SEXIST DISEASES

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Introduction

In human populations, females usually have a lower mortality than males at any age. This pattern is observed for most causes of death due to chronic diseases, accidents, and violence [1–4]. However, lower female mortality is not universal, and a reverse pattern of excess female mortality has been observed for some infectious diseases. Whooping cough is often quoted in the medical literature as being more lethal for girls than for boys [5]. Another such recently documented disease is measles [6]. Both are airborne diseases for which the incidence is virtually identical for males and females. This implies that differences in mortality demonstrate a difference in case fatality. The excess female mortality from measles and whooping cough is found throughout the world, in places as different as Europe, Japan, North America, Africa, and Latin America. This implies a biological difference rather than a cultural pattern, and therefore a higher susceptibility for females. In casual reports made throughout the world, and especially among older children and young adults, excess female mortality has been observed in certain other infectious diseases, such as tuberculosis, typhoid and paratyphoid, typhus, smallpox, scarlet fever, diphtheria, influenza, and congenital syphilis [7–9]. The two striking features of these early studies are the highly selective list of diseases exhibiting excess female mortality and the changing pattern by age. Late childhood and early adulthood appear to be the life periods when females are the most vulnerable compared to males.

The explanation for a higher vulnerability of females for certain infectious diseases could be sought in differences between the male and female

The authors would like to thank Prof. Samuel Preston (University of Pennsylvania) and Dr. Brian Ward (McGill University) for comments on the demographic and immunologic aspects of the manuscript; Dr. Desmond Martin (National Institute for Virology, South Africa) for personal communications on various diseases; and Ms. Shelah Bhatti (Harvard University) for editorial comments.

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0031-5892/98/4102-1049$01.00

immune systems. Recently, lymphocytes have been divided into two subsets, Th-1 and Th-2, according to the cytokines they produce [10, 11]. Th-1 are major producers of IL-2, and IFN-γ, whereas Th-2 produce high levels of IL-4, IL-5, IL-6, and IL-10. Stimulation of Th-2 lymphocytes activates antibody secretion, whereas stimulation of Th-1 lymphocytes facilitates cytotoxic T cells. The balance between Th-1 and Th-2 responses seems to be essential for resistance to disease and survival. Recently, evidence accumulated showing that male and female immune systems do not mount immune responses in the same way [12]. Females seem to favor a Th-2 response, whereas males favor a Th-1 response. This is especially true during pregnancy, when there is a drop of Th-1 cytokines and an increase of Th-2 cytokines [13, 14]. The fact that sex hormones can regulate the Th-1/Th-2 balance [15, 16] could explain the differences between male and female mortality for certain infectious diseases, especially among young adults when the level of sex hormones is the highest.

The goals of this study were (1) to systematically search for groups of infectious diseases showing different male and female mortality during late childhood and early adulthood, (2) to investigate the characteristics of the Th-1 and Th-2 responses to certain infectious diseases, and (3) to test the plausibility of the sex hormones explanation. This hypothesis linking the hormonal and the immunological systems and the way the body copes with infectious diseases could explain both the direction and the changing pattern of gender differences in mortality by age.

Demographic Evidence

The demographic data originated from the World Health Statistics, a databank computerized by the World Health Organization from national causes of death statistics. Data originated from 110 countries throughout the world between 1950 and 1989. These were mostly developed countries from Europe, North America, and the Far East, and some developing countries from Latin America and Asia. This sample accounted for about 15 million deaths from infectious and parasitic diseases. The final analysis was limited to 21 causes of death attributable to well identified pathogens, and causing a number of deaths large enough to ensure statistical significance of mortality differences by gender. The sample and the statistical approach used have been described elsewhere [6]. Death rates were obtained by dividing the number of deaths by age, gender, and cause by the corresponding population in each country. In the original data files, deaths were grouped by five-year age groups, as shown in the figures. Erratic patterns may occur in five-year age groups above age 50 due to small number of deaths (e.g., for smallpox). Some diseases are not presented in the figures due to very erratic patterns in certain age groups (diphtheria, trypanosomi-

asis, meningitis). Gender differences in mortality were investigated by computing female gender ratios of age specific death rates, defined as 1000 times the ratio of female age-specific death rates to male age-specific death rates. For statistical testing of excess female (or male) mortality, the deaths were put together into four large age groups (0–4, 5–14, 15–44, 45+) and an age-standardized female gender ratio was computed [6]. Gender ratios measure the relative risk of death of females as compared to males. The statistical tests used to show a significant excess female (or male) mortality were standard tests for relative risks.

