5 Frank, S.A. (1993) *Proc. R. Soc. London Ser. B* 254, 191–197
6 Levin, S. and Pimentel, D. (1981) *Am. Nat.* 117, 308–315
7 Anderson, R.M. and May, R.M. (1982) *Parasitology* 85, 411–426
8 Ewald, P.W. (1983) *Annu. Rev. Ecol. Syst.* 14, 465–485
9 Loye, J.E. and Zuk, M., eds (1991) *Bird–Parasite Interactions. Ecology, Evolution and Behaviour*, Oxford University Press
10 Lehmann, T. (1993) *Parasitol. Today* 9, 8–13
11 Møller, A.P., Allander, K. and Dufva, R. (1990) in *Population Biology of Passerine Birds* (Blondel, J. *et al.*, eds), pp. 269–280, Springer-Verlag
12 Herre, E.A. (1993) *Science* 259, 1442–1445
13 Schall, J.J. (1990) *Parasitology* 100, S35–S52
14 Burnet, M. and White, D.O. (1972) *The Natural History of Infectious Disease*, Cambridge University Press
15 Allison, A.C. (1982) in *Population Biology of Infectious Diseases* (Anderson, R.M. and May, R.M., eds), pp. 245–268, Springer-Verlag
16 Toft, C. and Karter, A. (1990) *Trends Ecol. Evol.* 5, 326–329
17 Sibley, L.D. and Boothroyd, J.C. (1992) *Nature* 359, 82–85
18 Dwyer, G., Levin, S.A. and Buttel, L. (1990) *Ecol. Monogr.* 60, 423–447
19 Levin, B.R. and Svanborg Eden, C. (1990) *Parasitology* 100, S103–S115
20 Bull, J.J., Molineux, I.J. and Rice, W.R. (1991) *Evolution* 45, 875–882
21 Gross, R. (1993) *FEMS Microbiol. Rev.* 104, 301–326
22 Marsh, K. (1992) *Parasitology* 104, S53–S69
23 Hart, B.L. (1988) *Neurosci. Biobehav. Rev.* 12, 123–137
24 Read, A.F. *et al.* in *Ecology of Infectious Diseases in Natural Populations* (Grenfell, B. and Dobson, A.P., eds), Cambridge University Press (in press)
25 Behnke, J.M., Barnard, C.J. and Wakelin, D. (1992) *Int. J. Parasitol.* 22, 861–907
26 Svanborg Eden, C. and Levin, B.R. (1990) in *Disease and Populations in Transition: Anthropological and Epidemiological Perspectives* (Swedlund, A. and Armelagos, G., eds), pp. 31–46, Bergan and Garby Press
27 Smith, J.E. and Dunn, A.M. (1991) *Parasitol. Today* 7, 146–148
28 Werren, J.H., Nur, U. and Wu, C-I. (1988) *Trends Ecol. Evol.* 3, 297–302
29 Baudoin, M. (1975) *Evolution* 29, 335–352
30 Wülker, W. (1964) *Exp. Parasitol.* 15, 561–597
31 van Riper, C., III *et al.* (1986) *Ecol. Monogr.* 56, 327–344
32 Nowak, M. and May, R.M. (1994) *Proc. R. Soc. London Ser. B* 255, 81–89
33 Axelrod, R. and Hamilton, W.D. (1981) *Science* 211, 1390–1396
34 Haldane, J.B.S. (1949) *Ric. Sci. Suppl.* 19, 68–76
35 Hamilton, W.D. (1980) *Oikos* 35, 282–290

Short-sighted evolution and the virulence of pathogenic microorganisms

Bruce R. Levin and James J. Bull

For some microorganisms, virulence may be an inadvertent consequence of mutation and selection in the parasite population, occurring within a host during the course of an infection. This type of virulence is short-sighted, in that it engenders no advantage to the pathogen beyond the afflicted host. Bacterial meningitis, poliomyelitis and AIDS are three candidates for this model of the evolution of virulence.

B.R. Levin is in the Dept of Biology, Emory University, Atlanta, GA 30322, USA; J.J. Bull is in the Dept of Zoology, University of Texas, Austin, TX 78712, USA.

