Historical Intensity of Natural Selection for Resistance to Tuberculosis

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ABSTRACT

Infections have long been thought to exert natural selection on humans. Infectious disease resistance is frequently invoked as a mechanism shaping human genetic diversity, but such hypotheses have rarely been quantitatively evaluated with direct measures of disease-related mortality. Enhancement of genetically determined resistance to tuberculosis by natural selection has been proposed as a factor explaining the decline of tuberculosis in Europe and North America in the period 1830–1950 (before the advent of antimicrobial chemotherapy) and the apparently reduced susceptibility of Europeans and their descendants to tuberculosis infection and/or disease. We used Swedish vital statistics from 1891 to 1900 to estimate that individuals who escaped mortality from pulmonary tuberculosis (PTB) during the European tuberculosis epidemic would have enjoyed a fitness advantage of 7–15% per generation compared to individuals who were susceptible to PTB mortality; individuals with 50% protection would have had a selection coefficient of 4–7%/generation. Selection during the peak of the European TB epidemic could have substantially reduced the frequency of already rare alleles conferring increased susceptibility to PTB mortality, but only if the phenotypic effects of these alleles were very large. However, if resistant alleles were rare at the beginning of this period, 300 years would not have been long enough for such selection to increase their frequency to epidemiologically significant levels. Reductions in the frequency of rare susceptibility alleles could have played at most a small part in the decline of the epidemic in the century preceding 1950. Natural selection by PTB deaths during the European TB epidemic alone cannot account for the presently low level of TB disease observed among Europeans and their descendants just prior to the appearance of antibiotic treatment.

THE role of natural selection by infectious disease in shaping human evolution is a subject of considerable importance and growing interest. Since the discovery that individuals heterozygous for the sickle cell allele are protected against severe malaria (Allison 1964), a number of other alleles of human genes have been implicated in conferring resistance or susceptibility to infectious diseases. Such effects have been detected for a wide range of genes, including those affecting erythrocyte antigen expression and metabolism, iron storage, and components of the immune response, including pathogen receptors, cytokine and chemokine receptors, and class I and class II major histocompatibility complex loci (Hill and Motulsky 1998).

For natural selection to cause the evolution of any trait, including susceptibility to an infectious disease, there must be both genetic variation between individuals in the trait and a difference in reproductive fitness between individuals who differ in the trait. In the case of tuberculosis, both of these conditions appear to be satisfied.

Today, an estimated one-third of the world’s population is infected with Mycobacterium tuberculosis. While most of these individuals have asymptomatic infection, there are an estimated 8 million new cases of active tuberculosis disease and 2 million deaths from tuberculosis each year. Untreated pulmonary tuberculosis is lethal in \(\sim\)50% of cases (Murray et al. 1990); the remaining patients spontaneously resolve the disease. The most severe forms of tuberculosis are found in children (from the perspective of natural selection, before reproductive age) and are generally lethal. Estimates from the seventeenth, eighteenth, and early nineteenth centuries suggested that as many as 20–30% of all deaths were attributable to tuberculosis at the peak of the epidemics in European cities (Drolet 1942). Clearly, such a major cause of mortality has considerable potential to exert selective pressure in favor of human genes that confer protection against it.

Several lines of evidence suggest that individuals within a single human population vary genetically in their susceptibility to infection with and disease and mortality from M. tuberculosis. The most compelling support for this conclusion comes from twin studies. Monozygotic twins have considerably higher concordance rates for tuberculosis morbidity than do dizygotic twins, and concordance rates among relatives increase with the closeness of the blood relationship to a degree that would be difficult to explain by nongenetic factors.

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(Ciocco 1940; Kallman and Reisner 1943; Puffer 1944; Simonds 1963; Comstock 1978).

Other evidence is more controversial because of the difficulties of separating genetic and nongenetic factors. Rich (1944) reported that black patients infected with tuberculosis had more severe disease than did whites. Stead and colleagues found higher rates of skin test conversion (a marker for infection) among blacks than among whites in nursing homes exposed to index cases of active tuberculosis (Stead et al. 1990), even when stratifying by the race of the index case, although at least one other study has failed to detect racial differences in susceptibility to infection (Hoge et al. 1994).

