Why Did They Die?

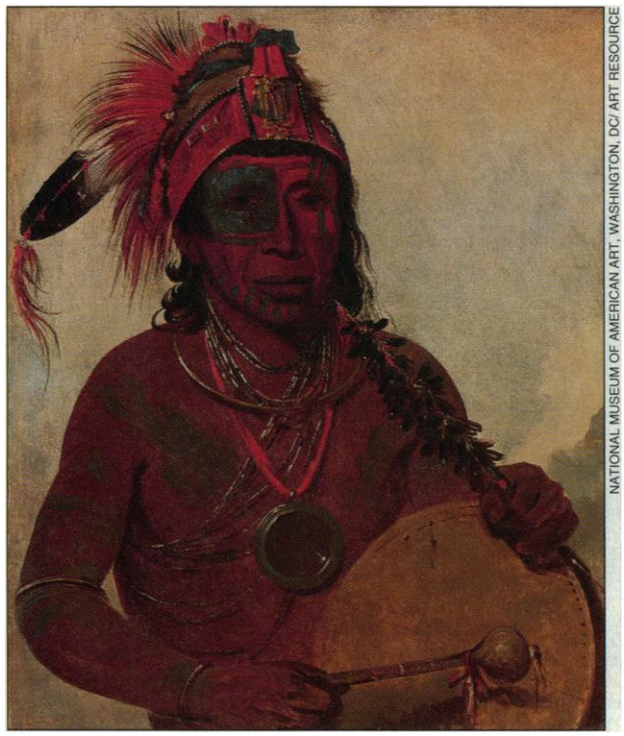
Francis L. Black

Approximately 56 million people died as a result of European exploration in the New World (*1*). In many areas, this translates into a reduction of the population to 10% of its initial size. Some died in combat and many as a result of social disruption, but most died of introduced diseases. Even as recently as the 1960's and 1970's when some of the last Amazonian populations were contacted, mortality rates up to 75% were recorded (*2*). Excess mortality continued in repeated bouts of the same diseases and in the presence of medical support. No one disease was responsible; rather, a wide variety of infections occurred, and often several acted together. New data from several sources suggest why this might have happened.

In this quinquecentennial year, both sides have been blamed for the tragedy: we cry mea culpa for being beneficiaries of this holocaust, or we dismiss the effect as due to lack of prior genetic selection and, by inference, the genetic inferiority of the affected people. In fact, the intruders could not have anticipated the consequences of their arrival. As for the Amerinds being genetically inferior, extensive studies by Jim Neel, Francisco Salzano, myself, and others (*3*) have failed to reveal any evidence of unusual individual susceptibility, except for lack of hemoglobin S and all other genetic traits conferring specific resistance to malaria and a minor elevation of temperature in response to attenuated measles virus (*4*). Genetic markers seldom serve to distinguish individuals of the New World from those of the Old. However, New World populations do differ in one important respect—they have much less internal genetic diversity. This distinction points to an alternative explanation for New World susceptibility to disease: it was not that the newly contacted people had inappropriate genes or, individually, deficient immune systems, but that the people of the New World were unusually homogeneous.

A key piece of evidence comes from West Africa and the studies of Peter Aaby and Michel Garenne (*5*). They found that a child who catches measles from a family member faces nearly twice the risk of death as a child infected by an unrelated passerby. Of course, the infecting dose acquired from a close contact is likely to be greater, but early studies with partially attenuated measles virus showed that the dose of this agent is not related to the severity of symptoms (*6*). The essential difference seems to be that virus grown in one host is preadapted to a genetically like host and thereby gains virulence.

Taking measles virus, with its RNA genome, as a model, we find that it replicates with low fidelity, changing even while infecting a single host (*7*). Some viral epitopes with essential functions are conserved, but many immunogenic sequences change without reducing the virus's infectious potential. Each of the host's histocompatibility (MHC) antigens presents a different broad, but still restricted, set of viral peptides to the immune system (*8*). The immune response selects against viruses with these peptide sequences, but when the selected progeny pass to a new host in an outbred population they usually meet new MHC genes, different peptides are presented to the nervous system, and the process starts over again. However, when successive hosts are closely related, the virus encounters many of the same host MHC genes and is preadapted. It is not unusual to find New World population groups in which the average two persons are more closely related, through a restricted initial gene pool and many lines of common descent, than siblings in an Old World population. In such a situation the virus is as fully adapted to its successive hosts as in the African families.



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Blue Medicine, a medicine man of the Ting-ta-to-ah Band (Eastern Sioux). The genetic homogeneity of Amerinds rendered them particularly susceptible to diseases introduced by explorers and immigrants from the Old World. [Painting by George Catlin]

Class I MHC genes illustrate the extent of differences in immune system polymorphism among human populations. Many molecular variants of these genes are now recognized, but those differences detected by serology are likely to reflect the most important functional variations, and only this method has been used widely enough to provide the needed numbers. The most extensive data pertain to the A and B loci. Serology has distinguished 40 A and B alleles in 1342 Sub-Saharan Africans, 37 in 1069 Europeans, and 34 in 4061 East Asians, but only 10 among 1944 South Amerinds (*9*). North Amerinds have 17 alleles in 1163 persons, and this number includes genes brought in by a second wave of migrants from Asia. Only 14 have been reported in 12,243 Polynesians, and Kuldeep Bhatia found 10 in 5499 Papua New Guineans without Austronesian admixture. For all these studies, the typing sera came from Old World donors and might be expected to miss some New World alleles. This procedure would result in an apparently excessive proportion of monotypic loci. In fact, one must postulate a small proportion of unrecognized alleles in all Old World populations but not in New World people. Novel rearrangements occur in the New World (*10*), but all A or B sequences found in the New World also occur in the Old World.

