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Syphilis in Renaissance Europe: rapid evolution of an introduced sexually transmitted disease?

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When syphilis first appeared in Europe in 1495, it was an acute and extremely unpleasant disease. After only a few years it was less severe than it once was, and it changed over the next 50 years into a milder, chronic disease. The severe early symptoms may have been the result of the disease being introduced into a new host population without any resistance mechanisms, but the change in virulence is most likely to have happened because of selection favouring milder strains of the pathogen. The symptoms of the virulent early disease were both debilitating and obvious to potential sexual partners of the infected, and strains that caused less obvious or painful symptoms would have enjoyed a higher transmission rate.

Keywords: syphilis; virulence; sexually transmitted disease; emerging infectious disease

1. INTRODUCTION

Newly emerging infectious diseases are among the most important and conspicuous problems in public health. This is not a new phenomenon, and novel diseases have often caused tremendous mortality and misery in the past. In 1495, for example, a horrendous new disease appeared in Europe. At the time it went by a variety of names including the 'Great Pox' or the 'French Disease', but it is more familiar to us as syphilis (Quétel 1990; Oriel 1994; Arrizabalaga *et al.* 1997; Cartwright & Biddis 2000; Meyer *et al.* 2002). Descriptions of the disease from this time make it clear that it was extremely unpleasant, and medical histories are filled with quotes from contemporary authors describing the horrors of the disease. A few years after its first appearance, however, the symptoms of syphilis were noticeably less severe, and within half a century it was widely observed that the disease was much less serious than it had initially been. Although this decline in virulence has been commented on before, it has not been examined with reference to modern ideas on disease evolution. Here, I briefly review the way in which the symptoms of the disease changed, and suggest possible evolutionary mechanisms that could explain the very high initial virulence of the disease and the subsequent decline in severity.

2. CHANGES IN THE SYMPTOMS OF SYPHILIS AFTER 1496

Syphilis, caused by the spirochaete *Treponema pallidum*, occurs in three stages. Primary syphilis is characterized by an indurated ulcer at the point of infection (the 'chancre'). This is followed by secondary syphilis, typically involving fever, a sore throat and a rash, but other symptoms may occur. Finally, tertiary syphilis occurs after a latent period that usually lasts for many years and has the most severe symptoms. These include the 'gummas' or gummy tumours formed in virtually any body tissue, and neurological damage sometimes leading to insanity (Wright & Csonka 1996). These stages of syphilis can be distinguished in descriptions of the disease from authors in the sixteenth and seventeenth centuries, but in its early years the progress of the disease seems to have been faster, many of the symptoms were much more severe, and some symptoms were reported that are completely absent nowadays. The following is a description of secondary syphilis, written by Ulrich von Hutten (1519), himself a sufferer.

> …truly when it first began, it was so horrible to behold that one would scarce think the Disease that now reigneth to be of the same kind. They had Boils that stood out like Acorns, from whence issued such filthy stinking Matter, that whosoever came within the Scent, believed himself infected. The Colour of these was of a dark Green and the very Aspect as shocking as the pain itself, which yet was as if the Sick had laid upon a fire.
>
> (Von Hutten (1519), translation from Major (1945), p. 31.)

The contrast between this and the description of some of the symptoms of modern secondary syphilis from a modern textbook is striking.

> The lesions are numerous, variable and affect many systems. Inevitably there is a symmetrical, non-irritating rash and generalized painless lymphadenopathy. Constitutional symptoms are mild or absent; they include headaches, which are often nocturnal, malaise, slight fever, and aches in joints and muscles. The rash is commonly macular, pale red and sometimes so faint as to be appreciated only in tangential light… Pustular and necrotic lesions are rarely seen in temperate climates but still occur in tropical regions.
>
> (Wright & Csonka 1996, p. 711)

Other reported symptoms of early syphilis that are not seen nowadays include severe ulceration of the part of the body first infected (often the genitals), necrosis following the appearance of the pustules, which could lead to soft tissue being eaten away to the bone, and the rapid onset of the 'gummy' tumours typical of tertiary syphilis today (Quétel 1990; Arrizabalaga *et al.* 1997).

