Genes and History

The Pride of an Emperor

Dante Alighieri's reputation as the grand master of Italian literature has eclipsed all the Italian poets and writers who followed him. Nevertheless, Dante was not the only great Italian poet. There were others, such as Petrarch, Ariosto, and Leopardi. The latter is perhaps the least well-known outside Italy, although he was not only a talented poet but also a remarkable philosopher.

I recently reread his play *Copernicus,* which I still find relevant and insightful. The characters include the Sun, the First and Last Hours of the Day, and Copernicus. In the opening scene, the Sun confides to the First Hour that he is tired of revolving around the Earth each day, and demands that the Earth shoulder some of the burden. The First Hour, alarmed by this prospect, points out that the Sun's retirement would create havoc. But the Sun is adamant and insists on informing Earth's philosophers of the impending change since he believes they can convince humans of anything—good or bad. By the second scene, the Sun has delivered on his threat. Copernicus,

surprised by the Sun's failure to rise, sets about investigating the cause. His search quickly ends when he and the Last Hour are summoned to hear the Sun's proposal: the Earth must renounce her position at the center of the Universe and instead revolve around the Sun. Copernicus notes that even philosophers would have difficulty convincing the Earth of that. Moreover, the Earth and her inhabitants have grown accustomed to their position at the center of the Universe and have developed the "pride of an emperor." A change of such magnitude would have not only physical but also social and philosophical consequences. The most basic assumptions about human life would be overturned. But the Sun is insistent that life will go on, that all the barons, dukes, and emperors will continue to believe in their importance, and that their power won't be weakened in the least. Copernicus offers further objections: a galactic revolution could begin—the other planets may assert that they want the same rights to centrality as the Earth had. Even the stars would protest. In the end, the Sun might lose all importance and be forced to find another orbit. But the Sun desires only rest and counters Copernicus's final fear—that he will be burned as a heretic—by telling him he can avoid such a fate by dedicating his book to the Pope.

In writing about Copernicus, Leopardi had the benefit of living several centuries after him. He knew what had happened to Copernicus, Giordano Bruno, and Galileo. But we do not have Leopardi's advantage when considering the scientific issues of our day. Any current theories may be modified or even destroyed at any moment. In fact, science progresses because every hypothesis can be confirmed or rejected by others. The great number of conditionals we use in our scientific prose underscore this truth. While correcting the translation of one of my books, I was terrified to see that all my conditionals had been changed to indicatives—my safeguards had been eliminated. When we write papers for scientific journals, we know that many statements cannot be supported in their entirety. This seems strange to the public: isn't science infallible? In the end, only religion claims to deliver certainty. In other words, faith alone is immune from doubt, although few believers seem troubled by the fact that each religion offers different answers. Mathematics

4

may be the only exception in the sciences that leaves no room for skepticism. But, if mathematical results are exact as no empirical law could ever be, philosophers have discovered they are not absolutely novel—instead, they are tautological.

Copernicus also reminded me of our attitudes about race and racism. Each population believes that it is the best in the world. With few exceptions, people love the microcosm into which they are born and don't want to leave it. For Whites, the greatest civilization is European; the best race is White (French in France and English in England). But what do the Chinese think? And the Japanese? Wouldn't most of today's recent immigrants return to their country if they could find a decent way of life there?

It is also true, as Leopardi observed, that the more things change, the more they stay the same. Noble or economically powerful families come and go—there is an increasingly rapid turnover of power—but power structures change very little. The Roman Empire lasted longer than many others in Europe, but it spanned only five centuries. It was similar in size to the Inca Empire, which lasted a little more than a century. Before the Roman Empire, several maritime powers—the Greeks, Phoenicians, and Carthaginians—colonized the Mediterranean coast. At the same time, the European interior saw Celtic princes establish control over most of Europe. During the second half of the first millennium B.C., the Celtic and maritime fiefdoms were each united by commercial, linguistic, and cultural ties, but were politically fragmented.

Ultimately, they would all fall to the Romans. The Romans built the first politically united culture in Europe, but it eventually fell to "barbarian" invaders from the East. The barbarians flourished, and only the eastern part of the Roman Empire—the Byzantine Empire—was to survive into the Middle Ages. In the west, Charlemagne founded the Holy Roman Empire in A.D. 800, the culmination of Frankish political development. France, Germany, and parts of Italy and Spain were briefly reunited. After A.D. 1000, Frankish power passed to Germany and, in part, to the Pope, although the

Papacy and the Empire were often in conflict. The Holy Roman Empire ceased to have any political importance by the fourteenth century, although Austrian emperors continued to take the title of Holy Roman Emperor until 1806. Several European states were formed or consolidated between 1000 and 1500. Although wars among them were frequent, none was able to conquer much of Europe before Napoleon. With the development of seaworthy ships, the armies and navies of Europeans attempted to extend their hegemony to the rest of the world, competing for national riches on other continents. The Portuguese, Spanish, English, Dutch, French, and Russians established overseas empires which would endure into the twentieth century, but in all of European history, not a single empire has lasted for more than five centuries. Napoleon rapidly conquered continental Europe, but his rule lasted for fewer than ten years.

