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THE MERRIMON LECTURE

THE EVOLUTION OF HUMAN GENETIC DISEASES

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THE MERRIMON LECTURESHIP IN MEDICINE

This Lectureship, which was established by the late Dr. Louise Merrimon Perry "in respect and honour of the Great Traditions of the Science and Practice of Medicine," was inaugurated in 1966. Dr. Perry's idea was that the lectures be open to all, but that they be concerned with "the Origins, Traditions and History of the Medical Profession and of that Ethical Philosophy which must dominate this Field of Human Endeavor." It was her intent that the Merrimon Lecturers be distinguished both for scientific or clinical skills and a notably humane attitude toward Medicine.

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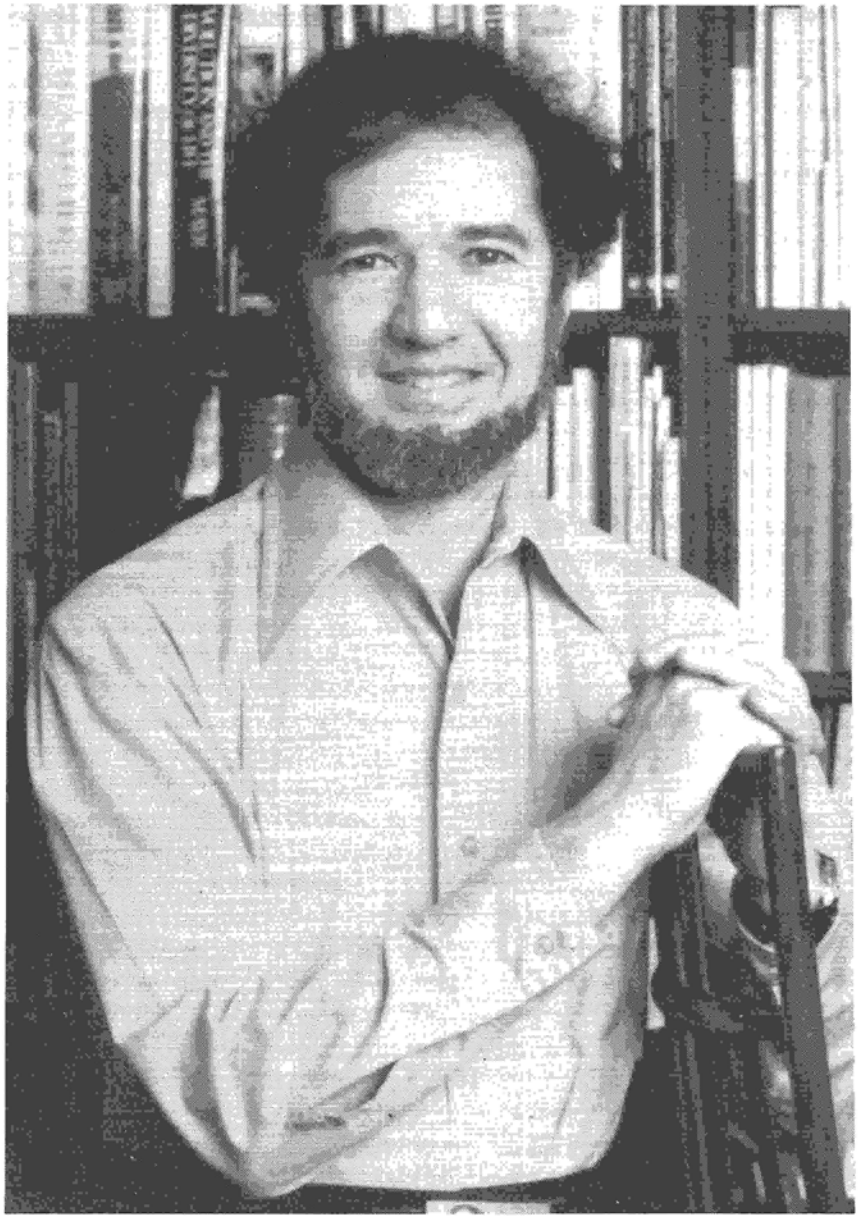

JARED M. DIAMOND, Ph.D.

JARED MASON DIAMOND was born in Boston in 1937. He is the son of Louis K. Diamond, a pediatrician at Harvard who was a frequent visitor to North Carolina in the 1940s and 1950s, and a favorite teacher in the itinerant system of post-graduate medical education then provided to the doctors of the state by the university.

Jared Diamond was educated at Harvard (B.A.) and Cambridge (Ph.D.). After a year at the Max Planck Institut in Munich, he returned to Harvard for three years. He moved to UCLA in 1966 as a member of its department of Physiology, and this has remained his base of operations.

