

# Genetics and Resistance to Tuberculosis

## Could Resistance Be Enhanced by Genetic Engineering?

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■ Recent observations strongly suggest a significant role for genetic factors in innate resistance to infection by *Mycobacterium tuberculosis*. This relation was discovered in a study of tuberculosis in Arkansas nursing homes and was supported by data from three outbreaks of tuberculosis in two prisons. A person's resistance level was found to correlate with the region of his or her ancestry. Ancestors of person's in the more resistant group tended to derive from densely populated areas and cities rife with tuberculosis, whereas the ancestors of person's in the more susceptible group tended to derive from areas once free of tuberculosis. In accordance with current genetic theory, those persons who are less resistant to tuberculosis would be expected to be more resistant to infections endemic to the region once inhabited by their ancestors. Isolation of the gene previously shown to confer specific innate (nonimmune) resistance to tuberculosis should result in the creation of a more rational approach to increasing the capacity of human macrophages to kill tubercle bacilli without producing a positive tuberculin skin test.

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The student who dates his knowledge of tuberculosis from Koch may have a very correct but a very incomplete appreciation of the subject.—Sir William Osler

Sir Patrick: Aye, phagocytes, yes . . . the phagocytes eat up the disease germs.—George Bernard Shaw, *The Doctors Dilemma*; 1907

The results of two recent reports concerning differing types of DNA analyses support the existing evidence that all humankind's racial groups are descended from common ancestors in Africa (1, 2). Obvious differences in skin pigmentation are recognized to represent natural selection in response to differences in sun exposure over many generations.

It was therefore a surprise when a recent epidemiologic analysis of more than 41 000 comparably housed and fed tuberculin-negative nursing home residents in Arkansas showed that whites were significantly more resistant than blacks to initial invasion by *Mycobacterium tuberculosis* (3). A similar disparity was also found in three outbreaks of tuberculosis in two prisons (3). Although no doubt exists regarding the importance of dietary and social factors to the development of tuberculosis (4), these highly consistent findings belie the accepted paradigm that such factors are *solely* responsible for the greater prevalence of the disease among blacks.

Fifty years ago, Lurie (5) and others reported convincing experimental evidence of a genetic factor in resistance to tuberculosis. In 1960, Motulsky (6) made a strong case for a genetic basis for variation in resistance to infection in humans. A recently published report has linked the strong resistance to tuberculosis among Ashkenazi Jews to the high death rate from tuberculosis in European ghettos (7). A clear genetic tie is also shown by a study of tuberculosis in identical twins (8).

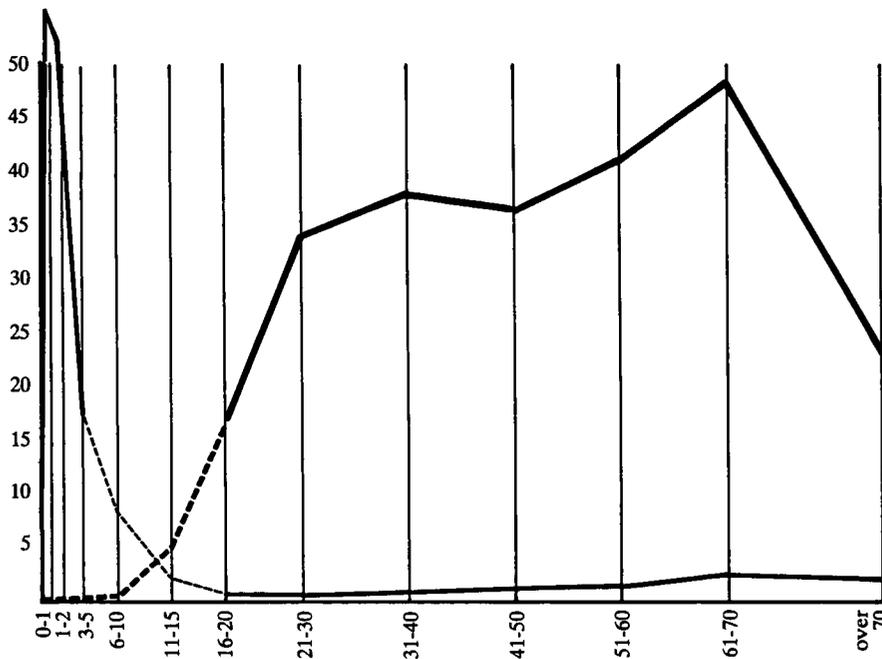
Recent experimental evidence strongly supports a genetic basis for resistance to tuberculosis. Skamene's group (9-11) has found evidence of a genetic basis for relative resistance to mycobacteria in mice. This resistance gene ( $Bcg^r$ ) maps to chromosome 1 in the mouse, and the human homolog appears to lie on the long arm of chromosome 2, not near any skin pigmentation genes (12). Crowle and Elkins (13) have presented in-vitro evidence that macrophages from whites permit less rapid replication of *M. tuberculosis* than do those from blacks. Zwilling's group (14) found that monocytes show a pattern of HLA-DR expression consistent with relative resistance to *M. tuberculosis* in 70% of whites but in only 30% of American blacks. This result is consistent with the fact that nonimmune resistance is about twice as common in whites as in blacks (3).