The Chinese Empire began in the third century B.C. and endured many vicissitudes under myriad dynasties, none of which lasted for more than four centuries. After several difficult periods, China fell to the Mongols in the thirteenth century. One hundred years later, the Ming restored Chinese dominance for three centuries. Then another foreign dynasty, the Qing, ruled for several centuries into the twentieth. The same pattern is found on every continent or subcontinent.

National pride is always more fervent in successful times. When a people feels strong, it is easier to say, "We are the best." However, power can have rather unusual origins. The wise decisions and shrewd political acts of a few leaders or small groups often produce enduring states. Even cruel regimes can sometimes succeed in introducing prosperous periods. The rise to political power frequently requires violence, which is not always physical. Favorable external circumstances can also help maintain stability, if only temporarily. Politicians who wield their power responsibly are difficult to replace with equally capable successors. During happy and prosperous years, people can convince themselves that their success is due to their excellent qualities, the intrinsic characteristics of their "race" that make them great. The illusion of immortality ignores all the lessons

of history. The self-critic is rare and tends to be absent or has no listeners when things are going well.

Perhaps Claude Lévi-Strauss most succinctly defined racism as the belief that one race (usually, though not always, one's own) is biologically superior—that superior genes, chromosomes, DNA put it at an advantage over all others. This is America's situation now. It is no coincidence that you must first dial the number one when calling the United States from abroad.

At any particular moment, a single people may be dominant despite the many countries that have been before, or will be soon. Of course, it is not necessary to *be* superior to be convinced that one is. Even a limited success can demonstrate power to others. Many believe such dominance is determined by biology.

Other Sources of Racism

Almost any society can find a good reason to consider itself predominant, at least in a particular activity. A simple claim to competence in any sphere—be it painting, football, chess, or cooking—is often sufficient to imbue a people with exaggerated importance.

One's daily routine, which is subject to both individual and cultural influences, is filled with superficial comparison of one's own habits with foreign, often significantly different, habits. Even if we do not know the sources of these differences, the simple fact that they exist can be enough to inspire fear or hatred. Human nature does not welcome change, even when we're dissatisfied with things as they are. Perhaps this devotion to habit and fear of melioration encourage a conservatism that could lead to racism.

There are unquestionable differences among peoples and nations. Language, skin color, tastes (especially in food), and greeting all differ among cultures and lead us to believe that others are essentially not like us. We typically conclude that our ways are the best, and too bad for the others. To the Greeks, all those who did not speak Greek were barbarians. Of course, when a person is

unsatisfied with life in his home country and migrates, he might more easily tolerate uncertainties and strange living conditions in another region or continent. He might even accept the necessity of learning new things. But in general, he prefers the cocoon in which he was born, terrified of discarding what is familiar.

Many other factors nourish racist sentiments. One of the most important is the desire to project one's unhappiness onto another. Everyone knows that self-alienation in modern society is often a very serious cause of irritation and angst. These feelings can arise from the fear of unemployment, being forced to perform inhumane work, the reality and experience of poverty and injustice, and the feeling of powerlessness which often results from the jealous observation that vast wealth is possible only for the very few. Everyone, even those who feel victimized by their superiors, can assume authority over those lower on the social ladder. The poor can always find somebody poorer.

Because of all these factors, racism is widespread. It is less apparent during times of peace and civil order. But hostilities about mass immigration from poor countries exacerbate it.

Is There a Scientific Basis for Racism?

Racism should be condemned because its effects are pernicious. It is criticized by virtually every modern religion and ethical system. However, can we exclude the possibility that a superior race exists, or that socially important, inherited differences between the races can be found? There are certain obvious differences between human groups for traits that depend to some extent on genes: skin color, eye shape, hair type, facial form, and body shape. Will these and other traits provide a scientific justification for racism? Do other differences exist that might?

We must first define the nature of the variation to be studied. Doing so helps us to understand what we mean by race, to decide which groups we should examine and what racial differences may tell us.

Biological and Cultural Variation

We must note that most people do not distinguish between biological and cultural heredity. It is often difficult to recognize which is which. Sometimes the cause of racial difference is biological (in which case we call it genetic, meaning that it comes with your DNA); sometimes it is behavioral, learned from someone else (these are cultural causes); and sometimes both factors are involved. Genetically determined traits are very stable over time, unlike socially determined or learned behavior, which can change very rapidly. As I said above, there are clear biological differences between populations in the visual characteristics that we use to classify the races. If these genetic differences were found to be genuinely important and could support the sense of superiority that one people can have over another, then racism is justified—at least formally. I find this genetic or biological definition of racism more satisfactory than others. Some would extend the domain of racist judgments to include any difference between groups, even the most superficial cultural characteristics. The only advantage of this broader definition is that it sidesteps the difficulty of determining whether certain traits have a genetic component or not. But it does not seem appropriate to speak of racism when one person resents another's loud voice, noisy eating habits, taste in dress, or difficulties with correct pronunciation. This type of intolerance, which is rather common in certain countries or social classes, seems much easier to correct and control through education than is true racism.