Dr. Diamond's career has been extraordinary. He is simultaneously an authority on the biophysics of membranes and on ecology and evolutionary biology. A man from Mars might regard this as merely what is expected of a good biologist, but biologists know that the concepts and languages of membranologists and ecologists have about the same relationship to each other as Persian and English. To put it simply, he was elected to the American Academy of Arts and Sciences for his contributions to physiology, and to the National Academy of Sciences for his contributions to ecology.

Quite aside from the interest and value of the publications themselves, Dr. Diamond's list of publications makes an interesting study. There are numerous original research articles and abstracts, book chapters and reviews, and books on membrane physiology, ecology and evolutionary biology. But two other of his facets deserve special mention. He has been a successful author of general articles about science, publishing in popular journals such as DISCOVER and regularly contributing fascinating interdisciplinary essays to the News and Views section of NATURE, the international journal of science. And he is also an explorer. Since 1960 he has participated in 13 field expeditions, usually as the Leader, to such places as Yugoslavia, the Amazon basin, and most often to the islands of the southwest Pacific. He is a prize winning teacher of medical students, and his laboratory has been the home of a succession of successful graduate students, postdoctoral fellows and undergraduates.

The university is pleased to have Jared Diamond as its 1987 Merrimon Lecturer, because he exemplifies the combination of high intellect, the imagination to see the connections between things, and the will and energy to carry through. He is a worthy modern successor to Elisha Mitchell, our first Professor of Natural Philosophy, who was a geologist, botanist, explorer (which cost him his life), and an ordained Christian minister who read the Old Testament in Hebrew and the New Testament in Greek.

EVOLUTION OF HUMAN GENETIC DISEASES

A major evolutionary puzzle is posed by the existence of genetic diseases or conditions with a strong genetic component, such as diabetes, ulcers, muscular dystrophy, Tay-Sachs disease, and cystic fibrosis. The puzzle is more acute for such diseases than for infectious diseases, which are caused by an external agent, the pathogen. Our struggle with pathogens is evolutionarily similar to familiar predator/prey or parasite/host relationships, in that not only we but also the pathogens evolve and may get the upper hand. But genetic diseases are ones that we bring on ourselves and that involve only our own genes, with which we commit genetic suicide. Natural selection supposedly acts to eliminate deleterious genes and promote favorable ones; even genes that bring an advantage of only 1% are likely to spread. How, then, is the operation of natural selection compatible with the existence of genes that carry a 100% disadvantage?

For the evolutionary biologist, human genetic diseases offer grimly rich study material. Among the animal species that we might study, humans are unique in that all individuals in a large population are named, their putative relationships are known, and we scrutinize our individual variation daily in minute detail. For the anthropologist or archaeologist as well, the study of human genetic diseases is productive, because the genetics of the disease traits are often well understood and they offer models for examining the evolution of human populations. But there is also an ethical element that draws us to the study of human genetic diseases. We all know innocent people who suffer from, and perhaps will die of, genetic diseases. Why did fate play these dirty tricks on us?

Mutation Pressure

A simple explanation for how genetic diseases manage to persist in the face of natural selection is that, while natural selection does tend to eliminate deleterious genes, the result is an equilibrial low frequency rather than complete elimination. The equilibrium value depends on the mutation rate, which continually generates new bearers of the genes, and on the coefficient of selection, which eliminates the genes. For example, in the case of a rare dominant allele that has high penetrance and causes severe reduction in fitness, the heterozygote frequency v equals m/s, where m is the mutation rate and s is the selection coefficient. v approaches the mutation rate m as the selection coefficient approaches 1, the value for a lethal allele. Similarly, one can show that a sex-linked recessive with high penetrance and causing severe reduction in fitness approaches a frequency of 3 m/s, while an autosomal recessive approaches a frequency of $(m/s)^{1/2}$.

Several deleterious genes appear to be maintained by mutation alone (Vogel and Motulsky 1986, Rotter and Diamond 1987). One example is acrocephalosyndactyly, a malformation of the skull and hand. Affected individuals reproduce only very rarely,

and the condition is probably dominant, so that over 95% of cases are "sporadic." That is, they arise in individuals with no family history of the condition and probably represent new mutants. The frequency, which may be taken to approximate the mutation rate, is $4x10^{-6}$. A second example is a type of dwarfism known as achondroplasia, another dominant condition associated with low reproduction. Over 80% of cases are sporadic (i.e., without family history) and presumably represent new mutations, so that the gene frequency of 10^{-5} approximates the mutation rate. Still another example involving a more familiar condition is Duchenne-type muscular dystrophy, a lethal sex-linked recessive that is incompatible with reproduction. The gene is expressed in males but hidden in female heterozygote carriers. Under these circumstances one expects one-third of observed cases to be new mutants, yielding an estimated mutation rate of $5x10^{-5}$.

