). Ten- to 100-fold diminution of these estimates have been observed in a few species, often following a severe population bottleneck. In some populations, more sensitive methods for measuring genetic variability [2-dimensional electrophoresis (2DE) gels, skin graft exchange, DNA analysis of mitochondrial DNA and hypervariable nuclear DNA segments] have been used to quantify the loss of genetic diversity as well[20].

Table 1 presents a list of animal species or populations which are thought to have suffered demographic contractions in their recent history. The number reduction was actually observed in each of the species except two (cheetah and golden lion tamarin). In most, but not all, cases population genetic surveys have revealed diminished genetic variation relative to closely related species. Although the correlation of genetic diversity loss with an historic population bottleneck would support the speculation that these species reduced variability because of the event, there are other possible explanations. For example, behavioral disposition to assortive (consanguinous) mating would produce genetically uniform populations. Similarly, a species could evolve to an adaptive optimum for a particular environmental niche and then gradually shed its variability (and its associated genetic 'cost' or 'load') during an extended period of niche stability, in a manner reminiscent of Wright's 'shifting balance theory'[21]. There are few empirical data that support (or exclude) these possibilities in the case of species listed in Table 1. The 'bottleneck hypothesis' for reduction of diversity appears to be a likely explanation for the correlative occurrence of demographic contraction and reduced genetic diversity in populations we have studied (e.g. cheetah, Asian lion, black-footed ferret, giant pandas).

Population bottlenecks followed by inbreeding produce a series of well-known genetic consequences known as 'founder effects'. The theoretical aspects of bottlenecks were first explored by Sewall Wright in 1921 (Ref. 22), but the usually deleterious effects of close inbreeding were recognized by Charles Darwin and by animal and plant breeders for over a century. A graphic illustration of these effects was presented by Ralls, Ballou and co-workers in their assessment of effects of inbreeding on increasing juvenile mortality among several captive-bred mammals[23]. Inbreeding depression is difficult to observe in natural populations, but some recently described physiological impairments in two free-ranging lion populations are likely to be genetic consequences of documented population bottlenecks[24].

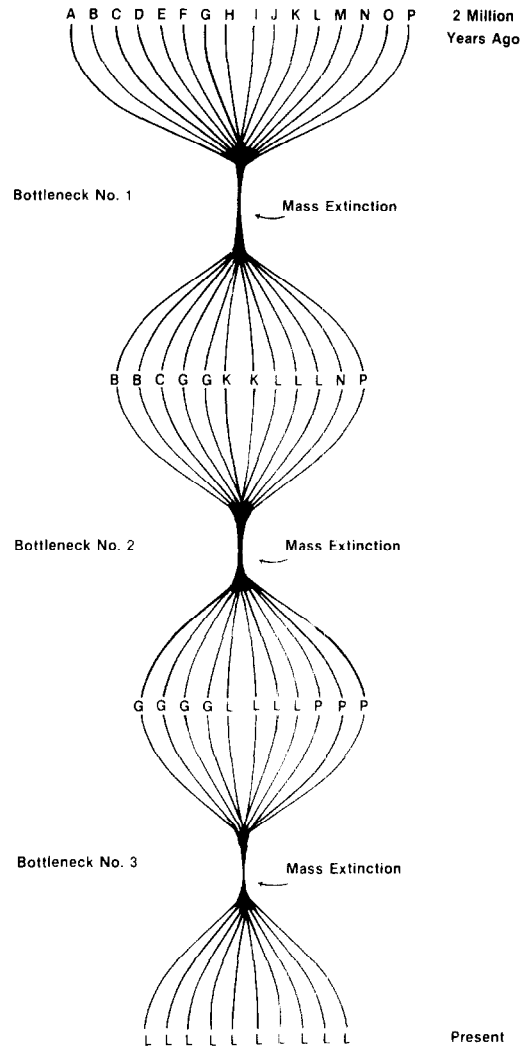

Fig. 1. A schematic representation of the effect of repeated bottlenecks on allelic diversity in a species.