Additional evidence, subject to the same qualifications, comes from cases in which M. tuberculosis has entered populations with little or no known prior exposure to the organism. In such cases, observers have noted extraordinarily high rates of primary pulmonary tuberculosis (TB) in adults, unusually severe forms of TB disease, high case mortality rates, and extremely rapid spread of infection, as indicated by tuberculin skin test positivity (Cummins 1908; Borrel 1920; Ferguson 1934; Wigley 1973; Sousa et al. 1997).

Within populations, variations in susceptibility to tuberculosis have been associated with polymorphisms in a number of genes, including those for the vitamin D receptor (Bellamy et al. 1999), natural resistance-associated macrophage protein 1 (NRAMP1; Bellamy et al. 1998), class I and class II major histocompatibility complex loci, interleukin-1β and its receptor antagonist (Wilkinson et al. 1999), interferon γ and its receptor (Altare et al. 1998), and others (Bellamy 1998, 2000). Clearly, many genetic loci are involved in determining susceptibility to tuberculosis (Abel and Casanova 2000). In some of the analysis that follows, we describe the population genetics of a single gene affecting susceptibility to tuberculosis, but we do so as a deliberate simplification.

Natural selection for resistance to tuberculosis has been proposed as an explanation for two well-known epidemiological features of the disease. First, it has frequently been suggested that the higher level of resistance of Europeans and their descendants to tuberculosis, compared to that of members of previously unexposed populations, reflects a difference in the history of natural selection by tuberculosis during the epidemics of tuberculosis in European and North American cities from the seventeenth century onward (Grigg 1958b; Stead 1992). Second, natural selection has been proposed as a major factor explaining the decline of these same epidemics between the mid-nineteenth century and the mid-twentieth century. During that period (before the availability of vaccination or effective chemotherapy), the death rate from tuberculosis declined about sixfold in Europe and the United States. Several authors have suggested that the decline was due to a reduction in the proportion of the population that was susceptible to TB by natural selection (Pearson 1912; Frost 1937, 1939; Grigg 1958a; Comstock 1975; Davies et al. 1999), although this explanation has been criticized on the grounds that the decline occurred too quickly to be a result of selection on the host population (Rich 1944).

In this article, we use statistics on fertility, pulmonary tuberculosis mortality, and all-cause mortality in Sweden in the period 1891–1900 to estimate the intensity of selection that would have existed in that population in favor of a genotype conferring partial or total resistance to mortality from pulmonary TB. We then use the estimates obtained to evaluate the plausibility of two hypotheses: (1) that natural selection played a major role in making Europeans, who had a long history of exposure to epidemic tuberculosis, more resistant to tuberculosis than less-exposed populations and (2) that reductions in the proportion of the population that was susceptible to TB, by natural selection, were an important cause of the decline in the tuberculosis epidemic in Europe in the century preceding the discovery of effective treatment.

In evaluating these hypotheses, we make the simplifying assumption of considering the effects of a single gene conferring protection against tuberculosis. The effects of this simplification are discussed.

METHODS

General approach: Well-known procedures exist for estimating selection coefficients in an age-structured population, given standard life tables for each genotype of interest (Cavalli-Sforza and Bodmer 1971; Charlesworth 1994). We developed a simple method to use the available data on all-cause and pulmonary tuberculosis (PTB) mortality to produce estimates of the entries in hypothetical life tables for susceptible and resistant individuals under various assumptions about the genetics of resistance to pulmonary tuberculosis mortality and then to use the calculated life tables to estimate the intensity of selection in favor of a particular disease-resistance gene.

Mortality data: Age-specific data on fertility and all-cause mortality for Sweden and age-specific pulmonary tuberculosis mortality for Stockholm were obtained from tables compiled by Sundbärg (1970), all for the decade 1891–1900. For each gender (i = M, F) and age (x = 0, 1, 2 . . .) we obtained the population-wide, gender- and age-specific, all-cause death rate d_i, and the death rate from pulmonary tuberculosis d_x. For multiyear age groups, we interpolated life table entries linearly between midpoints of the age groups.