Heritable nonimmune resistance to microbial invasion stems from a basic biologic phenomenon: When an infection takes a heavy toll of susceptible children in a closed population during an extended period, natural selection favors survival of genetically resistant individuals (15-17). Survival of naturally resistant individuals is by the same mechanism that allows a population of tubercle bacilli to become resistant to isoniazid or to rifampin when a patient with active tuberculosis is treated with only one of these bactericidal drugs. Thus, a significant difference in prevalence of resistance to a pathogen in two populations is caused by a great disparity in their past experiences with that pathogen.

Tuberculosis is currently a world-wide pathogen, and archeologic evidence indicates a great prehistoric prevalence for the disease in crowded cities of Europe and North Africa (18, 19). It appears, however, that this organism was once completely absent from several isolated areas (20, 21), the largest of which was sub-Saharan Africa.

### Effectiveness of *Mycobacterium tuberculosis* in Natural Selection

Tuberculosis develops in two distinct stages. Because the disease occurs in relatively resistant persons today, the primary infection usually heals, leaving only tuberculin sensitivity and considerable protection against a



**Figure 1. Mortality resulting from chronic pulmonary tuberculosis (phthisis) and from generalized tuberculosis per 100 000 untreated persons of various ages living in Bavaria in 1905. The heavy line represents phthisis. The thin line represents generalized tuberculosis. The dotted portions of the two lines represent the period of childhood when there were too few deaths to plot accurately. Although both forms exerted selective pressure, that in infancy was greater. (Adapted from reference 26.)**

second infection. In less resistant persons, however, the primary stage often produces a typhoidal illness characterized by wasting, lymphadenopathy, serous effusions, and fever, which often terminates with caseous pneumonia (22-25). In either case, survivors remain at risk for chronic pulmonary manifestations of the disease months or years after the initial infection.

In contrast, the postprimary stage most often produces a chronic pulmonary disease that advances so slowly and painlessly to death that the ancient Greeks called it "phthisis" (wasting) (18). Figure 1 shows a comparison of the age-specific mortality rates from the two syndromes in Germany at the turn of the century (26). Clearly, *M. tuberculosis* was a strong factor in the elimination of susceptible members of a population before they reached the age of reproduction. Recent studies (9-14) suggest that the phenotype on which such selection acts in tuberculosis may be the ability of macrophages to control the initial invasion by *M. tuberculosis*.

The subacute primary type of tuberculosis seen among black slaves was so different from the chronic illness familiar to physicians of the day that it was commonly mistaken for typhoid fever (22, 23). It was not until 1868 that Villemin (27) showed that the common typhoidal disease of French children and phthisis are two phases of the same infection. Fourteen years later, Koch discovered that the cause of both diseases was *M. tuberculosis* (28).