The more alleles in a population, the lower the frequency of each and the smaller the chance that a virus will encounter the same allele in successive hosts. This relation is more regular than might be expected because of balancing selection (*11*). It is magnified by the fact that the chance of a virus meeting the same gene in two successive hosts is proportional to the square of the phenotypic frequency and the chance of finding both genes of one locus the same is proportional to the fourth power. There is a 32% chance that a virus passing between two South Amerinds will not encounter a new MHC type at either the A or B locus, but only a 0.5% chance when it passes between Africans. Additionally, epidemics in newly contacted communities are intense, and a person is often exposed to virus from multiple sources almost simultaneously. If any of these

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viruses is preadapted, the disease will be more severe.

Differences between populations, similar to those for class I MHC, occur for class II and for immunoglobulin allotypes; these too, influence pathogens' virulence. Limited DNA diversity in Amerinds was emphasized by Sullivan's use of the Kidds' data from a South American tribe to show that DNA fingerprinting methods do not always distinguish between persons (*12*). Pathogen adaptation to populations with limited diversity may involve many agents other than RNA viruses. More complex parasites carry multiple interchangeable genes that function like hypermutability in avoiding immune responses and take about the same amount of time to switch (*13*). With reduced polymorphism at many loci and exposure to diverse mutable pathogens, it is not surprising that previously isolated people fared poorly. Intermarriage between populations reduces the problem, but an unfortunate consequence of intermarriage is often the loss of indigenous culture.

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Electron-Tunneling Pathways in Proteins

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Electron-transfer (ET) reactions are key steps in photosynthesis, respiration, drug metabolism, and many other biochemical processes. These ET processes commonly occur between protein-bound prosthetic groups that are separated by large molecular distances (often greater than 10 Å). Although the electron donors and acceptors in these reactions are expected to be weakly coupled, the ETs are remarkably fast and proceed with high specificity. On page 1748 of this issue, Pelletier and Kraut (*1*) present work on the crystal structures of cytochrome c–cytochrome c peroxidase complexes that could lead to a much deeper understanding of how the intervening medium controls interprotein ET reactions.

Theoreticians have been intensely interested in long-range protein ET reactions for many years. In standard formulations, the weak electronic coupling between distant donor and acceptor sites leads to rates that are proportional to a protein-mediated electronic-coupling factor, $|T_{DA}|^2$, and a nuclear factor that arises from nuclear motion coupled to the ET process (*2*). The simplest models describing long-range protein ET treat the medium between donor and acceptor as a one-dimensional square tunneling barrier (1DSB); accordingly, the rate (k_{ET}) is predicted to drop exponentially with distance (*3*, *4*). Accounting for the role of protein-mediated coupling in the 1DSB models amounts to assigning a barrier height for electron tunneling. Estimates of the exponential decay constants (β) made in the 1970s by Hopfield (1.4 Å^{-1}) (*3*) and Jortner (2.6 Å^{-1}) (*4*) stimulated numerous experiments on small molecules and proteins.

A simple formulation of the electronic-coupling problem in long-range ET describes the medium between donor and acceptor as a bridge comprised of identical repeat units:

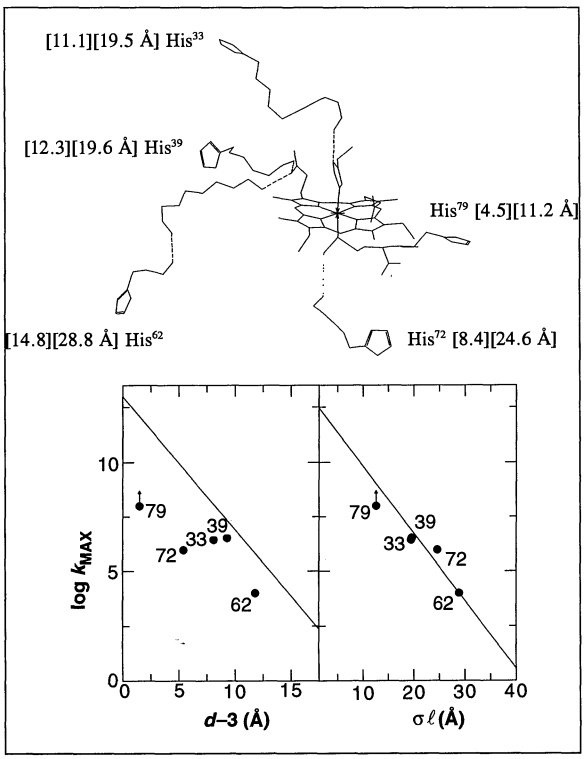

Fig. 1. (Upper) Electron-tunneling pathways in Ru(His^X)-modified cytochromes c (*2*). Edge-edge distances and tunneling path lengths are indicated in brackets ([*d*][$\sigma\ell$]). **(Lower)** Correlations of activationless ET rates in Ru(His^X)-modified cytochromes with *d* and $\sigma\ell$.

T_{DA} drops by a simple multiplicative factor ε as the chain is lengthened (*5*). The factor ε depends on the energy of the tunneling electron as well as on the composition of the repeat unit in the bridge. For simplicity, the decay can be divided into components associated with each bonded and nonbonded contact within the repeat unit.

A tunneling-pathway model for electronic coupling in proteins has been developed by generalizing the foregoing periodic-system model (*5*). Tunneling is much more efficient (decays more slowly) through bonded orbitals than through space because the effective potential barrier is lower. In proteins, the covalently bonded path between donor and acceptor can be extremely long compared to the direct through-space distance. In the pathway approach, the protein structure is analyzed for the combination of bonded and nonbonded interactions that maximizes T_{DA}. The tunneling pathways obtained contain mostly covalent and hydrogen bonds, with

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