Hypothetical age-specific mortality tables for PTB-susceptible and PTB-resistant persons: The first step in converting these cause-specific mortality tables to selection coefficients was to assume a particular, simplified population structure. Separate calculations were made
for males and females; we drop the gender subscript for brevity.

It was assumed that the population consisted of individuals of two types: those “susceptible” to pulmonary tuberculosis mortality and those “resistant” to pulmonary tuberculosis mortality. Age-specific death rates for susceptible persons carry the subscript $S$ and those for resistant persons, subscript $R$. The protection conferred by the resistant genotype, $y$, is the fractional reduction in annual risk of mortality from pulmonary tuberculosis for an $R$ individual compared to an $S$ individual (comparable to a measure of vaccine efficacy; $y = 1$ indicates complete protection):

$$t_R = (1 - y)t_S. \tag{1}$$

A fraction $f$ of the population was assumed to be resistant. (We assumed that $f$ was independent of age, a simplification that made a negligible difference in our calculations.) We further assumed that age-specific death rates from causes other than PTB were equal for susceptibles and resistent:

$$d_R - t_R = d_S - t_S. \tag{2}$$

For each age class, total death rates and PTB-specific death rates would be the weighted average of those for susceptibles and resistent:

$$d_i = f d_R + (1 - f) d_S \quad \text{and} \quad t_i = f t_R + (1 - f) t_S. \tag{3}$$

Equations 1–3 were solved to yield expressions for the age-specific total death rates for susceptible and resistant individuals,

$$d_S = d_i + \frac{y f t_i}{1 - y f} \tag{4a}$$

and

$$d_R = d_i - \frac{y (1 - f) t_i}{1 - y f}. \tag{4b}$$

For any given assumption about the values of $y$ and $f$, given the observed death rates $d_i$ and $t_i$, Equations 4a and 4b give constant values for $d_R$ and $d_S$. To obtain the standard life table entry $l_{xk}$—age-specific survivorship to age $x$ for persons of susceptibility $i (= S, R)$ and sex $k$, we applied the standard formula $l_{xk} = \prod_{x=0}^x (1 - d_x)$.

**Age-specific fertility rates**: For females, age-specific fertility rates $m_{xS}$ were directly available from Sundbärg (1970). As usual, corresponding values for males were not available. However, because the average age at first marriage in 1891–1900 in Sweden was 28.78 (males) and 26.84 (females; Sundbärg 1970), we made the approximation $m_{xM} = m_{x-2S}$.

**Selection coefficient**: These life table data provided the basis for calculating a selection coefficient, which we did separately for each gender, and then we used the arithmetic mean to approximate the population-wide selection coefficient. The selection coefficient was obtained by separately calculating the instantaneous population growth rates $r_M$, $r_S$, $r_R$, and $r_g$ for resistant and susceptible males and females, respectively, using the Euler-Lotka equation $\sum_{x=0}^\infty m_{xk} e^{-rx} = 1$ for susceptibility $i$ and sex $k$. The selection coefficient (per year) was then estimated as $s = [(r_M - r_S) + (r_R - r_g)]/2$. This may be more readily understood, in per generation terms, as the proportional reduction in the number of offspring expected for a susceptible parent, compared to a resistant parent; the per generation coefficient $\Delta w$ is obtained as $\Delta w = \exp(sT) - 1$ (sometimes expressed $\times 100\%$), where $T \approx 31$ years is the approximate generation time in the population (Cavalli-Sforza and Bodmer 1971, Equation 6.9).