An isolated population of about 110 lions living within the Ngorongoro Crater in the Serengeti ecosystem of East Africa is descended from a bottleneck population of less than 15 animals which survived an epizootic of blood sucking biting flies, *Stomoxys*, in 1962. The present population retains approximately 30% of the genetic variability (based on allozyme studies) found in the larger outbred founder lion population which is adjacent in the Serengeti Park. Wildt *et al.*[24]

Table 1. Animal species which have suffered demographic crashes: genetic and epidemiologic information

Species	Population Bottleneck				Measured loss of molecular genetic diversity	Post-bottleneck parasite
	Locale	Apparent cause	Lowest numbers of individuals	Date		
Wildebeest (*Connochaetes gnou*)	East Africa	Rinderpest	Unknown	1889	N.D.	Rinderpest
African Lion (*Panthera leo*)	Ngorongoro Crater, Africa	*Stomoxys*	6–16	1962	Yes	Unknown
Asiatic Lion (*Panthera leo*)	Gir Forest, India	Overhunting	≤ 20	1880–1920	Yes	Unknown
Black-Footed Ferret (*Mustela nigripes*)	Central U.S.	Poisoning of prey species	≤ 17	1900–1980	Yes	Canine distemper
Domestic Dog (*Canis familiaris*)	Worldwide	Domestication	Unknown	20 000 ybp* to present	Yes	Canine parvovirus
Big Horn Sheep (*Ovis canadensis*)	Western U.S.	Civilization	Unknown	1900–1980	Yes	Lungworm, *Pasteurella*, respiratory syncytial virus
California Condor (*Gymnogyps californianus*)	Western U.S.	Civilization	30	1985	N.D.	
N. Elephant Seal (*Mirounga angustirostris*)	West U.S. Coast	Overhunting	≤ 20	1820–1900	Yes	Unknown
Giant Panda (*Ailuropoda melanoleuca*)	China	Civilization	Unknown	1800–1980	N.D.	Unknown
Gypsy Moth (*Lymantira dispar*)	Northeast U.S.	Founder immigration	Unknown	1960	Yes	Unknown
Swiss Mouse (*Mus musculus*)	U.S.	Founder immigration	9	1926	No	Unknown
Golden Lion Tamarin (*Leontopithecus chrysomelas*)	Brazil	Civilization	Unknown		Yes	Unknown
Cheetah (*Acinonyx jubatus*)	East and South Africa	Pleistocene extinction of mammals	Unknown	10 000 ybp*	Yes	Feline infectious peritonitis

In all cases except cheetah and lion tamarin, the reduction in numbers has been reported in ecology literature. Measured loss of genetic diversity is based on electrophoretic estimates of allozyme and protein variation compared to closely related populations or species. N.D. – not determined. Post-bottleneck parasite: outbreaks with noticeable effect on population/species numbers. *ybp years before present.

examined several reproductive characters in the Serengeti lions, in the Ngorongoro lion population and in lions derived from a small relict population of Asiatic lions from the Gir Forest in eastern India. The Asiatic lions are also descendants of a severe population bottleneck (caused by over-hunting in India) and their measured allozyme variation is zero (≤ 1% of Serengeti levels). Both the Crater lions and the Gir lions showed elevated levels of developmentally abnormal spermatozoa plus diminished testosterone concentration relative to the outbred and abundantly polymorphic Serengeti lions. These measurements were thought to have a genetic etiology since similar damaging effects on sperm development have been observed upon inbreeding of mice and livestock[24].

Genetic theory and practice have told us that the effect of inbreeding on physiological processes varies with each inbreeding event[25]. The offspring of most sib mated attempts to derive inbred mice died out, but a few survived and form today's inbred mouse strains[26]. Much like a poker hand, the 'genetic deal' a population retains is in the luck of the draw, and few, if any, genetic hands (or bottlenecks followed by inbreeding) result in a royal flush!

A second important consequence of an inbreeding event is not so capricious; that is the removal of population genetic variability of those host loci that play a role in parasitic defense. It is rapidly becoming apparent that accumulated genetic variation of virus-interactive host loci is adaptive for the population. The reason is that parasites, especially viruses, can evolve much faster than their hosts[27], and there is intense pressure to overcome various host immunological defense mechanisms.