#### Role of *Mycobacterium bovis* in Natural Selection

Although this closely related species preferentially attacks cattle and several other domesticated animals, it can also produce disease in humans. It produces lesions called scrofula in the tonsils and cervical lymph nodes. Although it may have played a selective role in Europe and North Africa, *M. bovis* could not have done so in western Africa, where the tsetse fly eliminated its hosts (29, 30).

#### Evidence for Absence of *M. tuberculosis* in Central Africa

Without archeologic evidence, the absence of tuberculosis from sub-Saharan Africa rests on the consistent reports of persons who traveled or worked in the area before the development of widespread contact with Europeans (31).

Tuberculosis was known on the coasts of Africa as early as the 16th century, because of trade with India and Portugal (31). However, the great susceptibility of Europeans to several vector-borne infections of Africa prevented their significant penetration to the interior. Moreover, circumstances for ready transmission of tubercle bacilli, such as dense population, indoor living, and the presence of cities, were absent from the interior of Africa until the 20th century. In Europe and North Africa, however, crowding into cities was common (29, 30).

As recently as the first half of the 19th century, Lichtenstein (32) and Livingstone (33) wrote that tuberculosis did not exist among the tribes of South Africa. In 1867, Dr. William Budd (34) wrote that coastal "negroes are particularly liable to phthisis" with a high mortality, "but in the interior, where contact with Europeans is slight, there is reason to believe that phthisis does not exist." McVicar (35), a medical missionary with knowledge of tuberculosis, reported in 1894 that he had "seen not a single case of any form of tuberculosis" in his extensive experience in Nyasaland (Malawi). In 1907, Cummins (36) reported that, although no tuberculosis existed among natives of Sudan, the disease was a scourge among Sudanese soldiers in the Egyptian army, where they were exposed to the disease.

When black troops from Senegal, West Africa, were forced to fight as part of the French Army during World War I, their death rate from a typhoidal syndrome was so great that the French had to abandon the project. Borrel (37) identified the etiologic agent as *M. tubercu-*

losis. The African troops had no resistance to this unfamiliar pathogen.

### Introduction of *M. tuberculosis* into Central Africa

Toward the end of the 19th century, the situation in southern Africa began to change. It was thought that the absence of tuberculosis there was due to a curative effect of the salubrious climate. This assumption soon brought increasing numbers of Europeans with chronic pulmonary tuberculosis to "take the cure." Tuberculosis of the typhoidal form soon began to appear among the natives. By 1907, Millar (38) quoted an official report of the Chief Medical Officer of the Cape Colony, ". . . it is no longer possible to doubt that phthisis bids fair to decimate the natives. . . ." Turner (39) also noted in 1907 that pulmonary tuberculosis was present and spreading in South Africa, and in 1928, Macaullay (40) noted a heavy toll among young black men in the mines.

Thus, when Europeans did penetrate to the interior, the natives developed a virulent form of tuberculosis associated with a high mortality (31, 34). Survivors gradually accumulated, and the chronic pulmonary form began to appear. As the population of the region increased, followed by crowding into cities, the incidence of all forms of tuberculosis increased exponentially.

### Tuberculosis among Slaves in America

It seems certain that none of those crowded into slave ships for the passage to the New World had infectious tuberculosis. One infectious person in those close quarters for the 3 months of loading at several ports and making the crossing would have spread the infection to virtually every person in the ship. Tuberculosis would then have been a scourge among the new arrivals within weeks. They developed tuberculosis later, but it was acquired from the chronic pulmonary tuberculosis of their European "masters" (29).

In 1831, Dr. Lunsford Yandell (41) of Nashville, Tennessee, described the clinical and autopsy findings of five cases of what he called "Struma Africana (or Negro Poison or Negro Consumption)," a common, fatal illness among slaves. This subacute illness was characterized by fever, lymphadenopathy, splenomegaly, hepatomegaly, diarrhea, general wasting, and shortness of breath. Autopsy findings showed widespread tubercles and caseous pneumonia, but little of the fibrosis seen in cases of tuberculosis among whites. The clinical picture fits well with subacute primary tuberculosis in a person with little resistance (22, 23), and the autopsy results are consistent with Borrel's findings in Senegalese troops (37).