**Changes in resistance over time**: Changes in the frequency of a resistance allele assuming a particular selection coefficient $s$ were calculated according to the standard formula $dp/dt = (ph + q(1 - h))$ (Hartl and Clark 1997, Equation 6.14), where $p$ is the frequency of the resistance allele and $q = 1 - p$ is the frequency of the susceptibility allele. A range of dominance values $h$ from 0 to 1 were considered, where $h = 0$ corresponds to complete recessiveness for the resistance allele and $h = 1$ to complete dominance. The average frequency of the resistant phenotype is defined as the mean fraction of the selective benefit of resistance across both heterozygotes and homozygotes and is calculated as $\Phi(t) = p^2 + 2hp(1 - p)$. For any given starting value $\Phi(0)$ and duration of selection $t$, $\Phi(t)$ will depend on the degree of dominance $h$. To compute the maximum average frequency of the resistant phenotype at a given time, $\Phi_{max}(t)$, we numerically obtained $\Phi(t)$ for a range of values of $h$ between 0 and 1 and defined $\Phi_{max}(t) = \max_h \Phi(t)$.

**RESULTS**

**Mortality and fertility data**: Figure 1a shows the age-specific mortality from all causes and from pulmonary TB in this data set. The importance of pulmonary tuberculosis as a cause of mortality before and during the reproductive years is evident. Tuberculosis accounts for about one-half of all deaths among persons in each age class between 25 and 40; Figure 1b shows the corresponding age-specific female fertility data.

**Estimated selection coefficient**: We used these data to calculate the selection coefficient that would have been exerted in this population in favor of a hypothetical genotype conferring a defined level of resistance to tuberculosis mortality, assumed to be a constant reduction in mortality across the life span (see Methods). The protection is measured as the reduction in incidence of PTB mortality for resistent compared to susceptibles ($y$). The selection coefficient (per year) is the difference between susceptible and resistant genotypes in the Malthusian rate of increase, $r$.  

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**Figure 1a**: Age-specific total death rates for susceptible and resistant individuals (A) and PTB-specific death rates for susceptible and resistant individuals (B) for each age class. The age-specific total death rates and PTB-specific death rates were obtained as described in the Methods section.
resistance nearly complete, the estimated value of the selective coefficient could have been much higher, nearly 60% per generation or 0.015 per year. This is an extreme estimate, and we reemphasize here that this is for a single gene conferring complete protection, which in light of current knowledge seems highly unlikely.

Assessment of selective hypotheses: We compared these estimates of the intensity of selection imposed by tuberculosis against the intensity that would be required to support two hypotheses that invoke selection by tuberculosis to explain epidemiological phenomena. We used our estimate to evaluate in turn the hypotheses that:

1. The differences in susceptibility to tuberculosis between northern/western Europeans (and their American descendants) and other groups can be attributed primarily to the effects of natural selection by tuberculosis during the industrial period from the seventeenth to the early twentieth century.

2. The sixfold decline in tuberculosis mortality in the cities of western Europe and the northeastern United States between 1830 and 1950 can be attributed to the selective death of individuals susceptible to tuberculosis.

For this part of the analysis, we made the additional assumption that resistance to tuberculosis mortality is conferred by a single Mendelian allele of arbitrary dominance. This assumption was made to simplify the mathematics in a way that is “conservative,” in the sense that it should result in a more rapid increase in the resistant phenotype than would be the case if multiple, unlinked genes collectively conferred the same level of protection.

Reduced susceptibility of Europeans to PTB: To evaluate the hypothesis that natural selection imposed by tuberculosis is responsible for the observed resistance of Europeans to tuberculosis, we used a population genetic selection model to calculate the changes in the frequency of resistance during a 300-year period under various assumptions about the intensity of selection. Three hundred years was chosen to represent the time of peak epidemic tuberculosis in Europe, from the early seventeenth century to the early twentieth century. This assumption, too, is conservative, in the sense that the intense portion of the TB epidemic probably lasted <300 years in any given part of Europe, although it peaked at different times in different parts of the continent (Drolet 1942; Grigg 1958a). Increases in the frequency of the resistant phenotype, of course, are equivalent to declines in the frequency of the susceptible phenotype.