Mutation rates in humans have been estimated for various metabolic disorders and genetic markers. The highest estimate is the value of $5x10^{-5}$ for Duchenne-type muscular dystrophy. Almost all other genes yield estimates below 10^{-5}, and the median value is perhaps 10^{-7}.

Thus, if one observes a lethal allele with a frequency in the range of 10^{-7}, it is a plausible candidate to be maintained by mutation. On the other hand, a dominant allele with a frequency above 10^{-5}, or an autosomal recessive with a frequency above $(10^{-5})^{1/2}=3x10^{-3}$, is probably not being maintained by mutation. Hence, equilibria between mutation and selection are unlikely to account for our common genetic diseases at those or higher frequencies.

The Founder Effect

My discussion of equilibria between mutation and selection assumed a large, well-mixed population with a stable recent history. But many human populations are neither large, well-mixed, nor recently stable. Some populations were recently launched by a few founders (the so-called founder effect: Mayr 1963), while gene frequencies in small populations practising polygamy may be disorted by the genes of one or two popular individuals (genetic drift). If such a population with non-equilibrial gene frequencies then expands, it may take a long time for natural selection to eliminate deleterious recessives or at least to reduce their frequencies to equilibrial low values.

Until recently in human history, all humans practised the hunter/gatherer lifestyle and lived in effective breeding populations numbering not more than 500 individuals. Skew in male mating success was marked because of polygyny, and skew in reproductive success was also marked because of high mortality of pre-reproductive children. Those are conditions under which one expects the founder effect and genetic drift to be important. In fact, each small population of human hunter/gatherers has its own "private" genes that probably spread in this manner. But the genetic consequences of the founder effect can also be documented in historic times, as I shall illustrate by several examples (Diamond and Rotter 1987):

Tyrosinemia is a lethal autosomal recessive disease whose heterozygote frequency in French Canadians is around 4%, far above the expected equilibrial value in the face of natural selection. The high frequency of this gene has been traced to a single individual who lived in the 17th century at a time when the population of French Canada was still tiny and on the verge of expansion.

The Old Order Amish are a religious isolate in the United States, consisting of three separate demes founded in the 1700's. Each deme now has its own "private" autosomal recessive diseases that are probable legacies of the founder effect (McKusick 1979).

The Finnish-speaking population of central and northern Finland was founded by a small number of colonists from southern Finland around the 16th century. Finns now have 19 "private" diseases, of which 15 are autosomal recessives (Norio *et al.* 1973). Of the remaining four, two are dominant and two are sex-linked eye diseases that probably do not impair reproductive fitness.

Much of the Afrikaner population of South Africa is derived from a small number of European emigrants in the 17th century, who bred prolifically and expanded to the modern Afrikaner population of over two million (Botha and Beighton 1983). Among the characteristic genetic diseases of the Afrikaners is a dominant condition known as porphyria variegata, which had little effect on fitness until 20th-century medicine associated it with serious drug reactions. The gene's frequency among Afrikaners is $3x10^{-3}$. All Afrikaner carriers have been traced back to a single couple who emigrated from Holland to South Africa between 1685 and 1688 (Dean 1972). In Sweden there is a related dominant condition known as acute intermittent porphyria, which was also not deleterious until the advent of modern drugs, and whose frequency in northern Sweden reaches $1x10^{-3}$. As in the case of porphyria variegata among Afrikaners, carriers of acute intermittent porphyria in northern Sweden can be traced back to a single couple in the 17th century.

Thus, the founder effect is conspicuous in populations that were founded a few centuries ago and that have expanded from a small number of founding individuals. In such populations one observes deleterious genes at frequencies far above what could be maintained at equilibrium by the mutation rate. But the genes proved to be either autosomal recessives whose heterozygote carriers are protected from the effects of natural selection, or else dominant or sex-linked recessives that had little effect on reproductive fitness until recently.

Counterbalancing Selection

While mutation and the founder effect can thus account for the frequencies of some genetic disorders, that still leaves us with many conditions that are severely deleterious and surely not neutral; that exist in old large populations and are thus unlikely to be legacies of the founder effect; that are widespread in the world and thus cannot

be attributed to genetic drift; and that occur at frequencies too high to be maintained by mutation. For such genes it is necessary to assume that the gene's disadvantage is balanced by some advantage. A classical example is sickle-cell anemia, in which the homozygote disadvantage is balanced by heterozygote advantage. There has been speculation about similar heterozygote advantages for other autosomal recessive diseases. However, it is not only the case that the disadvantage must accrue to a homozygote and the advantage to a heterozygote. As I shall show, the disadvantage may fall to males, the advantage to females; or a disadvantage in adulthood may be balanced by an advantage in childhood or fetal life; or a disadvantage in one environment may be balanced by an advantage in a different environment (Rotter and Diamond 1987).