Among the 21 causes of death studied, a majority exhibited a significant ($P < 0.05$) excess female mortality in at least one age group below age 50 years. These diseases were (Fig. 1 and 2):

- among viral diseases: measles (*measles virus*), smallpox (*variola virus*), viral hepatitis (*hepatitis B virus*);
- among bacterial diseases: whooping cough (*Bordetella pertussis*), streptococcal infections such as scarlet fever, erysipelas, and streptococcal angina (*Streptococcus pyogenes*), diphtheria (*Corynebacterium diphtheriae*), cholera (*Vibrio cholerae*), paratyphoid (*Salmonella paratyphi*);
- among parasitic diseases: ancylostomiasis (*Ancylostoma duodenale* and *Necator americanus*);
- among mycobacterial diseases: respiratory and nonrespiratory tuberculosis (*Mycobacterium tuberculosis*), and leprosy (*Mycobacterium leprae*).

The pattern of excess female mortality was clearly age dependent. Some diseases exhibited a consistent excess female mortality even in childhood (measles, smallpox, whooping cough, streptococcal infections, and ancylostomiasis), whereas others did not (cholera, diphtheria, hepatitis, and paratyphoid). The pattern of excess female mortality peaked around age 25 for virtually all the non-mycobacterial diseases (first group: Fig. 1), and at age 10–19 for respiratory tuberculosis, most forms of nonrespiratory tuberculosis, and leprosy (second group: Fig. 2). However, tuberculosis of the intestines, peritoneum, and mesenteric glands exhibited a pattern closer to the first group than to the second (data not shown).

The remaining causes of death studied (third group) all exhibited a consistent excess male mortality at all ages. These diseases were (Fig. 3): malaria, poliomyelitis, anthrax, typhoid, meningococcal infections, schistosomiasis, and trypanosomiasis.

In virtually all the cases investigated, with the sole exception of streptococcal infections, female mortality was lower than male mortality above age 50 years.

Biological Plausibility: The Th-1/Th-2 Balance and the Immune Response

Some infectious diseases induce immune responses which are highly skewed towards Th-1 or Th-2 subsets. Depending on the specific response,