From an ecological–evolutionary perspective, the interaction between microparasites (primarily viruses, bacteria and protozoa) and their multicellular hosts can be likened to a genetic arms race. At one level, it is a race between whole species, the microparasite species versus that of the host, with both species (co)evolving over long periods. At another level, it is a race between the microparasite population(s) infecting an individual host and the somatic cells of that host (for vertebrates, primarily those of the immune system), with the outcome of this evolutionary microcosm having little or possibly no consequence for the long-term fate of either protagonist species.

Once a microorganism successfully traverses the gauntlet of physical barriers and constitutive defenses and begins to proliferate in the host, the genetic arms race commences. The parasite and host somatic cell populations will never be the same. Through clonal selection, the genetic composition of the immune system will literally evolve to control the parasite. In turn, the parasite population is under continuous selection to evade detection and destruction by those immune defenses, commonly responding by changing its antigenic characteristics. Some microparasites, such as *Trypanosoma brucei*, *Neisseria meningitidis*, *Streptococcus pyogenes* and *Salmonella typhimurium*, have mechanisms that seem to have evolved to generate variation (evolved to evolve, if you like) specifically for this arms race by augmenting the rate at which antigenic variation is produced[1,2]. For these pathogens,

this accelerated, within-host evolution of antigens is a dimension of virulence that may be essential for maintenance of the pathogen, both within individual hosts and in the population of hosts at large.

Yet it is possible that, for a wide variety of microparasites, including the bacteria responsible for meningitis, poliovirus and HIV, virulence itself is a consequence of within-host evolution that provides no benefit to the pathogen beyond the host. For other microparasites, such as *Mycobacterium tuberculosis*, this short-sighted, within-host evolution may be responsible for the diversity of symptoms observed and tissues infected.

Within-host evolution of virulence

Our model for the evolution of virulence in pathogenic microorganisms postulates that virulence evolves within the microenvironment of individual hosts, without regard to the ultimate 'survival' (transmission) of the pathogen in the population of hosts. In this model, the virulence of a pathogen is analogous to that of a clone of neoplastic somatic cells, which are the product of mutation and selection within a 'host'. Also like malignant neoplastic cells, the advantage of these virulent mutant microparasites is entirely local (within the host) and short-sighted. They may kill the host they need for their survival and, at the same time, reduce or eliminate their chance of transmission to new hosts. This model rests on three main conditions (assumptions):

(1) The microparasites responsible for the increased morbidity and mortality of the host are genetically distinct subpopulations that arise by mutation, recombination or transposition within the host during the course of infection.

(2) These subpopulations become established because of a local advantage that they have within the host over their ancestral population, because of a greater ability either to evade the defenses of the host or to enter and proliferate in cells, tissues and spaces not open to that ancestral population (in ecological terms, they undergo niche expansion). They are virulent solely because of this local advantage.

(3) The selective advantage of the virulent subpopulation is short-sighted because it is uniquely local, that is, within the host. Its members have a disadvantage in their capacity for, or likelihood of, infectious transmission to new hosts. In the extreme case, they are evolutionary dead ends.

To flesh out this model, and to evaluate its potential support, we consider how short-sighted, within-host evolution may account for bacterial meningitis, polio and AIDS.

Bacterial meningitis

The strains of *Haemophilus influenzae*, *N. meningitidis* and *Streptococcus pneumoniae* responsible for meningitis are transmitted between hosts by droplet infection[3,4]. Infections with these bacteria, including those of the specific strains responsible for meningitis, are usually asymptomatic. They establish and maintain their populations in the nasopharyngeal passages, and from those foci are transmitted to new hosts. In a minority of hosts, including hosts that are not compromised in their constitutive or inducible defenses, these otherwise commensal bacteria cause disease. Some of these diseases are respiratory, and the bacteria responsible for these respiratory pathologies may indeed have a selective advantage in the population of hosts because they have higher rates of infectious transmission, although this has not been formally demonstrated.

In contrast, meningitis is a disease caused by these bacteria that almost certainly provides no benefit in infecting new hosts (satisfying condition 3). This often fatal disorder is a consequence of these bacteria infecting and proliferating in the cerebrospinal fluid (CSF), with ensuing damage to the central nervous system (CNS), primarily because of inflammatory and other host responses to the bacteria and their metabolites. The CSF is clearly not a habitat that allows the infecting bacteria to be infectiously transmitted. Likewise, the bacterial populations that cause meningitis also appear to satisfy condition 2, because bacteria that can invade and establish populations in the CSF have a local advantage within the host by expanding their niche beyond the nasopharynx.