Homozygote disadvantage, heterozygote advantage

Sickle-cell anemia. Sickle-cell anemia is an autosomal recessive disease for which the chain of evidence concerning the balancing of homozygote disadvantage and heterozygote advantage is fairly complete. The genetic basis of the condition is well established. It is possible to identify both the heterozygote and the homozygote and to measure their frequencies. The molecular basis of the phenotype is well known to be an abnormal hemoglobin. The correlation between the geographical distributions of the gene and of the putative selective agent, malaria, has been established. In addition to this population-level correlation between the gene and the selective agent, it is possible to demonstrate the anti-malarial protective effect of the gene in individuals, and also *in vitro.* The cellular mechanisms of the homozygote disadvantage and the heterozygote advantage are both known. Finally, it is possible to estimate the homozygote's loss of fitness and the heterozygote's gain of fitness in malarial regions. A similar balancing of homozygote disadvantage against anti-malarial protection in heterozygotes is suspected for other conditions of the world's malaria belt, such as other abnormal hemoglobins, thalassemias, and G6PD deficiency, though the evidence is not nearly as complete as for sickle-cell anemia.

Sickle-cell anemia is instructive in demonstrating the components of a complete chain of evidence for maintenance of a deleterious recessive by heterozygote advantage. No other autosomal recessive disorder is as well understood. However, I shall mention two other candidates for the status of autosomal recessives maintained by heterozygote advantage.

Congenital adrenal hyperplasia. The classical, salt-wasting form of 21-hydroxylase deficiency is an autosomal recessive disease that is geographically widespread, occurs at high frequency, and therefore is likely to be maintained by some selective advantage. The disease's frequency is only 10^{-4} in Caucasians but $5x10^{-2}$ in Yupik Eskimos, who have a carrier frequency of about 10%, the highest in the world.

It turns out that Yupik Eskimos also have the world's highest frequency of Haemophilus influenzae B, about 100 times that elsewhere. Among Yupik Eskimos certain HLA haplotypes are tightly linked with congenital adrenal hyperplasia, and these

haplotypes prove to be nearly absent in influenza patients. Thus, 21-hydroxylase deficiency, despite its deleterious effects, may have been selected among Yupik Eskimos as protection against influenza (Petersen *et al.* 1984). The mechanism of protection is unknown but may involve modulation of the immune response by raised hormone levels.

The chain of evidence for maintenance of 21-hydroxylase deficiency in Yupik Eskimos by heterozygote advantage is much less complete than that for sickle-cell anemia. However, the evidence does include demonstration of an association between the gene and the putative selective agent both at the population level and at the individual level.

Tay-Sachs disease. Tay-Sachs disease is an autosomal recessive condition that is fatal by the age of five. It is a lipid storage disease in which there is storage of GM2 ganglioside because of deficiency of a lysosomal enzyme, hexosaminidase A. The disease is rare except among Ashkenazi Jews, the Jews of Eastern Europe, where the disease frequency is about 0.3% and the heterozygote frequency is 3–10%. The ancestors of the Ashkenazi reached France and Germany from the Mediterranean around 900 A.D., reached middle Europe (Austria, Hungary, Czechoslavakia, and Poland) around 1250 A.D., and reached the Ukraine in the 1500's.

Given this relatively recent founding of the Ashkenazi Jewish population, could the high frequency of Tay-Sachs disease merely represent genetic drift? It is true that Ashkenazi Jews have 11 autosomal recessive diseases at high frequency, suggesting operation of drift (Goodman and Motulsky 1979). But three of those diseases prove to be lysosomal lipid storage diseases, an astonishing concidence if due to drift alone. Those three conditions are Tay-Sachs disease; Niemann-Pick disease, which involves sphingomyelin accumulation due to lack of the lysosomal enzyme sphingomyelinase and is fatal by the age of four (homozygote frequency $4x10^{-5}$, heterozygote frequency 0.01 among Ashkenazi Jews); and the adult type of Gaucher's disease, which involves an accumulation of glucocerebroside because of absence of the lysosomal enzyme glucocerebrosidase (homozygote frequency $2x10^{-4}$, heterozygote frequency about 0.05 among Ashkenazi Jews). This co-occurence of three autosomal recessive diseases at high frequency among Ashkenazi Jews, all involving deficiencies of three different enzymes resulting in lysosomal lipid storage, suggests some balancing advantage of lysosomal lipid storage in the Ashkenazi Jewish population.