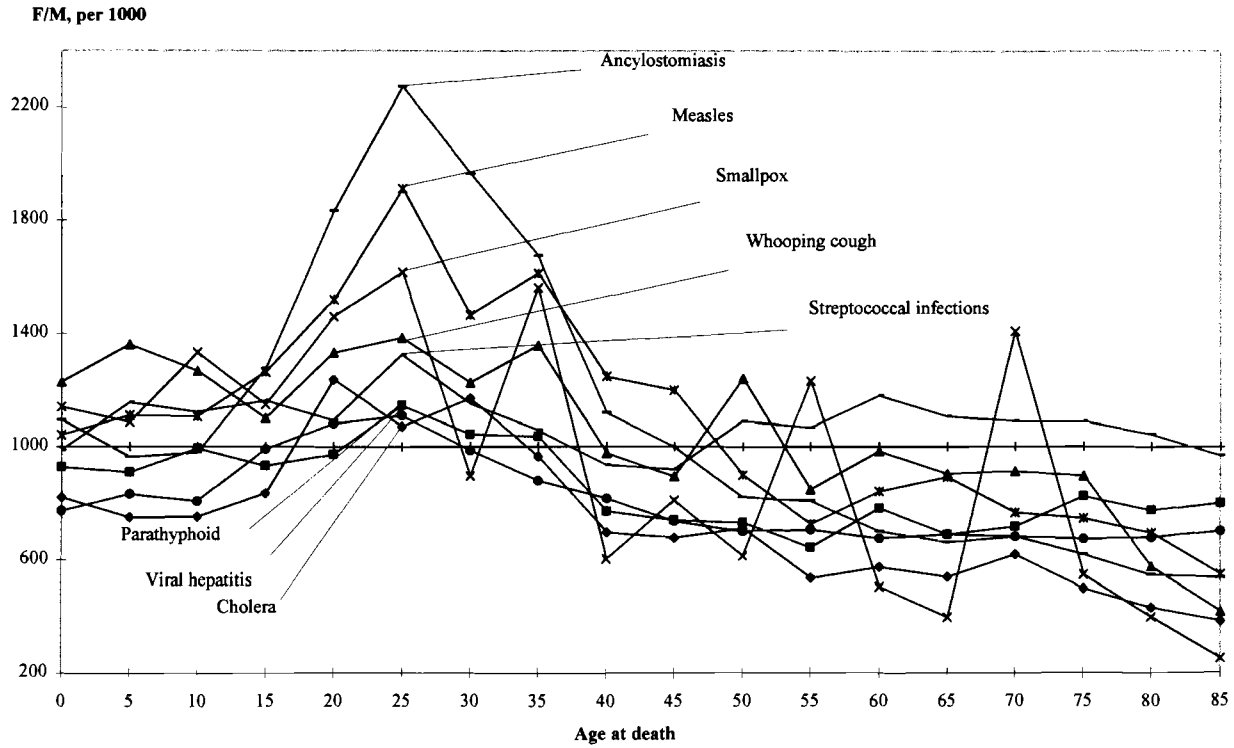

FIG. 1.—Gender differences in mortality by age: First group of diseases, with excess female mortality among young adults (selected diseases).