By the 1860s, chronic pulmonary tuberculosis was recognized among American blacks (29). By that time, 300 years had elapsed in which susceptible individuals had died of the disease. Enough resistant individuals had survived the primary infection for chronic pulmonary tuberculosis to occur with increasing frequency.

### Tuberculosis in American Blacks Today

In his chapter on pulmonary diseases in Williams' *Textbook of Black Related Diseases*, Mays (42) writes,

"There is considerable evidence that some races have a weaker genetic resistance to tuberculosis. The higher morbidity and mortality among Blacks in many parts of the world are ascribed by some to poor living conditions, a point of considerable merit; however, the clinical manifestations of the disease in some Blacks are so striking that little doubt can exist that other forces are also operative. Blacks have a high incidence of a disease type which tends to present as acute tuberculous pneumonia, undergo caseation rapidly, and spread by lymphatic and hematogenous routes to extrapulmonary sites."

### Resistance of Blacks to Other Infections

It is important to dispel any notion that whites are generally more resistant than blacks to infectious diseases. As pointed out by Motulsky (4), nonimmune resistance to infection is never general, but is instead quite specific. The considerable literature on this matter has been summarized elsewhere (43-45). Hamilton and colleagues (46) point out the importance of sexual reproduction in the provision of greater genetic polymorphism for defense of higher hosts against parasites with more frequent mutation.

Thus, it is not surprising that blacks are remarkably more resistant to the major killers in sub-Saharan Africa (malaria, yellow fever, and trypanosomiasis) where their "genetic background" evolved (47). In some, heritable resistance to malaria is genetically linked to sickle-cell disease; however, in others it is linked to major human lymphocyte antigens common only in West Africa where the disease abounds (48).

Africa once was referred to as "missionary's graveyard." About half of the European missionaries died during their first year in Africa (30), most commonly from malaria or yellow fever, which are vector-borne diseases not dependent on high population density. Only 10% ever returned to their home countries, and, for this reason, they often shipped their gear in a coffin (Lofgren JP. Personal communication). In the Bahamas as well, the death rate from yellow fever was 200 per thousand among white troops, but only 40 per thousand among black troops (49).

Thus, had Europeans been forced to live in tropical Africa, their decimation probably would have been quicker than that of the Senegalese troops in France, but would have resulted from diseases to which Africans were quite resistant (50).

### Increasing Resistance of Blacks to Tuberculosis

In the novel, *The Andromeda Strain*, Michael Crichton (51) describes a tragedy that occurs when an unfamiliar microbe is introduced from outer space. It appears that *M. tuberculosis* was such an organism for native Africans. Now, 300 to 400 years (15 to 20 generations) after their forebears first were brought into contact with tuberculosis in America, greater susceptibility is only about twice as common in blacks as in whites (3, 14).

Tuberculosis in American blacks is currently a chronic pulmonary disease similar to that seen in

whites. In blacks, however, the disease runs a somewhat more rapid course (42). In central Africa, however, only about 80 years (4 generations) have elapsed since tuberculosis began to penetrate the interior. Now, because of great crowding and because tuberculosis and the acquired immunodeficiency syndrome (AIDS) are on the ascending limb of separate but related epidemic curves, the threat to Africa is unprecedented in recorded history.

### Why a Difference in Resistance to Such a Primitive Microbe?

Both the development and maintenance of relative resistance of a population to an infectious agent depend on a high mortality rate among the youth of its natural host, leaving those who are more resistant to survive and reproduce (15). In this way, the small number of persons who have some genetic mechanism that allows them to resist invasion by that parasite gradually increases at the expense of those who are less resistant to the pathogen.