Thus, the ecological stage is set for bacterial meningitis to be the product of short-sighted, within-host evolution. But what about the genetic aspect? Is the progression of bacteria from the nasopharynx to the CSF a product of within-host evolution, or is it just an occasional accident in which bacteria happen to bypass the usual barriers? The CSF would seem to be a conducive habitat for bacterial growth. It contains plenty of resources, is devoid of competing microorganisms and is largely unprotected by the humoral and cellular immune defenses (although the CNS appears to have immunological defense mechanisms of its own and antibodies can cross the blood–brain barrier[3]). So it is not immediately obvious that colonizing the CSF requires a genetic change.

However, getting from the nasopharyngeal passages to the CSF normally involves a bacteremia as an intermediate stage[4], which can be symptomatic and even lethal in its own right (purpura fulminans). Blood, with its abundance of marauding defensive cells, bactericidal and bacteriostatic chemicals, is not a particularly amenable habitat for bacteria adapted to the cooler and seemingly more hospitable climes of the nasopharynx. This is doubtless a major reason that not all strains of *H. influenzae*, *N. meningitidis* or *S. pneumoniae* can cause meningitis. Capsules and other structures are needed to protect the cell from the circulating constitutive and induced immune defenses[4]. Fimbriae, which are needed for adherence to epithelial cells in the nasopharynx, are typically absent from bacteria isolated from the blood and CSF in *H. influenzae* type b meningitis[5] (which is not the case for meningitis caused by *N. meningitidis*, which is invariably piliated). Thus, for at least *H. influenzae*, to get from the nasopharynx into the blood and ultimately to the CSF appears to require physiological and/or genetic changes in the bacterial population.

Experimental evidence on CSF invasion by *H. influenzae* is consistent with a genetic change being required. Moxon and Murphy[6] found that, in a rat model, the bacteria responsible for the bacteremia are the progeny of single (or very few) cells derived from the nasopharyngeal population. Approximately equal mixtures of otherwise isogenic streptomycin-sensitive and streptomycin-resistant (Str^s and Str^r) strains of *H. influenzae* type b were introduced into the nasopharynx of infant rats. Using an inoculum of approximately 10^5 bacteria, both Str^s and Str^r strains were recovered from the nasopharynx. In contrast, of the 36 (out of 120) rats in which a nasal inoculum of this size produced a bacteremia, only one blood sample yielded both Str^s and Str^r; the rest were monomorphic for either Str^s or Str^r. This result is qualitatively consistent with the hypothesis that a mutation (which is a rare event) is required for *H. influenzae* to establish a bacteremia.

Continuing along these lines, one might expect that invasion of the CSF from the blood would likewise be a low-probability event. In this case, the frequency of monomorphic CSF from dimorphic bacteremias (13/19) is significantly lower than the 35/36 monomorphic bacteremias from dimorphic infections of the nasopharynx ($P<0.003$, for the χ^2 test). However, bacterial densities in the blood were not monitored, so the numbers of *H. influenzae* in the blood may have been so high that any requisite mutations occurred in both the Str^s and Str^r populations.

Thus, at this juncture, the evidence in support of the hypothesis that genetic changes are required for *H. influenzae* (or other meningitis-causing bacteria) to invade and proliferate in the blood and CSF is largely indirect and circumstantial. A direct test of this model is possible, however. If correct, bacteria isolated from a bacteremia or the CSF would have an advantage when competing with their nasopharyngeal or bacteremial ancestors in the new habitat. Bacteria isolated from the CSF and possibly the blood may even have a disadvantage in colonizing the nasopharynx. However, this disadvantage is not a necessary condition for this model, as the physical isolation of the CSF would be sufficient for colonization of that habitat to be short-sighted.

Poliomyelitis

Poliomyelitis is caused by an RNA virus of the picornavirus group. As for bacterial meningitis, only a minority of infected hosts show symptoms of the disease, and the site of the pathology (neurological tissue and the CNS) is not on the oral–fecal route of infection and transmission. As noted some time ago[7], infection of the CNS probably offers no benefit to the ultimate transmission of the virus.