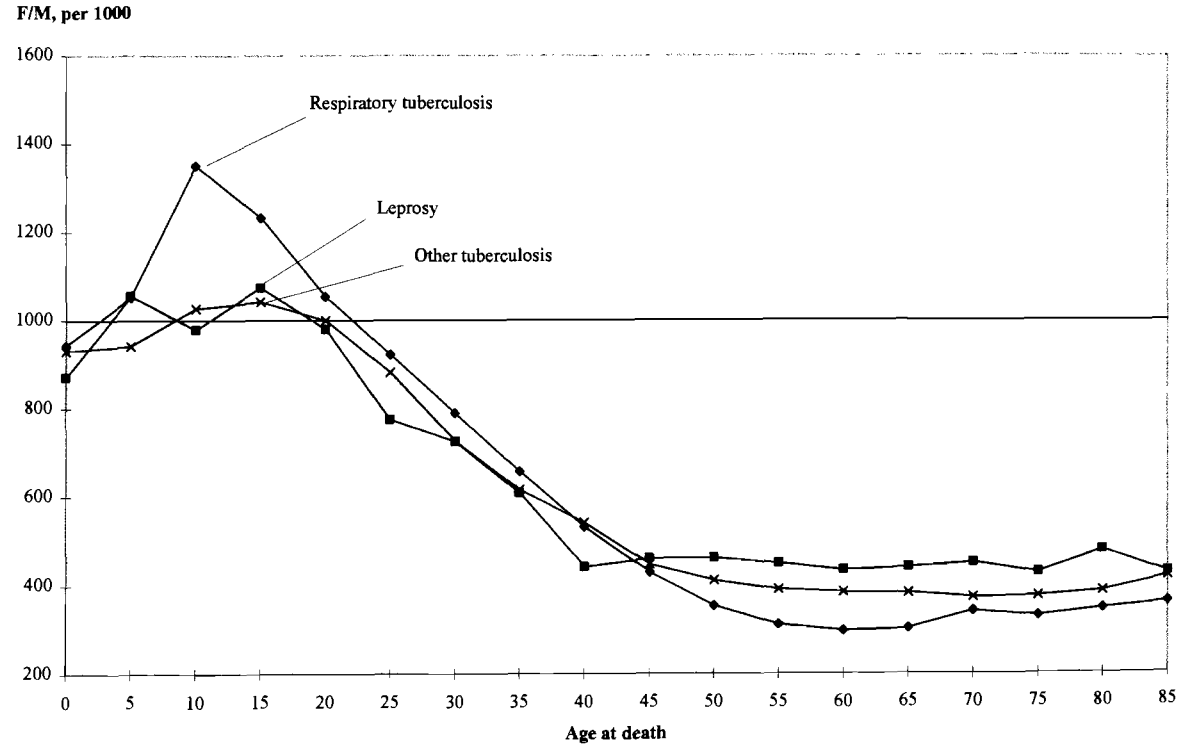

FIG. 2.—Gender differences in mortality by age: Second group of diseases, with excess female mortality among older children and young adults (mycobacterial infections).

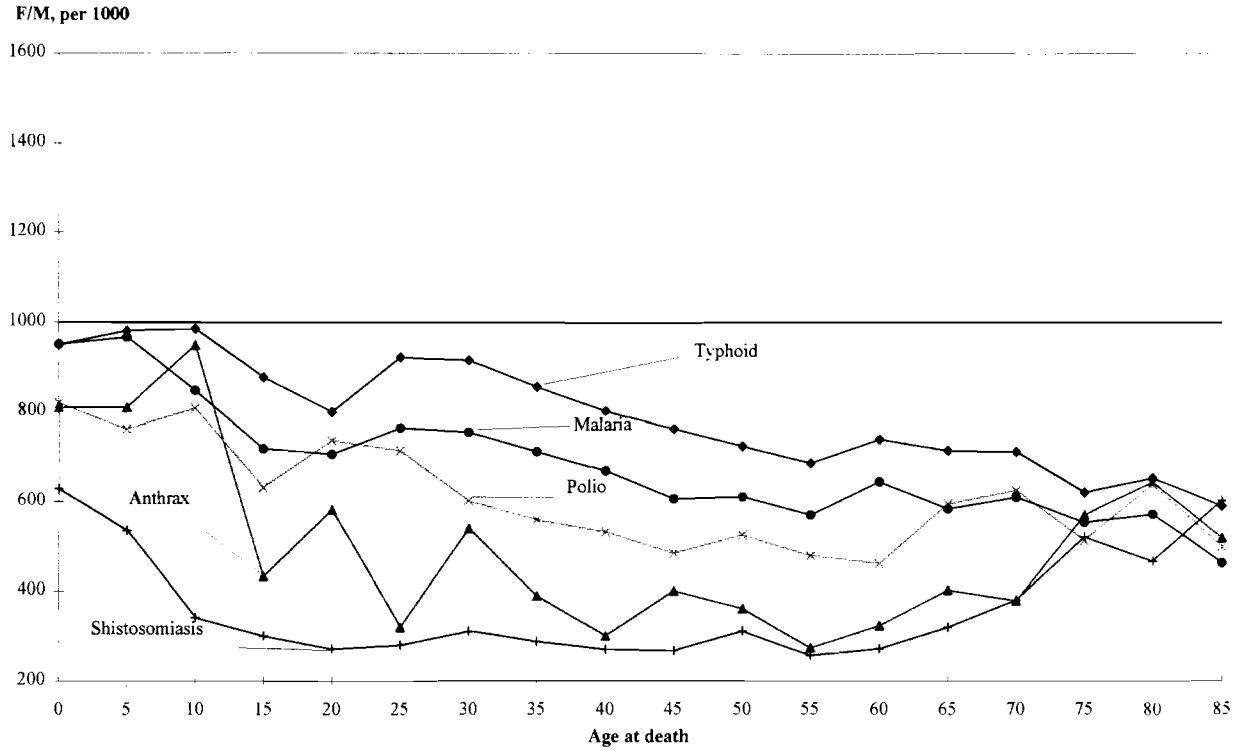

FIG. 3.—Gender differences in mortality by age: Third group of diseases, with systematic excess male mortality (selected diseases).

the host may either be cured (Th-1 or Th-2 response-healing disease), or develop a T-specific pathology (Th-1 or Th-2 response-exacerbating disease). Experimental evidence of differential Th-1 and Th-2 responses is currently limited to a few diseases, for which an animal model is usually available and on which intensive research has been conducted over the past decade.