Evidence for the timing of these changes comes from the writings of several first-hand witnesses. Quétel (1990) discusses this, quoting writers from the early sixteenth century such as Johannes Benedictus (1508), Ulrich von Hutten (1519) and Jean de Bordigné (1529) to demonstrate that changes in the virulence of the disease were observed in as short a time as 5–7 years from the initial epidemic. He quotes Fracastorius in 1546: '…the sickness is in decline, and very soon it will no longer be transmissible even by contagion, for the virus is getting weaker day by day…' (Quétel 1990, p. 50). Certainly, by the early to mid sixteenth century it seems that many of the symptoms of the early disease, such as the pustules (Von Hutten's boils), the foul smell and the pains had become rare among sufferers (Quétel 1990; Oriel 1994; Arrizabalaga *et al.* 1997). It seems, therefore, that following its first appearance, syphilis quickly changed from an acute, severe and debilitating disease to the milder chronic infection that is modern syphilis.

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3. MECHANISMS LEADING TO CHANGES IN VIRULENCE

Why did the symptoms of the disease change, and why so rapidly? To answer these questions, it is useful to consider the origins of the disease. There are four theories for the origin of syphilis, summarized by Meyer *et al.* (2002). These are

(i) that syphilis was always present in Europe and was misdiagnosed as (for example) leprosy prior to 1495;
(ii) that syphilis evolved from a less virulent, non-venereally transmitted treponemal disease;
(iii) that syphilis was introduced from Africa; and finally
(iv) that syphilis was brought to Europe from the New World following Columbus's voyage in 1492. This last theory is the most widely accepted, although it is still controversial (Baker & Armelagos 1988; Rothschild *et al.* 2000; Meyer *et al.* 2002).

Assuming that the New World theory is correct, one possible explanation for the decline in the severity of the disease is that the new host population developed a degree of immunity (Oriel 1994; Cartwright & Biddis 2000). This may explain some of the longer-term changes in disease symptoms, but the speed of the change in virulence means that this is unlikely to be a useful explanation for the changes seen during the early years of the epidemic. A decline in the virulence of syphilis was noted between 5 and 7 years from the start of the epidemic, which, being less than a single generation, is too short a time for any form of resistance to arise in a human population by selection. If this argument is correct, then there is one alternative explanation that immediately springs to mind—that rather than the host population changing, it was in fact the disease that evolved during this period.

What might cause a disease to evolve in this way? A few authors have suggested that syphilis evolved to become less virulent (Hudson 1963, 1965; Guerra 1978; see also Garnett & Holmes 1996), but none has put forward a plausible mechanism for the change in virulence. To do so, we have to consider the selective consequences of virulence to the disease agent. Over the past 20 years, biologists have come to realize that the virulence of an infectious disease agent is not necessarily an unpleasant side-effect of infection that brings little benefit to the agent. Instead, virulence is now thought of as being an adaptive characteristic that will have been influenced by selection to give an infectious agent with maximum fitness (Anderson & May 1982; Ewald 1983; Bull 1994; Frank 1996). There are obvious costs associated with causing pathology to the host, the most dramatic of which is the death of the agent when the host dies, but there are also fitness benefits for infectious disease agents that harm their hosts, such as an increased transmission rate or a reduced probability of clearance by the host's immune system (Frank 1996; Lipsitch & Moxon 1997). Infectious agents will therefore trade-off the benefits and costs associated with virulence, and selection will favour those that achieve the best balance between the costs and benefits associated with virulence. This optimal virulence is usually expected to be at some intermediate level, so infectious diseases that cause intermediate degrees of damage to their hosts, rather than minimal or maximum damage, will often evolve.

The best empirical example of an infectious disease evolving to an intermediate level of virulence is that of the myxoma virus in Australia and Europe (Fenner & Ratcliffe 1965; Fenner 1983; see also Escriu *et al.* 2003 for a more recent example from a plant virus). The virus strain used was isolated from a South American rabbit species, and was exceptionally lethal when it infected European rabbits in Australia and Europe. Because virus transmission was highest at an intermediate level of pathology, however, within a few years the virus evolved to a much lower level of virulence. This has obvious parallels with the changes in virulence seen in syphilis after 1495. Like the myxoma virus, syphilis found itself infecting a new host population in which it caused considerable pathology. Less virulent strains already present in the introduced pathogen population, or new mutants that caused less virulence, would then spread if they enjoyed higher transmission rates than the more virulent strains, leading to the changes in virulence noted by contemporary authors.