The usual course of a poliovirus infection begins with the virus entering and replicating in the mucosal cells of the mouth, throat and intestine (there is some uncertainty as to whether it replicates in epithelial or other cells)[4,8,9]. Although most poliovirions are merely disseminated into the lumen of the gut, some enter the lymph nodes, where various degrees of progressive infection may ensue. The infection may be halted in the lymph nodes, or it may progress into the blood (a viremia) and be disseminated to other tissues in which it can replicate further, generating a transient or persistent viremia. Ultimately, poliovirus may enter the CNS. Damage to the CNS (poliomyelitis) is seen in only a small proportion of infections, so the major pathologies of poliomyelitis can be regarded as abnormalities of viral infection caused by replication in atypical tissues.

Our main reason for considering that poliomyelitis may be the product of short-sighted evolution is that the invasion of the CNS appears to be a dead end for those viruses (condition 3). There is no ready path by which such viruses can return to the gut and be disseminated[4,7].

Currently, it is not clear whether the polioviruses infecting the CNS are genetically distinct from the viruses in the original infection (condition 1) and adaptively superior to these viruses in the CNS (condition 2). There is some evidence that supports this genetic change–adaptation hypothesis. Mutations affecting neurovirulence occur in a number of different regions of the viral genome, and the high degree of neuropathogenicity of intracerebral isolates may be dissociated from the ability of these viruses to establish infections by the oral route[7,10–12]. Three additional lines of more or less circumstantial evidence also support this genetic change–adaptation interpretation: first, mutation rates in these RNA viruses are notoriously high; second, a wide spectrum of genotypes are generated within any individual host; and third, changes in virulence have been observed in populations of poliovirus over the course of passage through one or two hosts[9–11]. On the other side, there is also evidence that can be interpreted as being inconsistent with conditions 1 and 2: polioviruses disseminated from the gut during an epidemic are neurovirulent when injected into the CNS of monkeys[13]. Of course, this does not rule out the possibility that additional mutations are required for the injected poliovirus population to be pathogenic, especially because of the high mutation rates.

Thus, as for bacterial meningitis, the hypothesis that poliovirus virulence stems from within-host mutation and selection needs to be tested directly. One way to do this is to compare the nucleotide sequences of viruses from a poliomyelitis victim's alimentary tract with those proliferating in the CNS. If the within-host evolution hypothesis for the virulence of the poliovirus is correct, there should be sequence differences between the population infecting the gut and those in the CNS, with these sequence differences being responsible for the neurotropism and neuropathology of the viruses. We are unaware of any direct comparison of this sort. Evidence that might seem to bear on this comparison comes from polio vaccines, where reversion of a critical attenuating mutation is selected in the gut, sometimes leading to vaccine-derived cases of poliomyelitis[9]. However, the original mutation in the vaccine virus contributed to attenuation because it reduced the overall rate of viral multiplication rather than neurovirulence specifically. Selection for mutant polioviruses with higher proliferation rates would be

expected whether or not these mutations contributed to neurovirulence. In testing the short-sighted evolution model, it is necessary to compare sequences that are specifically responsible for the neuropathology of the poliovirus.

AIDS

AIDS is an immunodeficiency disease resulting from a long-term infection with either of two retroviruses, HIV-1 or HIV-2. While a great deal is known about the cell and molecular biology of HIV infections, the specific reason why HIV causes AIDS remains unclear[14]. There are, however, a number of models that can explain the major features of HIV infection[15]. Three of these models are consistent with our short-sighted evolution hypothesis: (1) within-host evolution of more virulent HIVs occurs[16], (2) the accumulation of HIV variation exceeds a 'diversity threshold' beyond which the immune system cannot control the virus[17], and (3) HIV evolves mutants that cannot be recognized by the existing effector lymphocytes[18].

In accordance with all three of these models, the HIV population infecting a naive host will initially proliferate and achieve relatively high densities before being reduced by the primary immune response. After this acute viremia, there is a period during which the HIV population is maintained at low levels – an 'asymptomatic' phase. During this asymptomatic period, HIV mutants with novel antigenic epitopes and other properties, 'escape mutants', would be continuously generated, and $CD4^+$ cells would continue to be killed directly or indirectly by HIV.

The three models differ in the way that virulence is manifested, but all three involve a genetic arms race between the immune system and the virus, with the virus ultimately winning. Models 1 and 3 both involve the proliferation of increasingly virulent viral lineages. In model 3, the immune system simply fails to recognize the HIV epitopes, which enables the virulent forms to increase; in model 1, the immune system recognizes the epitopes, but cannot keep pace with the virus. Model 2 (the diversity threshold model) is different again, in that virulence is not a property of any single virus. Individual escape mutants continually arise but come under immune system control because of epitopes they have in common with earlier and established HIV variants. Eventually, because of the continuous killing of $CD4^+$ cells and the generation of new HIV variants, the specific lineages of T cells responsible for controlling HIV and other microorganisms become denuded and can no longer keep these microorganisms in check.