Figure 2 shows \( \Phi_{\max} \), the maximum average frequency of the resistant phenotype after 300 years, as a function of its starting frequency (different curves) and the selection coefficient per generation (\( w \)), expressed as a percentage. As described in methods, the average frequency of the resistant phenotype is calculated as the
sum of the proportion of individuals homozygous for the resistant allele and the proportion heterozygous, weighted by the degree of dominance of the resistant allele.

Figure 2 shows that if a gene conferring some degree of resistance to tuberculosis started at a low frequency in the population, e.g., 1 or 20%, then 300 years of selection with selection coefficients < ~20%/generation would have done little, in epidemiological terms, to change the susceptibility of the population. Although the frequency of the resistant phenotype could have increased severalfold from these low levels (from 1 to 10% or from 20 to 42%), this is not enough in absolute terms to markedly reduce the average susceptibility of the population, since these would correspond to approximately a 9% reduction (99% → 90%) or a 28% reduction (80% → 58%) in the susceptible proportion of the population.

There is, however, one scenario in which selection by tuberculosis could have noticeably reduced the susceptibility of the population. Suppose that at the start of the TB epidemic, the majority of the population (say, 80%) was of a resistant genotype, but a minority carried a gene that substantially increased their susceptibility to PTB mortality (e.g., resistsants are 75% protected against PTB mortality compared to susceptibles). From Table 1, this could have produced a selection coefficient on the order of up to 20%/generation. With selection of 20%/generation (see Figure 2), the frequency of the resistant phenotype could have gone from 80 to 96%, equivalent to a fivefold reduction in the frequency of the susceptible phenotype (from 20 to 4%).

### Table 1

<table>
<thead>
<tr>
<th>Protection from PTB mortality (γ)</th>
<th>1%</th>
<th>10%</th>
<th>25%</th>
<th>50%</th>
<th>85%</th>
<th>95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>0.0002</td>
<td>0.0002</td>
<td>0.0002</td>
<td>0.0002</td>
<td>0.0002</td>
<td>0.0002</td>
</tr>
<tr>
<td>25%</td>
<td>0.0006</td>
<td>0.0006</td>
<td>0.0006</td>
<td>0.0006</td>
<td>0.0007</td>
<td>0.0007</td>
</tr>
<tr>
<td>50%</td>
<td>1.8</td>
<td>1.8</td>
<td>1.9</td>
<td>2.0</td>
<td>2.2</td>
<td>2.3</td>
</tr>
<tr>
<td>75%</td>
<td>0.0017</td>
<td>0.0018</td>
<td>0.0021</td>
<td>0.0027</td>
<td>0.0047</td>
<td>0.0059</td>
</tr>
<tr>
<td>90%</td>
<td>5.4</td>
<td>5.8</td>
<td>6.7</td>
<td>8.8</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>100%</td>
<td>0.0023</td>
<td>0.0025</td>
<td>0.0030</td>
<td>0.0045</td>
<td>0.015</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Per year (λ, top entry) and per generation (Δw, bottom entry) selection coefficients inferred from Swedish demographic data for a hypothetical allele conferring varying degrees of protection (γ) against mortality from pulmonary tuberculosis (PTB), assuming varying frequencies of the resistant type in the population from which the data were obtained.

**Figure 2**—Maximum prevalence $\Phi_{\text{max}}(300)$ of the resistant phenotype after 300 years of selection starting from a prevalence of 1, 20, 50, or 80% (different curves) at various selection coefficients (x-axis). See METHODS for the definition of $\Phi_{\text{max}}(t)$. 
Figure 3.—Maximum prevalence $\Phi_{\text{max}}(120)$ of the resistant phenotype after 120 years of selection starting from a prevalence of 1, 20, 50, or 80% (different curves) at various selection coefficients ($x$-axis). See Methods for the definition of $\Phi_{\text{max}}(t)$.

As Table 1 shows, selection coefficients of $<20\%$ per generation are inferred for all combinations of allele-specific protective effect and frequency of the allele in the Stockholm population, except for the bottom right entries of the table, at least 85% frequency of the protective allele and $>75\%$ protective effect of the resistant allele. If we make the extreme assumption that the pulmonary TB mortality in Stockholm was concentrated in 15% of the population that was genetically susceptible, then the higher selection coefficient (60%/generation) inferred could account for considerably larger changes in the frequency of the resistant genotype over 300 years, from 1 to 38% or from 80 to 99.9%.