EXPERIMENTAL EVIDENCE OF TH-2 RESPONSE-EXACERBATING DISEASE AND TH-1 RESPONSE-HEALING DISEASE

The intracellular protozoan *Leishmania major* that causes cutaneous leishmaniasis in humans, the intracellular bacteria *Bordetella pertussis* causing whooping cough, and the fungus *Candida albicans* are three well-characterized murine models demonstrating that hosts who mount a Th-1 response are protected, whereas those mounting a Th-2 response are susceptible to infection [17–21]. Treatment of susceptible mice infected with *Leishmania major* with Th-1 type cytokine IFN-γ improved survival, whereas treatment of resistant mice with antibodies that neutralize the action of this cytokine increased pathogenicity [22]. Cure of murine candidiasis and leishmaniasis was obtained by treating mice with antibodies against Th-2 type cytokine or by the transfer of Th-1 cells [22–24]. On the contrary, a transfer of Th-2 cells was disease promoting [24].

The protective role of Th-1 cells and the promoting effect of chronic infection of Th-2 cells were also found in influenza type A, and in murine hepatitis virus strain 3 (MHV-3) infections [25, 26].

For measles, no animal model is yet available. Natural measles is dominated by a mixed Th-1/Th-2 response, with Th-1 predominance in the early phase, and a gradual switch towards Th-2 predominance over two to three weeks [27]. Moreover, MV infection of human monocytes was found to be an inhibitor of IL-12 production, a cytokine which stimulates differentiation of uncommitted CD4T lymphocytes into Th-1 cells. The down regulation of IL-12 could explain abnormalities in cell-mediated immunity in natural infection and suggests that measles is primarily a Th-1 response-healing disease [28].

EXPERIMENTAL EVIDENCE OF TH-1 RESPONSE-EXACERBATING DISEASE

A skewed response towards Th-1 usually helps the host in fighting intracellular pathogens. However, a strong Th-1 response can turn into a disadvantage, when the Th-1 cytotoxic response or Th-1 type cytokines create damage to the host tissues. This has been documented in murine models for *Plasmodium* and *Coxsackievirus* infections.

In humans, *Plasmodium* infected children exhibit high plasmatic levels of IFN-γ and TNF-α [29]. The possible involvement of these Th-1 cytokines

in cerebral malaria was investigated in a mouse model [30]. IFN-γ secreted by Th-1 in response to malaria infection stimulated macrophages to produce TNF-α. This cytokine modifies the adhesion molecules of the cerebral blood vessels. As a consequence, cerebral blood vessels are weakened and hemorrhage occurs, provoking death. Strains of mice that were strong Th-1 responders were highly susceptible to cerebral malaria and produced large amounts of TNF-α and IFN-γ, whereas strains of mice that developed a Th-2 pattern were resistant to the disease.

Another example of Th-1 dependent pathology was described for *Coxsackievirus* B3 (CVB3) infection, a cause of severe myocarditis, a disease to which males are more susceptible than females. CVB3 infection in male mice resulted in severe pathology of the myocardic cells that was related to a strong virus-specific Th-1 mediated cytotoxic response, whereas the female response was characterized by a limited Th-1 response and a strong virus-specific Th-2 response [31]. Furthermore, males could be protected against the development of myocarditis by the adoptive transfer of T cells from females infected with CBV3.