We have observed indirect evidence for this notion in our studies of the African cheetah[20,28]. Relative to other feline species, the cheetah has diminished genetic variability when measured using allozymes, 2D gels and DNA markers, presumably as a consequence of a severe population bottleneck in its recent history. Remarkably, the cheetahs fail to reject skin grafts surgically exchanged between unrelated animals. This result indicates an

extreme level of genetic monomorphism at the major histocompatibility complex (MHC). By comparison, the domestic cat has abundant MHC variability as evidenced by graft rejection and DNA variation.

A recent epizootic of a feline coronavirus, feline infectious peritonitis (FIP), swept through several cheetah colonies and caused 50–60% mortality over a three-year period[28]. The same virus in domestic cats has an average morbidity of 1% and seldom exceeds 10%. We do not know the precise reason for the extreme mortality in cheetahs; however, the simplest explanation may be that an FIP virus acclimated to one cheetah and rapidly spread to other cheetahs which were genetically uniform in their immunological defenses.

Other epizootics have been reported in species or populations with diminished genetic variation and it is possible that their genetic uniformity was a significant cofactor in the disease progression. The black-footed ferret (*Mustela nigripes*) (Fig. 2) once had an extensive range across middle America from Saskatchewan to Mexico. Its primary prey species, the prairie dog (*Cynomys* spp), was systematically eliminated by poisoning on agricultural land over the last century, driving the black-footed ferret to presumed extinction in the mid-1970s. In 1981, a tiny relict population was discovered in Wyoming, and a survey of genetic markers showed that the species had very limited allozyme variability, comparable, for example, to East African cheetahs[29]. An outbreak of canine distemper threatened the ferrets in early 1984, prompting the capture and vaccination of the 17 remaining ferrets[30]. The distemper epizootic, which may have been enhanced by genetic diminishment in the small population was caught literally at the last moment.

Bighorn sheep populations (*Ovis canadensis*) in the western U.S. have been continually diminished by human development for decades. The demographic history has resulted in compartmentation of the species into several small isolated populations which receive attention from the U.S. Fish and Wildlife Service[31]. A continued plight of the sheep has been an epizootic of *Pasteurella* spp. pneumonia which was thought to be augmented by a lungworm helminth infection[31]. More recently, the discovery that the sheep pneumovirus, respiratory syncytial virus (RSV) is endemic in bighorn sheep raises the possibility that this infection also predisposes the bighorn sheep (as it does in domestic sheep) to *Pasteurella* spp. pneumonia[32]. Several recent electrophoretic surveys have revealed that these sheep have limited genetic diversity, raising the specter of a genetically uniform immune response as well. The interaction of parasitic cofactors and the genetic structure of isolated populations present an interesting, but perhaps tragic, natural ecological experiment.

Fig. 2. The black-footed ferret, *Mustela nigripes*. *Photo by LuRay Parker*

Genetic defense mechanisms of host populations

Over the past few decades a remarkable series of advances has been achieved in mammalian genetics which relate to this discussion. Extensive gene maps have been constructed for several mammalian species (man, primates, mouse, cat, etc.)[32]. The mammalian genome, prototype human, consists of about 3.2×10^9 nucleotide pairs and encodes approximately 50 000–150 000 active structural genes. We know most about the mouse and human gene maps, and in the present topic the mouse map is relevant.

The development of inbred mouse strains has provided invaluable models for the study of mammalian genetics in a variety of areas, including virology. A large number of pathological mouse viruses has been shown to elicit very different disease responses among inbred strains, in most cases because of genetically controlled allelic differences between the strains. One group of viruses which has received particular attention are retroviruses or RNA tumour viruses. So far, nearly 50 different genetic loci located on various mouse chromosomes have been described[34] whose phenotypic expression involves the regulation of retroviral infection, replication, pathology, or immune response in the mouse (Table 2). Because retrovirus genomes normally integrate in host chromosomal DNA, there have been historic infections whereby retroviral genomes have become part of the host species genetic information. In some of these instances, the endogenous viruses were pathologically defective and are thought to have conferred a novel form of virus defense mechanism to infected individuals and to their descendants[35].