In summary, the analysis indicates that natural selection by pulmonary TB may have been strong enough to have substantially reduced (e.g., by fivefold) the prevalence of an allele conferring a strong degree of susceptibility to tuberculosis, if such an allele was already rare at the start of the TB epidemic. However, if a gene conferring resistance to pulmonary TB mortality was rare in the European population at the start of the epidemic, selection during the TB epidemic in Europe would have been insufficient to bring it to such a high frequency that the average susceptibility of the population as a whole would have been substantially changed.

Decline in the tuberculosis epidemic: Figure 3 shows the maximum increase in the prevalence of a resistance phenotype achievable over 120 years from various starting frequencies and at various selection coefficients. The calculations are identical to those of Figure 2 except for the span of time considered. These calculations were performed to assess the hypothesis that natural selection for increased resistance to tuberculosis contributed substantially to the approximately sixfold decline in the epidemic from the mid-nineteenth century to the mid-twentieth century, in the ~120 years before the advent of effective chemotherapy. The absolute changes are smaller than those in Figure 2 because of the shorter time span, but the qualitative picture is the same; the increase in the proportion of resistance in the population (or the decline in susceptibles) would have been small over such a short period of selection.

Again, if the resistant phenotype was rare in the population in 1830, its frequency would have increased by only a few percent in absolute terms by 1950; such an increase would be unlikely to have affected the overall incidence of PTB mortality. However, if resistant individuals were already in the majority, then the average level of susceptibility in the population could have been noticeably reduced, even over this short period. For example, with a selection coefficient of 20%/generation, the prevalence of resistance could have gone from 80 to 88% or from 90 to 95% (not shown), corresponding to reductions in the prevalence of susceptibles from 20 to 12% or from 10 to 5%, approximately a halving of the susceptible fraction. Because of the nonlinearities inherent in infectious disease transmission, a halving of the susceptible fraction could lead to a decline in cases of more than one-half (Blower et al. 1995). We suspect that even a decline in susceptibility of this magnitude would be unlikely to explain the whole decline in PTB mortality over that period; it could have been a contributing factor if in ca. 1830 there was a small proportion of individuals (20% or less) whose genes made them highly susceptible to PTB. However, without further, data-free assumptions, it is difficult to translate a decline in the fraction susceptible quantitatively into a decline in cases of mortality, since these quantities depend on the state of the TB epidemic, changes in population size, and contact patterns, etc.

DISCUSSION

We set out to evaluate the plausibility of the idea that natural selection by pulmonary tuberculosis made an important contribution to the apparently reduced susceptibility of individuals from populations with a long history of exposure to TB, compared to individuals from...
populations with little or no history of exposure to the infection. Essentially, our analysis indicates that the plausibility of this hypothesis depends on whether the “naive” population, prior to the epidemic, was primarily susceptible, containing only a few resistant individuals, or whether the preepidemic population was composed largely of resistant individuals, but contained a minority of susceptible individuals. (Of course, these are two extremes, and intermediate possibilities exist.)

In the first case (starting with a population in which most individuals were susceptible), even under highly favorable assumptions, the duration of the TB epidemic would not have been long enough for selection to bring alleles conferring resistance to sufficiently high frequency to effect a noticeable change in the susceptibility of the population. In the second case (starting with a population in which only a few individuals are susceptible), 300 years would have been long enough to effect a noticeable change in the average level of susceptibility in the population, but only under highly favorable conditions. Specifically, individual loci (or groups of loci that were very closely linked) would have had to confer very large differences in susceptibility to PTB mortality [e.g., human interferon-γ receptor deficiency (Altare et al. 1998)] to experience enough selection for their frequency to change noticeably in 300 years.