In a population with innate resistance to a given infection, such resistance can be seen at three levels: high, medium, and low. If the trait is inherited from only one parent, the resistance is medium; if from neither, it is low; and if from both, it is high. The last level is familiar to tuberculosis specialists, all of whom probably have known persons who are tuberculin negative, despite extensive exposure to the infection for many years.

This increased resistance is, however, not only specific to a particular parasite but is reversible (15, 49, 50). If elimination of prereproductive persons ceases (due to eradication of the parasite, as with small pox today; to widespread use of effective immunization, as with measles today; or to widespread use of effective bactericidal chemotherapy, as with tuberculosis today), the frequency of the trait will decrease over several generations (50).

The mechanism by which inhabitants of sub-Saharan Africa became and remain less resistant to *M. tuberculosis* was somewhat different. Humans are the only natural host for this organism, and, in immunologically normal persons, the organism can produce another infectious case in only about 5% of new hosts. For the organism to survive in a population, each infectious person must infect 20 others. Otherwise, the organism will eventually die out, as it did in sparsely populated sub-Saharan Africa.

After this evolutionary pressure was removed, the gene complex that conferred increased resistance to tuberculosis was eventually lost. The pressure of the many vector-transmitted diseases that are largely limited to sub-Saharan Africa remains, however, and genetic resistance to these diseases has not decreased.

### Effect of HIV Infection on Resistance to Tuberculosis

All statements regarding levels of resistance to tuberculosis are negated by infection with the human immunodeficiency virus (HIV). Selwyn and associates (52) have shown that the presence of HIV infection makes persons with a dormant tuberculous infection likely to develop tuberculosis. More alarming are three recent reports showing that HIV infection makes those with no

previous experience with *M. tuberculosis* extremely susceptible if exposed to it. Di Perri and colleagues (53) report that 7 of 14 tuberculin-negative residents of a day hospital for HIV-infected persons developed clinical tuberculosis within 60 days of inadvertent exposure to tuberculosis. In a residential facility for HIV-infected persons in San Francisco, 12 of 24 residents developed culturally proven tuberculosis within 106 days of exposure. Three of these cases were fatal (54, 55).

In four U.S. hospitals, clear evidence of nosocomial spread of multidrug-resistant *M. tuberculosis* existed among 139 HIV-infected persons. Seventy (50%) died within a median of 8 weeks (56). In one of the hospitals, DNA "fingerprinting" showed that 13 of 14 isolates were of an identical pattern. Similar spread of tuberculosis among HIV-infected inmates and guards of the New York State prison system has now been associated with 13 deaths (57).

Neither such a high attack rate nor rapidity of disease progression has ever been seen in tuberculosis. Infection with HIV strips patients of both nonimmune and immune defenses against *M. tuberculosis*.

The devastation resulting from the combination of *M. tuberculosis* and HIV infection in central Africa is so great that a recent article seriously poses the question, "Is Africa lost?" (58). If this combined epidemic is to be slowed before it engulfs the world, ways must be found to reduce the spread of tubercle bacilli among HIV-infected persons.

One measure that has promise in developed countries is more widespread use of the germicidal portion of the ultraviolet spectrum (254 to 260 nm) in places where these two diseases are likely to meet: jails, prisons, shelters for the homeless, and hospitals and hospices caring for HIV-infected persons (59-63). This technology could at least afford greater protection to these particularly susceptible persons while we await an effective vaccine against both tuberculosis and HIV infection.

### Implications

This report is not intended to show another difference between blacks and whites. Rather, it is offered as a challenge to genetic engineers to identify the gene or genes responsible for enhanced resistance to *M. tuberculosis* in about 70% of whites and in 30% of American blacks (14). It should then be possible to identify the gene products that enhance the ability of macrophages to kill tubercle bacilli. After this effect is better understood, a more rational approach to increasing resistance to infection by *M. tuberculosis* can be developed, an approach that would not interfere with the epidemiologic value of the tuberculin skin test in the identification of infected persons.

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