Possible biological mechanisms whereby cellular genes restrict or promote viral pathology are multiple, but in several cases they have been specifically defined. The major histocompatibility (MHC) locus, encodes two classes of cell surface antigens (class I and class II) that play a key role in viral antigen presentation to circulating T-lymphocytes involved in immune surveillance[5,7]. The MHC is the most extensively polymorphic

Table 2. Mouse genetic loci which affect retroviral infection, expression, replication, pathology, or immune response (For specific citations, see Ref. 28)

Gene symbol	Phenotype	Chromosome
Rmc-1	receptor, MCF virus	1
Ril-2	resistance to radiation-induced leukemia-2	1
Sxv	susceptible to xenotropic MuLV	1
A^{y}, A^{vy}	lethal yellow, viable yellow; increased incidence of mammary tumors	2
abl	oncogene of Abelson MuLV	2
Rec-1	receptor, Asian mouse ecotropic MuLV (M813)	2
Ril-1	resistance to radiation-induced leukemia-1	2
Rvil	resistance to RadLV-induced leukemia	2
If-1	NDV-induced circulating interferon	3
Cxv-2	high xenotropic MuLV antigen (Xen CSA)	4
Fv-1	restricted replication of N or B tropic MuLVs	4
Ifa	α-interferon	4
Ifb	β-interferon	4
Ril-3	resistance to radiation-induced leukemia-3	4
Inc-1	enhanced induction of ecotropic MuLV	5
Rec-1	receptor, ecotropic MuLV	5
Rmcf	resistance to MCF MuLVs	5
W	dominant spotting; resistance to Friend MuLV	5
ob	obese; enhanced appearance of mammary tumors	6
Gv-2	G_{1X} antigen expression	7
Int-2	MMTV integration site in mammary tumors	7
Inb-1	enhanced induction of ecotropic MuLV	8
Ram-1	receptor, amphotropic MuLV	8
d	dilute; increased incidence of spontaneous leukemias	9
Fv-2	resistance to focus formation by Friend SFFV	9
Ifg	γ-interferon	10
S1	steel; resistance to Friend MuLV	10
Trp-53	transformation-related protein	11
Fv-4 (Akvr-1)	resistance to NB tropic Friend MuLV	12
f	flexed tail; resistance to Friend MuLV, susceptibility to chemically induced leukemia	13
hr	hairless; increased incidence of spontaneous leukemias	14
Rvil-1	resistance to radiation virus-induced leukemia	15
Int-1	MMTV integration site in mammary tumors	15
dw	dwarf; decreased incidence of mammary tumors	16
Mtvr-1	cell surface receptor, MMTV	16
Cxv-1	high X-MuLV expression	17
Rfv-1 (H-2D)	recovery from Friend virus induced splenomegaly-1	17
Rfv-2 (H-2K)	recovery from Friend virus induced splenomegaly-2	17
Rgv-1 (H-2K)	resistance to Gross virus leukemogenesis-1	17
Rmv-1 (H-2IC)	resistance to Moloney virus-1	17
Rmv-2 (H-2D)	resistance to Moloney virus-2	17
Rmv-3 (H-2D)	resistance to Moloney virus-3	17
Rrv-1 (H-2D,I)	resistance to radiation MuLV	17
Tla	thymus-leukemia antigen	17

locus in mammals. The extreme genetic diversity of the MHC has been interpreted as a defense mechanism against invading pathogens[7]. For example, an invading virus may escape cellular immune defenses by interfering with the normal expression of MHC molecules of infected cells. Since T-cells require the combination of viral and MHC antigens for recognition, virus-infected cells which display the wrong (non-self) or no MHC determinant will not be destroyed by cytotoxic T-cells.

At least one virus, adenovirus[36], has been shown to specifically extinguish normal MHC expression in rat cells in a manner that effectively protects the cell (and the virus) from immune recognition and clearing[36]. Another virus, human T-lymphotropic virus-I (HTLV-I) uses a different strategy. HTLV-I-infected lymphocytes do not turn off cellular MHC genes, but rather, they cause cells to express a novel MHC antigen, which could confound the immune system in the self-recognition step[37]. It would seem adaptive, then, for a host population to have abundant functional polymorphism at the MHC locus, because a polymorphic population would display a heterogeneous response to viruses which evolve to interfere with MHC function.