In the United States most Tay-Sachs patients are of eastern European (Polish and Russian) Jewish ancestry, initially prompting a search for selective factors in Poland and Russia. The suggestion was made that Tay-Sachs protects against tuberculosis, because Ashkenazi Jews suffered lower mortality from tuberculosis, than the non-Jewish population from the same area, and because the extended families of Tay-Sachs patients had a low frequency of tuberculosis deaths compared to control families (Myrianthopoulos and Aronson 1972). A seeming objection to the tuberculosis protection hypothesis was that the frequency of tuberculosis was *lower* in eastern European Jews than in other European Jews. If Tay-Sachs did protect against tuberculosis, one would have expected more rather than less of the putative selective agent in the

supposed distributional center of Tay-Sachs disease. However, Petersen *et al.* (1983) recently pointed out that most American Jews by far are of eastern European ancestery, so that a predominance of eastern European Jews among American Tay-Sachs patients was to be expected on those grounds alone. By studying large Jewish samples whose ancestors came from various parts of Europe, Petersen *et al.* were able to show that the gene frequency is only 3% in eastern European Jews but 8% in the Jews of middle Europe (Austria, Hungary, and Czechoslavakia), the portion of the Ashkenazi Jewish realm where the frequency of tuberculosis was highest. Thus, there is indeed a geographic association between the gene and the putative selective factor, and it is plausible to postulate that Tay-Sachs heterozygotes receive protection against tuberculosis, though the mechanism of the protection remains unknown. Note that Tay-Sachs protected only 8% of the middle European Jewish population against tuberculosis. Might some of the others have been protected by the other lipid storage diseases of the Ashkenazi Jews, Niemann-Pick and Gaucher's diseases?

The question remains why Tay-Sachs disease should have risen to such high frequencies in the Ashkenazi Jews, when many other ethnic groups of Europe were also exposed to tuberculosis. The answer may be that Ashkenazi Jews were unique among European ethnic groups in consisting solely of an urban population. In general, cities before the advent of modern medicine and public health measures were population sinks where people died of disease and whose populations were maintained by immigration from rural areas, so that no specialized urban population with genetic protection against disease arose. The Ashkenazi Jews, however, were confined to urban ghettos, where all members of the population became exposed to tuberculosis. Thus, tuberculosis has affected a much larger fraction of the Ashkenazi Jewish population for a much longer time than has been the case for other European ethnic groups.

Just as was true of congenital adrenal hyperplasia, the evidence for maintenance of a deleterious gene by heterozygote advantage is far less complete for Tay-Sachs disease than for sickle-cell anemia. However, the evidence does include association between the gene and the putative selective agent both at the population level and at the family level. In addition, just as there are numerous genetically independent abnormal hemoglobins and thalassemias thought to be maintained by selection for resistance to malaria, so too the Ashkenazi Jewish population exhibits three genetically independent conditions that may have been maintained by selection for resistance to tuberculosis.

Female advantage, male disadvantage

In the cases just discussed, the lethal advantage fell to the homozygotes, while heterozygotes gained the advantage. Let us now consider a condition known as hemochromatosis, where the advantage and disadvantage again are distributed between different individuals but the distribution is on the basis of sex (Crosby 1987).

Iron deficiency is a familiar, common, clinical problem. The opposite problem of iron surfeit arises in idiopathic hemochromatosis, an autosomal recessive disease that leads to iron accumulation through excessive intestinal absorption of iron. The homo-

zygote frequency is around 0.2%, while the frequency of heterozygotes (as detected by HLA linkage) is around 10%. Not all homozygotes, however, express clinically serious symptoms. Instead, symptoms appear only when body iron stores rise to levels 5–10 times above normal. But women normally lose iron through pregnancy, lactation, and menstruation and rarely develop an iron surfeit. The symptoms of hemochromatosis appear 10 times more often in men than in women, and then mainly in men on a high-iron diet, such as Australian men eating a lot of meat or South African blacks who brew a beer high in iron. Furthermore, affected males do not develop symptoms until the age of 40 to 60, as intestinal absorption of iron even in hemochromatosis is so slow that it takes a lifetime of accumulating iron to develop the symptoms.

Thus, in hemochromatosis we have a gene that is usually good for women, whose main risk is that of incurring iron deficiency and who need every help they can get in absorbing iron. The gene is occasionally bad for men, and mainly only late in life. If most physicians, geneticists, and evolutionary biologists were women, we might not even refer to hemochromatosis as a disease but as a wonderfully adaptive blessing, and we might merely note in passing that a few middle-aged men pay a penalty so that their womenfolk can better survive to pass on their genes.

Advantage and disadvantage in the same individual

Disease protection: peptic uclers and tuberculosis. We have considered genes deleterious to one individual but maintained by selection through an advantage gained by another individual, whether a heterozygote or person of the opposite sex. We now turn to diseases in which the same individual may gain both the advantage and the disadvantage. The first example involves the possible protection against tuberculosis provided by peptic ulcers (Petersen and Rotter 1983).

