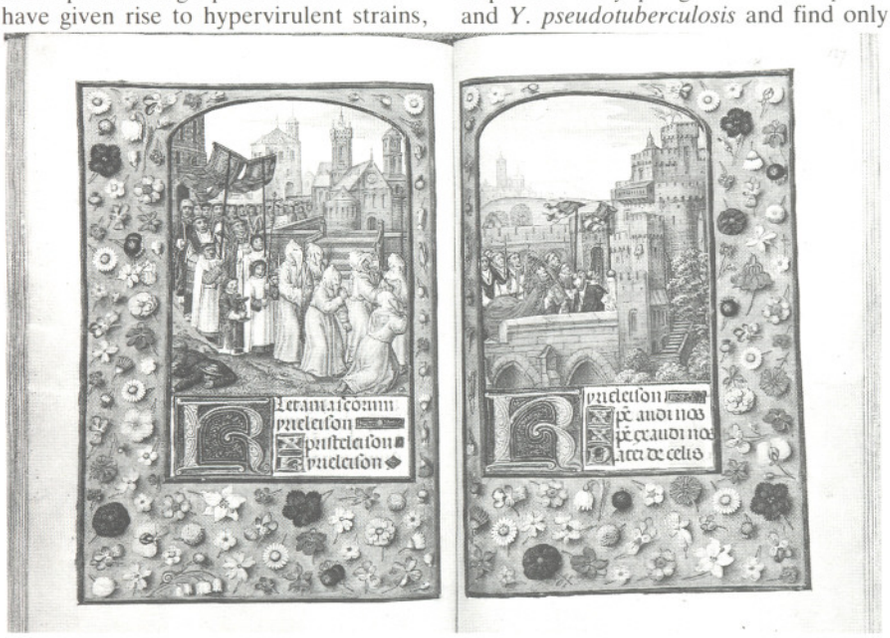
Reprinted from Nature, Vol. 334, No. 6182, pp. 473-474, 11 August 1988

Epidemics

Evolution of plague virulence

Richard E. Lenski

WHAT was the ancestral form of the human immunodeficiency virus (HIV)?[1] How did HIV become so virulent? We do not yet know the answers to these questions, but on page 522 of this issue[2], Rosqvist, Skurnik and Wolf-Watz present an interesting hypothesis for the genetic basis of the evolution of virulence in a former scourge, the bubonic plague. They hypothesize that less virulent strains of *Yersinia pestis*, the bacterium that causes bubonic plague, were harboured by non-human hosts, rats and fleas, during endemic phases. Single point mutations could have given rise to hypervirulent strains, which spread to cause the plague epidemics.



Soane Museum, London/E.T. Archive

St Gregory's procession against the plague. From the Soane Book of Hours, ca *1500.*

Rosqvist *et al.* base their hypothesis on their elucidation of the genetic determination of virulence in *Y. pseudotuberculosis*, which is closely related to *Y. pestis*. The two are essentially indistinguishable from DNA hybridization data[3] and *Y. pseudotuberculosis* infections in rats provoke immunity to *Y. pestis*. Previous work has implicated two outer-membrane proteins in mediating the invasion of mammalian cell cultures by *Y. pseudotuberculosis*: invasin, which is encoded chromosomally[4], and Yop1, which is encoded by a plasmid[5]. Rosqvist *et al.* demonstrate that mutations in one or the other of the genes encoding these proteins have little effect on virulence of *Y. pseudotuberculosis* in mice. But when mice were administered bacteria containing mutations in both genes, that is, *Inv*$^-$ and *Yop1*$^-$, the LD_{50} went down dramatically, indicating a heightened degree of virulence. *Y. pestis* apparently expresses neither invasin nor the Yop1 protein, consistent with its much greater virulence relative to *Y. pseudotuberculosis* and with its inability to grow invasively in mammalian cell cultures.

Wolf-Watz and colleagues have shown previously that virulence plasmids pYV019 and pIB1, carried by *Y. pestis* and by *Y. pseudotuberculosis*, respectively, have a high degree of homology[6]. Both carry the *yopA* gene, although only *Y. pseudotuberculosis* expresses the corresponding Yop1 protein[7]. In the work reported in this issue, Rosqvist *et al.* have sequenced the *yopA* genes from *Y. pestis* and *Y. pseudotuberculosis* and find only 15 nucleotide differences among 1,230 base pairs. One of these differences, however, is a one-base deletion that throws off the reading-frame in *Y. pestis*.

The non-functional *yopA* gene in *Y. pestis* is presumably derived from a functional ancestral state. When Rosqvist *et al.*[2] introduce the functional gene from *Y. pseudotuberculosis* into *Y. pestis*, they observe a corresponding reduction in the virulence of *Y. pestis*. Thus, *Y. pestis* has apparently undergone a mutation in the past that caused loss of function of the *yopA* gene, with a concomitant increase in its virulence. This supports the hypothesis that single mutations played an important role in triggering plague epidemics[2].

But mutations alone cannot drive epidemics. The necessary genetic variability in the pathogen must exist and so must the appropriate selective conditions for the spread of hypervirulent mutants. Hence, there remains the equally perplexing question concerning the selective pressures that were responsible for the increase in the frequency of hypervirulent strains, once they appeared by mutation. Indeed, for many years, conventional wisdom favoured the view that evolution would select those pathogens which had the least harmful effects on their hosts[8]. On the other hand, pathogenicity, or virulence, is often associated with transmission[9]. Mathematical analyses by May and Anderson[8,9] and by Levin and Pimentel[10,11] have shown that the evolution of pathogens is highly dependent on this coupling between transmissibility and virulence.

To see this, consider a simple equation for the rate of change in the number of infected hosts in a population: $dY/dt = \beta XY - \alpha Y$, where X is the number of susceptible hosts, Y the number of infected hosts, β is the transmission rate of the pathogen and α the rate of mortality including that induced by the pathogen. If the number of susceptibles is very high, the rate of increase of the pathogen — as reflected by the rate of increase of infected hosts — will generally be maximized when the transmission rate is high, even if this entails a high rate of host mortality. In contrast, reduced virulence could be favoured if perpetuation of the pathogen depends on prolonged survival of infected carriers, as may occur when the number of surviving susceptible hosts is very low. In a sense, a critical factor from the perspective of the pathogen is whether there is ample opportunity for infectious exploitation of other hosts or whether being 'nice' to a current host is the best way of achieving maximal fitness[12].

The dramatic declines of the human population in Europe during the great plague epidemics of past centuries were presumably accompanied by comparable declines in the population of susceptible rodents. Not only might these epidemics have been triggered by the appearance of hypervirulent strains of *Y. pestis*, as Rosqvist, Skurnik and Wolf-Watz hypothesize[2], but the declining populations of susceptible hosts may in turn have favoured less virulent strains.

In a similar way, mortality among groups at high risk for AIDS, together with changing patterns of behaviour, may radically alter selection acting on the human immunodeficiency virus (HIV). How that might effect the evolution of the virus is not clear, owing to our present ignorance. As May and Anderson[13] have emphasized, we do not even know if heterosexual transmission of HIV is self-sustaining in developed countries. □

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Printed in Great Britain by Turnergraphic Limited, Basingstoke, Hampshire