Each of these models can account for the variation in the length of the asymptomatic period. For the virulent mutant and unrecognized epitopes (hypotheses 1 and 3), this variation would, in part, be a consequence of differences in the amount of time before the HIV mutants responsible for AIDS are produced by random mutation. Also contributing to this between-host variation in time before the onset of AIDS would be differences in the infecting HIV population, and thus in the number of steps before more virulent or immune-evasive HIVs will be produced (or in the number of ways in which they can be produced). In the case of the diversity threshold hypothesis, variation in time before the onset of AIDS would also be due largely to the stochastic nature of the mutation process and differences in the proliferation rate and in the lymphocyte-killing capacity of the mutant HIVs produced. For all three hypotheses, differences in the efficacy of the immune and constitutive defenses of the host would also contribute to the variation in the time before the onset of AIDS.

Thus, in all of these models, the virulence of AIDS is a direct result of mutation and within-host selection on the HIV virus (fulfilling assumptions 1 and 2). Unlike meningitis and poliomyelitis, in which there are many asymptomatic carriers, AIDS appears to be an inevitable outcome of infection.

On first consideration, it would seem that condition 3 (virulence is short-sighted) would not be met. The density of circulating HIV virions is considerably greater after the onset of AIDS than it is during the asymptomatic period. As a result, the probability of transmission, either sexually or via sharing needles, could be greater then than during the asymptomatic period. Thus, mutations that reduce the time before the onset of AIDS would have an advantage in the community of hosts because of greater rates of infectious transmission. The validity of this interpretation, however, can be queried. AIDS may not contribute much, if at all, to the spread of the virus through the human population. Most of the evolutionarily relevant transmission of HIV is likely to occur during the initial viremia and the asymptomatic period. During an epidemic, transmission occurring early in the course of the infection of a host will have a much greater impact on the spread of a disease than transmission occurring late in the course of an infection. Transmission occurring late in the infection would be severely discounted[19]. (An analogy would be with compound interest and the relative contributions of early and late investments.) Moreover, it would seem that the symptoms of AIDS would reduce the level of the social activities essential for transmission of HIV. [The opposite interpretation has been suggested to us by an AIDS physician, Harold Katner (pers. commun.).] Therefore, based on this admittedly speculative and circumstantial argument, there are reasons to doubt the view that AIDS is an adaptation that promotes the transmission of HIV.

Additional evidence that supports condition 3, as well as conditions 1 and 2, comes from a recent study[20] suggesting that much of the HIV proliferating within a host may not contribute to viral transmission because the virions being transmitted are not representative of the entire HIV population in an infected host. Two heterosexual couples were studied in which one member was a long-term HIV carrier and the other had recently been infected by that partner. In both couples, the virus carried by the newly infected partner was a genetically distinct subset of the HIV population present in the donor. This subset was characterized by the ability of the transmitted virus to propagate in

macrophages but not in certain other cell types that supported growth of the HIV of the donor.

Thus, in contrast to the meningitis and poliomyelitis examples, to us, the major obstacle in reconciling AIDS with this short-sighted evolution model lies in demonstrating that the disease, i.e. AIDS, is in fact short-sighted for HIV. (The evidence for within-host mutation and selection in HIV being responsible for AIDS is more compelling.) More data on which HIV variants infecting a host are transmitted and on the relative contributions of different stages of the infection to this transmission could either support or reject this short-sighted evolution hypothesis.

Manifestations and implications

In the three examples, we have elaborated on the hypothesis and have suggested how it may explain the virulence of specific microorganisms. We now describe some of its implications.

Virulence determinants

Much of the effort in current studies of the microbiology, genetics and molecular biology of infectious diseases is directed towards characterizing the nature and inheritance of virulence determinants, i.e. parasite-expressed characteristics required for virulence but not essential for the viability or proliferation of that microorganism[4,21]. The short-sighted virulence evolution model requires there to be two types of virulence determinants. One is the standard or classical virulence determinant that is expressed in a host without any change in the genes coding for its synthesis, such as the adhesins, toxins, capsules and hemolysins of pathogenic bacteria. The other class is the virulence precursor, analogous to the products (or regulatory functions) of oncogenes. These products are encoded by a gene or genes that require heritable alteration before virulence is expressed.