It is difficult to know whether these restrictive conditions (loci of large effect, with most of the population already resistant at the beginning of the epidemic) were fulfilled in Europe during the period 1600–1900. However, recent studies of the effect of alleles at polymorphic loci affecting susceptibility to TB disease suggest that, at a given locus, a resistance allele confers less than a 50% reduction in the risk of TB disease (Bellamy et al. 1998, 1999). If all resistance at each locus controlling TB susceptibility confers less than a 50% reduction in susceptibility to mortality from TB disease, then selection coefficients favoring resistant alleles would have been at most 7%/generation (Table 1), so even 300 years of selection would have changed their frequency only modestly (Figure 2).

Our analysis further suggests that changes in the genetic makeup of the population alone would have been unlikely to account for the rather steep drop in tuberculosis mortality during the century before the advent of chemotherapy for TB. A number of other explanations for this decline have been put forth, including improved social and nutritional conditions (McKeown 1976), natural population dynamics of the TB epidemic (Blower et al. 1995), and isolation of infectious patients (Wilson 1990).

Given that much about the genetics of susceptibility to TB mortality remains unknown, we have of course had to make simplifying assumptions to make our calculations. Wherever possible, especially in calculating rates of change in the resistant phenotype, we have chosen simplifying assumptions that are conservative, in the sense that they tend to increase the effectiveness of natural selection in increasing resistance. For example, although TB susceptibility is multigenic, and the different genes involved presumably have different degrees of dominance for the resistant alleles, we considered the dynamics of a single gene, with an arbitrary degree of dominance. The choice of a single gene was made because phenotypic change will be more rapid for a single gene conferring a particular degree of protection than for multiple genes conferring the same total protection. Furthermore, we considered various levels of dominance for the resistant allele and considered the degree of dominance that resulted in the largest phenotypic change in the population. Thus, for the more realistic scenario of multiple genes with fixed degrees of dominance conferring resistance to pulmonary TB mortality, the ability of selection to change the average phenotype of the population would be less than that estimated here. Indeed, for genes of more modest effect, selection coefficients would have been considerably smaller than the largest selection coefficients considered here.

However, some assumptions in this analysis may have biased our estimate of natural selection downward. The reason for these assumptions was simply lack of data on which to base more conservative assumptions. First, we have considered only the effect of pulmonary tuberculosis, because data were not available for deaths from other forms of tuberculosis. Omission of extrapulmonary TB from our analysis will likely result in an underestimate of the selection coefficient, if the same genes that protect against mortality from pulmonary TB also confer protection against extrapulmonary TB. From archaeological findings and historical descriptions, we know that extrapulmonary forms of TB, such as TB meningitis and TB of the bone and lymph nodes, were frequent in the past. The ratio of pulmonary to extrapulmonary cases is unknown, but two estimates we have found (methods of estimation are not specified) are 10:1 (Wilson 1992) and 3:1 (Bultrode 1908). Mortality up to age five in our data set was ~14% (females) to 16% (males); if (to take a very high upper bound) one-half of this mortality were due to extrapulmonary TB, then alleles offering protection against this mortality would enjoy at least a 7% per generation additional fitness advantage, which would increase some of the entries in Table 1 considerably (especially those at the bottom right) but would not change our main conclusions. More generally, we have assumed that the only effect of our hypothetical gene on fitness is reducing mortality from pulmonary TB; actual genes may have pleiotropic effects on susceptibility to other diseases or on other components of fitness. Such effects could bias our estimates either up or down.

Another simplification we have made is to calculate individual fitness effects rather than attempting to estimate inclusive fitness, thereby ignoring the importance
of family members in the transmission of tuberculosis. If an individual’s risk of infection with tuberculosis is significantly increased by cohabitation with a tuberculosis patient (Rouillon et al. 1976), then a gene protecting an individual against tuberculosis disease will offer indirect protection to the household contacts of that individual. If these household contacts are relatives, then the inclusive fitness selection coefficient will be greater than that obtained for individual fitness.