EXPERIMENTAL EVIDENCE OF TH-2 RESPONSE-HEALING DISEASES

Th-2 responses play a critical role in disease resistance when antibodies are the most important protective factor. For instance, strains of mice that preferentially mounted Th-2 responses were protected against infection with two nematodes (*Trichiuris muris* and *Heligmosomoides polygyrus*) [32] and with the spirochete causing Lyme disease (*Borrelia burgdorferi*). On the contrary, strains of mice that preferentially mounted Th-1 responses developed severe disease. Production of IL-4 was correlated with resistance, and production of IFN-γ with susceptibility. Moreover, neutralization of IL-4 or IFN-γ in resistant and susceptible mice respectively, reversed the pattern of susceptibility [33, 34].

In schistosomiasis, IgE and IgG4 (antibodies stimulated by IL-4) seemed to play an important protective role because they actively participate in the destruction of parasites via the antibody-dependent cell-mediated cytotoxicity mechanism [35]. This is supported by the significant correlation found in humans between the acquisition of immunity and the production of IgE antibodies [36].

In light of these findings, it is striking to note that Th-1 response-healing diseases or Th-2 response-exacerbating diseases (measles, whooping cough, tuberculosis) belong to first and second groups (evidence of excess female mortality), whereas diseases regarded as Th-1 response-exacerbating disease or Th-2 protective (cerebral malaria, schistosomiasis) belong to the third group (systematic excess male mortality). This suggests that females tend to be more susceptible to Th-2 response-exacerbating diseases, and males to Th-1 response-exacerbating diseases.

The two subsets Th-1 and Th-2 most likely derive from a common precursor (T0), to which future differentiation is modulated by external factors, including the nature of cytokines and the nature of the cells (antigen presenting cells) which first encounter the microorganism. There is growing evidence that hormones, and sex hormones in particular, also regulate the Th-1/Th-2 balance [37–40]. In particular Th-1 cells seem to be modulated by androgens, whereas the female hormone progesterone was found to promote Th-2 clones [15, 16, 40]. During pregnancy in particular, large amounts of progesterone are produced, Th-1 cytokines IFN-γ and IL-2 decline, and Th-2 cytokines increase, particularly IL-4 [13, 14].

The most striking evidence of the involvement of sex hormones in the Th-1/Th-2 balance and the resulting resistance to diseases was provided by an experimental model of male and female mice infected with *Coxsackie virus B3* (CBV3) [31]. Male and female mice differ in susceptibility to myocarditis induced by this virus. Experimental CBV3 infection induces predominantly a Th-1 response among males and predominantly a Th-2 response among females. Treatment of females with a male hormone (testosterone) and of males with a female hormone (estradiol) altered the subsequent Th-1/Th-2 subset differentiation, had a profound effect on CD4+ lymphocyte response and on cardiac virus loads, and ultimately controlled the evolution of the disease.

Similarly, injection of DHEA (dehydroepiandrosterone), a prohormone that modulates the Th-1 response, prevented infection from *Coxsackie virus* (C4), *Herpes virus,* and *Enterococcus faecalis* [15]. Evidence showed that the protective action of this steroid hormone was not directly antiviral or antibacterial, since DHEA failed to be protective in athymic mice. Thus, it was surmised that DHEA functioned by regulating specific components of the immune response to achieve resistance to infection [41–43].

Discussion

In this study, we have hypothesized a link between male/female hormones, the Th-1/Th-2 balance, and resistance/susceptibility to certain infectious diseases. The role of female sex hormones is further supported by the relationship between susceptibility to diseases and variations in the level of circulating hormones by age. First, many diseases in the first group, such as rubella, measles, viral hepatitis, influenza, and tuberculosis, are more severe during pregnancy, when the level of progesterone dramatically increases [44]. Second, female disadvantage for Th-2 response-exacerbating diseases seems to disappear after menopause, when the level of female hormones markedly diminishes (Fig. 1). Third, higher susceptibility of women to streptococcal infections during pregnancy might explain the outstand-

ingly high maternal mortality from these diseases in the 18th and 19th centuries [45].

The diseases reviewed here are among the leading infectious causes of death in the world. Despite the limited number of diseases investigated, the examples discussed here have an heuristic value. Available data have shown a consistent agreement between gender differences in mortality and Th-1/Th-2 responses to the corresponding diseases. Despite limited information, so far no obvious discrepancy has been found between demographic and immunologic evidence.