Multiple consequences of infection

In our three examples, we have suggested how the major pathologies may result from short-sighted, within-host evolution. Yet even when the major pathology of a disease has evolved for some other reason, within-host evolution may occur, and may lead to a variety of changes in the pathogen that are largely irrelevant to its transmission to new hosts. These changes can include niche expansion and various forms of escape from the immune system, and they may (but need not) contribute additional characteristics to the virulence of the pathogen. Possible examples include the neurological symptoms of HIV (AIDS-associated dementia[22]) and *M. tuberculosis* infections of bone and the CNS (Ref. 4).

Intervention

We see three implications of within-host evolution of virulence for antimicrobial intervention strategies (vaccination, prophylaxis and treatment of microparasite infections). First, the optimal target for a vaccination program may not be the microparasite genotypes immediately responsible for the disease, but rather the genetically distinct population being transmitted. This point was raised by Zhu and colleagues for HIV (Ref. 20). If, as their results indicate, the HIV variants being transmitted are different from those circulating, and the antigenic diversity of the transmissible subset of HIV is relatively modest, then a vaccination program directed at these transmitted virions would be more feasible and could be more effective than one directed at all variants of HIV. Second, within-host evolution provides an additional reason to control the densities of generally commensal microorganisms that have the potential to be pathogenic, such as the strains of *H. influenzae*, *N. meningitidis* and *S. pneumoniae* responsible for meningitis, since the likelihood of mutation, transposition and recombination generating virulent mutants increases with the number of microorganisms in the host. Finally, in developing attenuated microorganisms for live vaccines, it may not be sufficient to knock out the genes responsible for classical virulence determinants. If the virulence is a consequence of short-sighted, within-host evolution, the virulence precursor genes should also be identified and modified to prevent mutation to virulent states.

Inferences and tests

We consider this short-sighted, within-host evolution model to be an appealing hypothesis for the virulence of specific microparasites, but a hypothesis that has not yet been tested formally. There are at least two other hypotheses for the evolution of virulence that have to be rejected. The first is that virulence in a given host is a coincidental by-product of some other feature of the phenotype of that microparasite[23]. In this 'coincidental evolution' hypothesis, the genes responsible for the pathology evolved for some other function (possibly in a different host). The second alternative hypothesis is that virulence itself is adaptive: the host morbidity and mortality resulting from infection is to the advantage of the parasite for its transmission between hosts[19,23–26].

Distinguishing between the two latter hypotheses for the evolution of virulence of a particular microparasite is a difficult task. A great deal of hard-to-get data about the epidemiology of the infection and its within-host biology are required. However, it may be relatively easy to distinguish both these hypotheses from the short-sighted evolution hypothesis. Both the coincidental and adaptive hypotheses can be rejected by demonstrating that condition 1 holds, i.e. that the microparasites responsible for symptoms are genetically distinct from the infecting pathogens with respect to virulence factors. The short-sighted evolution hypothesis can be rejected by demonstrating that any of the three assumptions does not hold. Inference in support of this hypothesis will be strongest if all three conditions can be demonstrated to occur.

By the latter standard, none of the cases we have reviewed here offers unqualified support for the short-sighted evolution of virulence model. However, we are unaware of any evidence suggesting that these conditions do not hold for any of the diseases considered. Most importantly, and quite unlike many evolutionary

hypotheses, this short-sighted, within-host selection model can be tested experimentally for at least some microparasites. This is the primary reason we consider it so appealing.

Acknowledgements
We wish to thank Angela McLean, Richard Moxon, Olen Kew, Rustom Antia and Craig Bloch for useful suggestions, some of which we agreed with and have incorporated. We also appreciate conversations with Hamid Jafari, Francis Lee, Alexandra de Sousa and the EcLF luncheon group. This endeavor was supported by grant number GM33782 from the US National Institutes of Health (B.R.L.) and grant number DEB9106746 from the US National Science Foundation (J.J.B.).