Peptic ulcers were formerly rare in North America and Europe until their frequency rose in the late 18th and 19th centuries to 8–10%. It has traditionally been assumed that the rapid rise must have been due to environmental factors promoting ulcers, such as changes in diet or stress. However, it has now become clear that ulcers are a heterogeneous grab-bag of conditions that include several genetically distinct subgroups. One subgroup of duodenal ulcer patients is marked by high serum levels of pepsinogen I and by hypersecretion of gastric acid, which is a contributing cause of ulcers. This condition appears to be inherited as an autosomal dominant. Why did it rise to a high frequency?

Half-a-dozen lines of evidence suggest that ulcers may be a by-product of a mechanism that protects against tuberculosis, through gastric acid killing the TB bacillus. The evidence includes the following. The frequency of tuberculosis rose to high levels during the industrial revolution and dropped in the late 18th and 19th centuries, before modern medicine and public health could make an impact but in parallel with the rise of ulcers. Scotland, which has the highest frequency of duodenal ulcers and the highest proportion of ulcers arising from high rates of acid secretion, also had the

highest British frequency of tuberculosis. Thus, there was a population-level association between the disease (ulcers) and the putative selective agent (tuberculosis). One may object that ulcers are positively associated with tuberculosis, as was formerly claimed. In realidy, those ulcer patients who tend to get tuberculosis proved to be gastrectomized ulcer patients who thereby lost the gastric barrier to ingested bacilli. Tuberculosis patients tend to have low rates of acid secretion. In particular, people under the age of two or over 50 are the ones most susceptible to tuberculosis, and they are also the age groups with the lowest rates of acid secretion.

As for the mechanism of protection against tuberculosis from gastric acid secretion, acid may provide a barrier against bovine TB bacilli ingested from milk, against air-borne TB bacilli entering via the gut, and (perhaps most importantly) against the secondary spread of TB bacilli coughed up from the lungs. By this reasoning, one might also expect other bacilli sensitive to gastric acid to select for high acid secretion. In fact, it has been noted that cholera as well as tuberculosis is associated with low rates of acid secretion.

This putative link between tuberculosis and peptic ulcers is instructive as a possible much more general paradigm of infectious disease. We routinely distinguish infectious diseases from genetic diseases. The two types of conditions are the provinces of different textbooks, different medical specialists, and different departments. Tuberculosis is considered a classical example of an infectious disease. However, it must also have a genetic component, since there is a big difference between monozygotic and dizygotic twins in their susceptibility to tuberculosis. Perhaps genetic factors modulating the acid secretion rate provide part of that genetic susceptibility to tuberculosis. Thus, a classical infectious disease is in fact partly a genetic disease. Conversely, the rise in frequency of ulcers used to be attributed to environmental reasons, but those environmental reasons may have been a genetic disease, in that ulcers were selected by tuberculosis. The decline in frequency of tuberculosis may have occurred because of the rise in genetic protection offered by uclers. Thus, the traditional dividing lines between infectious diseases, genetic diseases, and environmentally triggered diseases are becoming blurred.

As for the apparent paradox of the same gene providing advantages and disadvantages to the same individual, note that ulcers tend to come at a post-reproductive age, while tuberculosis can kill one in childhood. Thus, one may regard late-life ulcers as a reasonable price to pay for the ability to survive childhood in a high-tuberculosis area.

Finally, the ulcer/tuberculosis example is also interesting because, if confirmed, it would represent an example of rapid recent evolution. Creationists like to decry evolution on the grounds that natural selection operates so slowly that it can only be inferred from historical examples, not witnessed directly. In fact, there are quite a few examples of natural selection witnessed in modern times, but they mostly involve creatures of little human interest, such as moths developing industrial melanism or House Sparrows developing climatically adaptive morphs following their introduc-

tion to North America one century ago. In the case of ulcers and tuberculosis, however, we may have an example of natural selection operating in the human species within the past 200 years. A more rapid and spectacular example of natural selection in humans may lie ahead of us, if exposure to AIDS becomes as widespread as feared and if the enormous individual variability in susceptibility to AIDS infection and rate of progression of the disease proves to have a genetic component. We may well have the grisly opportunity to observe the genes of those genetically resistant to AIDS increasing in frequency at the expense of genotypes lacking AIDS resistance factors (Diamond 1987).

Prenatal advantage, adult disadvantage. In the next example of advantage and disadvantage accruing to the same individual, the fetus gains the advantage, while the born child reaps the disadvantage. The disease in question is insulin-dependent diabetes mellitus (IDDM), alias juvenile-onset diabetes (Vadheim *et al.* 1986).

The gene for IDDM is linked with the HLA alleles DR3 and DR4 and has a penetrance of 20%. Thus, one can consider IDDM as an immune gene, or a gene closely linked with an immune gene, that happens to cause diabetes. It turns out that the HLA alleles DR3 and DR4 are preferentially transmitted from parents to offspring in families of IDDM patients. From parents who carry a single DR3 allele, one expects a 50% probability that the allele will be passed on to an offspring, but in fact DR3 is transmitted from the father to 68% of his offspring, and from the mother to 65% of her offspring. DR4 is similarly subject to selective paternal transmission, from the father to 72% of his offspring, but is transmitted by the mother to only 56% of her offspring, a value that does not differ significantly from 50%. Thus, there is selective paternal and maternal transmission of DR3, but only selective paternal transmission of DR4.