The classification of diseases as being Th-1 (or Th-2) response-exacerbating (or healing) disease was generally the result of experimental evidence from the murine models. For some of the diseases analyzed in the demographic part, there was either no murine model (measles, rubella), or no recent investigation due to lack of interest in the disease (anthrax, typhoid) or to eradication of the disease (smallpox). However, the classification of smallpox in the first group (excess female mortality) seems to be justified by the fact that vaccinia virus (a very close virus which induces protective immunity against smallpox) was recently identified as Th-1 response-healing disease and Th-2 response-exacerbating disease [46]. Ancylostomiasis, the most striking example of excess female mortality in the demographic analysis, remains a puzzle since very little research has been devoted to its immunopathology. However, the observation that Th-2 responses have been associated with high helminth loads in humans is consistent with the higher female susceptibility for this helminthic disease [47].

Mortality rates are only proxies for case fatality rates, the closest measure of susceptibility controlling for exposure. For diseases for which exposure can be assumed to be similar for males and females (measles, whooping cough, malaria, meningitis, streptococcus, typhoid, poliomyelitis, trypanosomiasis), mortality is a close proxy. However, this may not be the case when gender related behavior interacts with exposure (such as schistosomiasis) or when specific risks exist for one of the genders (such as tetanus during delivery).

It is sometimes argued that excess female mortality reveals poorer care of females. If this argument is true in certain human populations for all causes combined, it cannot explain why females have an excess mortality for certain diseases and lower mortality for other diseases in the same country. Furthermore, experimental murine evidence is here to remind us that most gender differences have a biological base.

Tuberculosis and leprosy, which exhibit a different demographic pattern (Fig. 2), are examples of further complexity. For instance, the tuberculoid form of leprosy was correlated with a Th-1 response, whereas the lepromatous form was correlated with a Th-2 response [48]. For tuberculosis, two different waves of Th-1 and Th-2 responses have been identified which seem to roughly match the second pattern found in the demographic analy-

ses [49]. In this case, the relationship with the hormonal pattern may be either weaker or more complex than in the other diseases investigated.

The fact that a majority of 21 leading infectious causes of death exhibited a pattern of excess female mortality is impressive in itself. Among those investigated at the biological level, there was also a majority of Th-1 response-healing diseases/Th-2 response-exacerbating diseases, which suggests that this was possibly the most common case in natural situations—that is, before the development of modern medicine and efficient treatments. This might explain why the pattern of gender differences in mortality from infectious diseases changed so dramatically over the past 100 years. If mortality from Th-2 response-exacerbating diseases declined more rapidly than mortality from Th-1 response-exacerbating diseases, female survival could have improved faster, and the gap between male and female mortality could have widened.

When compared to men, women were found to have proportionately more CD4+ T cells (most of which have a Th-2 phenotype) than CD8+ T cells [50]. The origin of this observation could be investigated along the same lines, in particular in relationship with sex hormones, and its biological consequences could be examined in a disease-specific framework.

Gender differences in susceptibility seem to extend beyond infectious diseases. For example, females are more susceptible to certain autoimmune diseases, such as systemic lupus erythematosus, idiopathic thrombocytopenic purpura, Sjögren syndrome, Graves disease, and rheumatoid arthritis [12, 51]. These diseases are usually more severe at puberty, during menses, and during pregnancy, suggesting again a relationship with progesterone [52]. It is unclear whether this is due to differential Th-1 and Th-2 responses, since the immunopathogenicity of these diseases remains controversial.

The same typology of diseases could also be applied to contexts other than gender differences. For instance, it is striking to note that AIDS, a disease which also down regulates IL-12 and therefore the Th-1 response [28], is associated with an increased mortality from measles, hepatitis, candidiasis, and tuberculosis, all diseases in the first and second group, but not with mortality from malaria and shistosomiasis, which are typical diseases of the third group.

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