Why was virulence so high when syphilis first appeared? We can speculate that the syphilis spirochaete in the New World had evolved to an optimum virulence in a coevolving host population with a variety of resistance mechanisms. On introduction to a European host population with none of these mechanisms in place, the pathogen would have been 'released' from these constraints on virulence, and ironically was then more pathogenic than necessary to give the highest fitness. Alternatively, the constraints on virulence of the pathogen may have been other aspects of host physiology that were not resistance adaptations and were not present in the European population for reasons unrelated to host–parasite coevolution. A final possibility is that the transmission mechanism of the disease changed, leading to changes in pathology. Baker & Armelagos (1988) suggested that syphilis only became venereally transmitted when introduced to Europe, and that before this time in America it had been directly transmitted by other forms of close contact, particularly among children. A change to venereal transmission would mean that adults would become infected with no prior exposure to the disease when younger, which could mean that any acquired immune response to it was reduced.

What of the mechanism by which selection occurred? Several authors have recently considered the evolution of sexually transmitted diseases (STDs), and it has been pointed out that STDs that advertise their presence to potential sexual partners of the infected host are likely to be selected against (Hurst *et al.* 1995; Knell 1999). The venereal nature of syphilis transmission was well known only a few years after the beginning of the epidemic (e.g. Alexandri Benedicti, writing in 1497, cited in Quétel (1990) and Francisco Lopez de Villalobos, writing in 1498, cited in Oriel (1994)). Many of the symptoms of primary and especially secondary syphilis described during the early part of the epidemic, such as the pustules and the foul smell, would have been obvious to any potential sexual partner of a sufferer, enabling people to avoid the infected person and thereby reducing transmission. Furthermore, some of the symptoms that have been described for early syphilis, such as the agonizing pains in the joints, would have effectively disabled the sufferer, or at least

distracted them considerably from seeking out new sexual partners. It is noteworthy here that the pustules, probably the most visible sign of disease in early sufferers, were singled out by early sixteenth century authors as a symptom that became noticeably rarer in the years after the start of the epidemic. These two mechanisms, the obvious nature of the infection and the disabling nature of the symptoms during the most infectious period, would both lead to reduced transmission of virulent strains. It should, however, be noted that these mechanisms may not be sufficient to explain all of the changes seen in the disease; for example, the increase in the latent period before the onset of tertiary syphilis does not have a clear adaptive explanation, but it may well be that both played important roles in the evolution of the disease.

4. SUMMARY AND IMPLICATIONS FOR MODERN SYPHILIS

To summarize, syphilis appeared in Europe at the end of the fifteenth century and caused very severe symptoms. In a matter of years, the severity of those symptoms was much reduced. This happened too fast for any heritable change in host resistance to be responsible, and the alternative, that the disease rather than the host changed, is the more likely explanation. The very severe symptoms seen at the start of the epidemic can be attributed to a disease newly introduced into a naive host population with none of the coevolved resistance mechanisms that would previously have constrained it, possibly aggravated by a change in transmission route. The mechanism leading to the reduction in virulence is likely to be that less virulent disease strains achieved better transmission rates, probably because the symptoms of the more virulent strains were both obvious to potential sexual partners, enabling them to avoid infection, and also debilitating to the extent that infected hosts may have been unable to transmit the disease.

Finally, what of the evolution of modern syphilis? Like the myxoma virus, syphilis has not evolved to minimal virulence, although the pathology caused by modern primary and secondary syphilis is trivial compared with that experienced by those who contracted it in the early years of the epidemic. Tertiary syphilis will still cause severe pathology, but the host is no longer infectious at this point in the disease so there will be little selection for strains that are less virulent. The twentieth century saw the development of effective treatments for syphilis, initially salvarsan and then penicillin, which led to syphilis changing from a common, endemic disease to a rare one, at least in the developed world. This fast and easy treatment will be selecting for strains of syphilis that are harder to detect and are more infective in the earlier stages of the disease. A total of 17% of cases surveyed in a recent study of a syphilis outbreak in the UK had symptoms that were insufficient to make them seek medical attention (Cook *et al.* 2001), and asymptomatic cases were reported from an earlier outbreak (Battu *et al.* 1997). Given the approximately 30-fold increase in the transmission probability of HIV that accompanies infection with syphilis (Chesson & Pinkerton 2000), the prospect of a future outbreak of asymptomatic syphilis is something that should be given more attention.

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