Could these instances of selective transmission arise from selective survival of zygotes bearing the DR3 or DR4 alleles, as compared to other zygotes? Or could the explanation instead be in-utero selection for a DR3- or DR4-bearing fetus over a fetus carrying neither allele? The latter interpretation appears to be the correct one, because there is an increased incidence of miscarriage in diabetic families with a DR4 father and a DR3 mother. Evidently, a fetus lacking the DR3 or DR4 allele is more likely to be rejected by the mother than a fetus with the diabetogenic alleles. Thus, the diabetogenic gene is favored because its bearer is more likely to survive to birth than bearers of normal alleles.

If all bearers of the diabetogenic alleles proceeded to die of IDDM, a condition that was virtually fatal until the advent of modern medicine, preferential prenatal survival would have done the gene bearers no good. But recall that IDDM has only 20% penetrance: 80% of those genetically predisposed will never come down with the illness. Given the numbers that 20% of the gene bearers will die or fail to reproduce while 80% survive, and given the observed 65% selective transmission of the diabetogenic genes, one can calculate that this preferential transmission suffices to maintain the gene's frequency in the face of the removal of 20% of the gene bearers.

Thus, insulin-dependent diabetes mellitus involves genes that are good for fetuses but bad for children and adults. Prenatal advantages may similarly account for the persistence of some other genetic diseases, such as cleft lip and palate (Dronamraju *et al.* 1984).

Advantage or disadvantage dependent on the environment. My remaining example is of a genotype that may either benefit or harm its bearer, depending upon the environment. The condition in question is non-insulin-dependent diabetes mellitus (NIDDM, alias "adult-onset diabetes"), which has a genetic basis, as illustrated by the 100% concordance for NIDDM between monozygotic twins within the same society. Despite this genetic basis, it is obvious that there is also a heavy influence of the environment upon whether people with the appropriate genotype exhibit diabetic symptoms. For example, the frequency of diabetes rose within 10 or 15 years to high levels in Yemenite Jews, Pima Indians, and Micronesians when they switched from their formerly spartan subsistence diet onto a westernized diet. Among Pima Indians the frequency of diabetics reached 50% (Knowler *et al.* 1983)! Thus, there was something about a westernized diet or associated living conditions that fostered the expression of diabetes.

A hypothesis to account for these findings is the so-called thrifty gene theory of Neel (1982). His argument is that a quick release of insulin in response to dietary carbohydrate intake might have been advantageous under the conditions prevailing throughout most of human evolution, when food was hard to obtain and when periods of near-starvation alternated with occasional gluts. However, when the spartan diet was replaced by a regularly generous diet including large quantities of carbohydrate, the quick insulin release led to insulin resistance and symptoms of diabetes. Thus, the genotype responsible for quick insulin release would be adaptive under one set of dietary conditions but harmful under another set. An animal model that supports this interpretation is the diabetic rat, which survives starvation better than control rats, presumably because the diabetic rat is able to convert more of its food intake into energy reserves while on an adequate diet and thus is better buffered against starvation.

One can think of numerous other predispositions that today express themselves as diseases but that might have been favorable under formerly prevalent conditions. For example, the genes that dispose towards hypertension on the high-salt diets common today could be highly advantageous under conditions of extremely restricted salt availability, such as prevailed in the mountainous interior of New Guinea until recently. Similarly, while hyperlipidemias and familial hypercholesterolemia are today considered diseases, there may also be dietary or environmental conditions under which accumulation of lipid or cholesterol would be valuable rather than harmful.

Conclusions

Let us now return to our original question regarding what permits human genetic diseases to persist in the face of natural selection. We have seen that some deleterious genes are maintained at equilibrial low levels by mutations, which generate new copies

of the gene as fast as the gene bearers of the previous generation die without reproducing. Other deleterious genes transiently rise to high levels in expanding populations recently derived from a small number of founders, one or a few of whom happened to bear the gene. If the deleterious condition involved is an autosomal recessive whose heterozygotes are protected against the effects of natural selection, or is a dominant that expresses itself only late in life, it may take many generations after the founding event for the gene frequency to be reduced to equilibrial low levels by the operation of selection.

There remain many genetic diseases whose persistence cannot be attributed either to mutation pressure or to founder effects, and where one must posit some counterbalancing beneficial effect of the gene. There is much variation in what the benefit is and who gets that benefit. In the case of autosomal recessive diseases such as sickle-cell anemia or Tay-Sachs, homozygotes suffer the disadvantages while heterozygotes reap the benefits. In the cases of hemochromatosis, women profit while men lose. In the case of IDDM, fetuses benefit at the expense of some post-natal gene bearers.