References

1 Seifert, H.S. and So, M. (1988) *Microbiol. Rev.* 52, 327–336
2 Parson, M., Nelson, R.G. and Agenedian, N. (1984) *Immunol. Today* 5, 43–50
3 Smith, A.L. (1993) in *Mechanisms of Microbial Disease* (Schaechter, M., Medoff, G. and Eisenstein, B.I., eds), pp. 716–734, Williams & Wilkins
4 Davis, B.D. *et al.* (1980) *Microbiology* (4th edn), J.B. Lippincott
5 Weber, A.K. *et al.* (1991) *Infect. Immun.* 59, 4724–4728
6 Moxon, R.E. and Murphy, P.K. (1978) *Proc. Natl Acad. Sci. USA* 75, 1534–1536
7 Fenner, F. and Cairns, J. (1959) in *The Viruses* (Burnet, F.M. and Stanley, W.M., eds), pp. 225–249, Academic Press
8 Almond, J.W. (1987) *Annu. Rev. Microbiol.* 41, 153–180
9 Racaniello, V.R. (1988) *Adv. Virus Res.* 34, 217–246
10 Lwoff, A. (1961) in *Proceedings 5th International Poliomyelitis Conference*, pp. 13–20, J.B. Lippincott
11 Kew, O.M. *et al.* (1981) *J. Gen. Virol.* 56, 337–347
12 Nottay, B.K. *et al.* (1981) *Virology* 108, 405–423
13 Sabin, A.B. and Boulger, L.R. (1973) *J. Biol. Stand.* 1, 115–118
14 McCune, J.M. (1991) *Cell* 64, 351–363
15 McLean, A.R. (1993) *Trends Microbiol.* 1, 9–13
16 Miedema, F., Termette, M. and van Lier, R.A. (1990) *Immunol. Today* 11, 293–297
17 Nowak, M.A. *et al.* (1991) *Science* 245, 963–969
18 McLean, A.R. (1992) in *Theoretical Immunology: Part Two* (Pearlson, A.S., ed.), pp. 77–84, Addison and Wesley
19 May, R.M. and Anderson, R.M. (1990) *Parasitology* 100, S89–S101
20 Zhu, T. *et al.* (1993) *Science* 261, 1179–1181
21 Finlay, B. and Falkow, S. (1989) *Microbiol. Rev.* 53, 210–230
22 McArthur, J.C. (1992) in *Infectious Diseases* (Gorbach, S.L., Bartlett, J.G. and Blacklow, N.R., eds), pp. 956–973, W.B. Saunders
23 Levin, B.R. and Svanborg Eden, C. (1990) *Parasitology* 100, S103–S115
24 Axelrod, R. and Hamilton, W.D. (1981) *Science* 221, 1390–1396
25 Levin, S.A. and Pimentel, D. (1981) *Am. Nat.* 117, 308–315
26 May, R.M. and Anderson, R.M. (1983) *Proc. R. Soc. London Ser. B* 219, 281–313

Virus strategies for evasion of the host response to infection

Geoffrey L. Smith

The attack on viruses and virus-infected cells by the mammalian immune system has provided considerable selective pressure for viruses that have evolved vigorous countermeasures to pre-empt, neutralize or evade this host attack. These countermeasures are astonishingly diverse, and their study imparts fundamental information about immunology and the mechanisms enabling viruses to survive and cause disease.

G.L. Smith is in the Sir William Dunn School of Pathology, University of Oxford, South Parks Road, Oxford, UK OX1 3RE.

Mammalian viruses possess many defences to combat host responses to infection. This is especially true for large DNA viruses which, because of their greater coding capacity, may have several defensive strategies. Some of these have been discovered by sequencing the virus genomes and identifying sequence similarities with host proteins that function in the immune system. Collectively, these defensive strategies illustrate the need for many viruses to respond to the formidable attack of the immune system to replicate sufficiently to survive in the mammalian host, and emphasize the coevolution of viruses and their hosts. Here, I review some of the strategies used by viruses to escape or suppress components of the host response to infection (summarized in Table 1), excluding antigenic variation and latency, and with an emphasis on DNA rather than RNA viruses.

Counteracting complement

Complement is a major non-specific host defence against microorganisms and may be activated in two ways: the classical pathway requires a specific antibody–antigen interaction, while the alternative pathway may be activated in the absence of antibody by certain antigens, such as lipopolysaccharide. Each pathway contains a cascade of enzymatic reactions that greatly amplifies the original signal and leads to the formation of a membrane attack complex that damages the surface membrane of enveloped viruses or infected cells (Fig. 1). Each pathway is carefully controlled by factors that