Viruses enter target cells by cell surface receptors; most (but not all) host range restrictions of virus infectious agents are mediated by host loss of receptors or blocks in receptor–virus recognition. Polymorphic domains of virus receptors confer different individual responses to infection. A cogent example of genetic variation in receptor presentation is seen in differences in the response of inbred mouse strains to mouse hepatitis virus[38]. In natural populations, viral pathogens continually change their host range and their method often involves molecular acclimation to a new receptor molecule.

A fascinating example of host–virus restriction systems involves a polymorphism for a gene termed *Fv-4* which was found in wild mouse populations in California and simultaneously in mouse populations endemic to Japan. Resistance alleles of the *Fv-4* locus suppressed retroviral induced leukemia in both wild and inbred mice and kept the free-ranging pandemic of murine leukemia virus (MuLV) in check. The *Fv-4* gene has recently been molecularly cloned and shown to be a transcriptionally active but truncated (and therefore pathologically disarmed) endogenous retrovirus DNA sequence[39,40]. The virus restriction imposed by the mouse *Fv-4* gene apparently involves the saturation of target cell surface viral receptors with endogenous retroviral envelope proteins (products of the *Fv-4* gene), thereby blocking entry (and pathology) of the homologous, but pathological MuLV.

Consequences of disease outbreaks on parasite evolution; the case of viruses

Based on these sorts of natural genetic examples, it is becoming apparent that there are multiple host strategies for abrogation of viral/parasitic pathology. These host defenses exert a selective pressure on the virus population and promote genetic counter-adaptation by the viruses. The consequence of this reciprocal tug-of-war is rapid evolution and selective modification of virus phenotype and genotype. The raw material for viral change is both mutation and recombination. Viral genes evolve at a rate proportionate to generation time[41], which in at least one measured case was about a million times faster than the rate for the same genes in the host genome[27]. Furthermore, viruses have ample opportunity to recombine with each other as well as with cellular genetic information. An example of such recombination is again seen in the retroviral literature docu-

menting that a score of cellular 'oncogenes' have been recombinationally captured by retroviruses and placed under the control of strong viral promoters which drive their transcription. Such rapid evolution and genetic plasticity is evident in a number of viruses. For example, influenza virus and HIV, display extreme genetic variation between epidemics and between individual virus isolates. Influenza changes its serotype on an annual basis and the envelope gene sequence of different HIV isolates varies by up to 20% (Refs 42 and 43).

Occasionally a disease epizootic results in a quantum genetic change of the entire virus population that can be reflected as a change in host range, a change in virulence, in pathology or in any of the ecological components which may influence a disease episode. The canine parvovirus epizootic of the late 1970s is a recent illustration of two such events. In 1977, a virulent new parvovirus appeared in domestic and wild canids and spread rapidly throughout the world. The virus, referred to as canine parvovirus-2 (CPV-2), was closely related to feline panleukopenia virus (FPV) and mink enteritis virus (MEV). Canine parvovirus presumably evolved from one of these (or a close relative) in a host range adaptation[44,45]. In 1981, an antigenically distinct strain appeared in association with a resurgence of clinical disease. The new strain, CPV-2a replaced CPV-2 entirely within two years and persists today in domestic dogs throughout the world[44]. A similar displacement of one viral strain with another in a host species has also occurred in a myxoma virus epizootic of rabbits in Australia in 1952. In this case, the virulence and pathogenicity of the new strain was actually diminished, perhaps reflecting an adaptive value to a virus which does not eliminate its host population[14].

In summary, any discussion of evolving host and parasite genomes and their impact on each other is circular. Host population genetic structure both regulates epidemic progression and is often significantly modified by the event. Parasite genomes also endure rapid adaptation during outbreaks and the successful vectors continually evolve creative strategies to escape host defenses – consider the AIDS virus, HIV, which had the evolutionary sense to disarm the very cell designed to eliminate it, the T helper lymphoid cell. Lastly, a population bottleneck, which itself can be the consequence of a parasitic epidemic, significantly stacks the odds in favour of a devastating infectious disease vector, because when the vector overcomes one individual defense system, it more likely than not will overcome the others in a genetically uniform population as well.

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