The benefits themselves are equally varied and range from protection against malaria (in sickle-cell anemia), tuberculosis (in Tay-Sachs and certain types of ulcers), and influenza (in congenital adrenal hyperplasia) to protection against miscarriage (IDDM) and starvation (NIDDM). Infectious diseases will undoubtedly prove to be a major agent of counterselection responsible for the persistence of many other genetic conditions besides Tay-Sachs, congenital adrenal hyperplasia, and ulcers. The interplay between genetic and infectious disease factors is based on two principles that are opposite faces of the same coin: infectious diseases are a major selective force on gene frequencies, but genes are a major source of resistance to infection.

In short, all the genetic diseases that are maintained by counterselection constitute Faustian tragedies in which humans unwittingly bargained away future health for present gain, with natural selection playing the role of Mephistopheles.

References

Botha, M.C., and P. Beighton (1983). Inherited disorders in the Afrikaner population of southern Africa. Part I. Historical and demographic background, cardiovascular, neurological, metabolic and intestinal conditions. *S. Afr. Med. J.* 64: 609–612.

Crosby, W.H. (1987). Hemochromatosis: current concepts and management. *Hospital Practice* 22: 173–192.

Dean, G. (1972). *The Porphyrias.* Pittman, London.

Diamond, J.M. (1987). AIDS: infectious, genetic, or both? *Nature* 328: 199–200.

Diamond, J.M., and J.I. Rotter (1987). Observing the founder effect in human evolution. *Nature* 329: 105–106.

Dronamraju, K.R., K.G. Wakim, D.J. Smith, and D. Bixler (1984). Fetal mortality in oral cleft families (IX): factors relating to the occurrence of sporadic clefts. *Clin. Genet.* 26: 322–330.

Goodman, R.M.., and A.G. Motulsky (1979). *Genetic Diseases Among Ashkenazi Jews.* Raven Press, New York.

Knowler, W.C., D.J. Pettitt, P.H. Bennett, and R.C. Williams (1983). Diabetes mellitus in the Pima Indians: genetic and evolutionary considerations. *Am. J. Phys. Anthrop.* 62: 107–114.

Mayr, E. (1963). *Animal Species and Evolution.* Harvard University Press, Cambridge, Mass.

McKusick, V.A. (1979). Nonhomogeneous distribution of recessive diseases. In: *Genetic Diseases Among Ashkenazi Jews,* eds. R.M. Goodman and A.G. Motulsky, pp. 271–284. Raven Press, New York.

Myrianthopoulos, N.C., and S.M. Aronson (1972). Population dynamics of Tay-Sachs disease. II. What confers the selective advantage upon the Jewish heterozygote? In: *Sphingolipids, Sphingolipidoses and Allied Disorders,* eds. B.W. Volk and S.M. Aronson, pp. 561–570. Plenum Press, New York.

Neel, J.V. (1982). The thrifty genotype revisited. In: *The Genetics of Diabetes mellitus,* eds. J. Köbberling and R. Tattersall, pp. 283–293. Academic Press, London.

Norio, R., H.R. Nevalinna, and J. Perheentupa (1973). Hereditary diseases in Finland: rare flora in rare soil. *Ann. Clin. Res.* 5: 109–141.

Petersen, G.M., and J.I. Rotter (1983). Genetic and evolutionary implications in peptic ucler disease. *Am. J. Phys. Anthrop.* 62: 71–79.

Petersen, G.M., J.I. Rotter, R.M. Cantor, L.L. Field, S. Greenwald, J.S.T. Lim, C. Roy, V. Schoenfeld, J.A. Lowden, and M.M. Kaback (1983). The Tay-Sachs disease gene in North American Jewish populations: geographic variation and origin. *Am. J. Hum. Genet.* 35: 1258–1269.

Petersen, G., J. Rotter, J. MacCracken, J. Raelson, M. New, P. Terasaki, M. Park, R. Sparkes, and J. Ward (1984). Selective advantage of the 21-hydroxylase deficiency (21-OH DEF) gene in Alaskan Eskimos: use of a linked marker to identify heretozygotes. *Am. J. Hum. Genet.* 36: 117S.

Rotter, J.I., and J.M. Diamond (1987). What maintains the frequencies of human genetic diseases? *Nature* 329: 289–290.

Vadheim, C.M., J.I. Rotter, M.K. Maclaren, W.J. Riley, and C.E. Anderson (1986). Preferential transmission of diabetic alleles within the HLA gene complex. *N. Engl. J. Med.* 315: 1314–1318.

Vogel, F., and A.G. Motulsky (1986). *Human Genetics.* Springer, Berlin.