We showed that the estimate of selection coefficients, especially for highly protective alleles, depends on the assumed prevalence of the resistant phenotype in the population from whom demographic data were taken (see Table 1). This dependence is particularly strong for alleles conferring a high degree of resistance. Thus (see Table 1), we have not calculated selection coefficients under the combined assumption that the resistant genotype was both very highly protective and very common (>85% prevalence for a 100% protective genotype or >95% prevalence of a 90% protective genotype) in the population for which we obtained our mortality data.

Selection coefficients were estimated for Stockholm in the decade 1891–1900 because these were the oldest data we could obtain from an area with intense tuberculosis mortality that included all necessary quantities for our estimation. How well does this represent the selection imposed throughout Europe during the period of intense tuberculosis mortality? Age-stratified PTB and total mortality figures are available from England and Wales in the years 1848–1854 (PTB) and 1861–1870 (total; Humphreys 1885) and use of these statistics gives comparable (~10% higher) estimates to those obtained here. We chose not to use these for the primary analysis because they were less detailed and lacked matching fertility data. From our primary source, we find that 15.3% of deaths in this decade were from pulmonary TB, about equal to the national average of 15.6%. While it is possible that the period for which data are available is not the absolute peak of the epidemic, we have no reason to believe it was substantially higher, on average, during the European epidemic than in the population from which we have data. Tuberculosis mortality was certainly higher in urban areas than in the country as a whole (Drolet 1942; Sundbärg 1970), and mortality in Stockholm was relatively high compared to that in other large European cities (Drolet 1942). In summary, the level of TB in some cities at some times undoubtedly exceeded what we have considered, but there is little evidence that it did so for an extended period in any whole European country (Drolet 1942). This conclusion must, however, be qualified by the fact that reliable data are scarce before the mid-nineteenth century and almost completely absent before the mid-eighteenth century.

In summary, our conclusions rely on a number of assumptions because some important data are unavailable both in the genetic and biological bases of TB resistance and on the demographic and selective parameters required to make the estimates on which our conclusions are based. Nonetheless, we believe that the conclusions are robust to these assumptions.

Our estimates of the intensity of selection for a hypothetical gene conferring resistance to PTB are comparable in magnitude to that estimated for the protective effect of heterozygosity for sickle-cell hemoglobin against severe malaria (Cavalli-Sforza and Bodmer 1971). Schliekelman et al. (2001) recently used data on progression to AIDS from human immunodeficiency virus (HIV) infection in individuals carrying allelic variants of the CCR5 gene to estimate selection coefficients under various intensities of HIV transmission; finding selection coefficients somewhat higher than those obtained in this study, they calculate that noticeable changes in haplotype frequency could be expected within 100 years in sub-Saharan African populations under current transmission conditions. A previous study (Stephens et al. 1998) hypothesized that the CCR5Δ32 mutation, well known for its highly protective effect against HIV-1 infection, might have reached high frequencies in European populations because it conferred resistance to the plague that caused extremely high mortality in Europe during the black death of the fourteenth century. Schliekelman et al. (2001) cite unpublished calculations to indicate that, even if CCR5Δ32 were highly protective against death from plague, the duration of selection by plague would have been too short to account for large increases in the frequency of CCR5Δ32. Many other hypotheses have been proposed and subjected to varying degrees of scrutiny, for the selective benefits of particular alleles in conferring resistance to particular infectious diseases, including resistance to diarrheal disease conferred on heterozygotes for the cystic fibrosis mutation (Quinton 1994), resistance to several infectious diseases conferred by genes that also predispose to peptic ulcers (Petersen and Rotter 1983), resistance to TB conferred by heterozygosity for the Tay-Sachs disease mutation (O'Brien 1991), and others (Rotter and Diamond 1987). Even if detailed mortality figures are not available to make these calculations, it may be possible to work backward, starting from the hypothesized genetic effect (change in gene frequency over a particular time period or maintenance by heterozygote advantage of an allele that is deleterious when homozygous), calculating the selective coefficient required to produce that effect and comparing that coefficient with whatever historical data are available about the impact of the infectious disease(s) of interest. Such quantitative approaches, even if approximate, will provide important complements to biological investigations into the mechanisms of hypothesized protective effects.

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