Visible and Hidden Variation

The racial differences that impressed our ancestors and that continue to bother many people today include skin color, eye shape, hair type, body and facial form—in short, the traits that often allow us to determine a person's origin in a single glance. Ignoring admixture, it is fairly easy to recognize a European, an African, and an

Asian, to mention those standard types with which we are most familiar. Many of these characteristics—almost homogeneous on a particular continent—give us the impression that "pure" races exist, and that the differences between them are pronounced. These traits are at least partly genetically determined. Skin color and body size are less subject to genetic influence since they are also affected by exposure to the sun and diet, but there is always a hereditary component that can be quite important.

These characteristics influence us a lot, because we recognize them easily. What causes them? It is almost certain they evolved in the most recent period of human evolution, when "modern" humans, or early humans practically undistinguishable from ourselves, first appeared in Africa, grew in numbers, and began to expand to the other continents. Evidence and details will be discussed later. What interests us here is that this diaspora of Africans to the rest of the world exposed them to a great variety of environments: from hot and humid or hot and dry environments (to which they were already accustomed) to temperate and cold ones, including the coldest ones of the world, as in Siberia. We can go through some of the steps that this entailed.

1. Exposure to a new environment inevitably causes an adaptation to it. In the 50,000–100,000 years since the African diaspora, there has been an opportunity for substantial adaptation, both cultural and biological. We can see traces of the latter in skin color and in size and shape of the nose, eyes, head, and body. One can say that each ethnic group has been genetically engineered under the influence of the environments where it settled. Black skin color protects those who live near the equator from burning under the sun's ultraviolet radiation, which can also lead to deadly skin cancers. The dairy-poor diet of European farmers, based almost entirely on cereals that lack ready-made vitamin D, might have left them vulnerable to rickets (our milk still has to be enriched with this vitamin). But they were able to survive at the higher latitudes to which they migrated from the Middle East because the essential vitamin can be produced, with the aid of sunlight, from precursor molecules found in cereals. For this Europeans have developed the whiteness of their

skin, which the sun's ultraviolet radiation can penetrate to transform these precursors into vitamin D. It is not without reason that Europeans have, on average, whiter skin the further north they are born.

The size and shape of the body are adapted to temperature and humidity. In hot and humid climates, like tropical forests, it is advantageous to be short since there is greater surface area for the evaporation of sweat compared to the body's volume. A smaller body also uses less energy and produces less heat. Frizzy hair allows sweat to remain on the scalp longer and results in greater cooling. With these adaptations, the risk of overheating in tropical climates is diminished. Populations living in tropical forests generally are short, Pygmies being the extreme example. The face and body of the Mongols, on the other hand, result from adaptations to the bitter cold of Siberia. The body, and particularly the head, tends to be round, increasing body volume. The evaporative surface area of the skin is thus reduced relative to body volume, and less heat is lost. The nose is small and less likely to freeze, and the nostrils are narrow, warming the air before it reaches the lungs. Eyes are protected from the cold Siberian air by fatty folds of skin. These eyes are often considered beautiful, and Charles Darwin wondered if racial differences might not result from the particular tastes of individuals. He called the idea that mates were chosen for their attractive quality "sexual selection." It is very likely that some characteristics undergo sexual selection—eye color and shape, for example. But the shape of Asian eyes is not appreciated only in Asia. If it is admired elsewhere, why is it not found in other parts of the world? Of course it is also characteristic of the Bushmen of southern Africa, and other Africans have slanted eyes. It probably diffused by sexual selection from northeastern Asia to Southeast Asia, where it is not at all cold. It is also possible that the trait may have originated more than once in the course of human evolution. If it first appears that climatic factors were most important in the creation of racial differences, we should not neglect sexual selection as a possible side explanation. Unfortunately, the genetic bases for these adaptations are not known; each of these traits is very complex. Considerable local variation in tastes further complicates the matter.

2. There is little climatic variation in the area where a particular population lives, but there are significant variations between the climates of the Earth. Therefore, adaptive reactions to climate must generate groups that are genetically homogeneous in an area that is climatically homogeneous, and groups that are very different in areas with different climates.

We could ask if sufficient time has passed since the settling of the continents to produce these biological adaptations. The selection intensity has been very strong, so the answer is probably yes. We could note in this regard that the Ashkenazi Jews who have lived in central and eastern Europe for at least 2,000 years have much lighter skin than the Sephardi Jews who have lived on the Mediterranean perimeter for at least the same length of time. This could be an example of natural selection, but it might also result from genetic exchange with neighboring populations. Some available genetic information favors the second interpretation, but better genetic data are desirable before we can exclude the influence of natural selection.

3. Adaptations to climate primarily affect surface characteristics. The interface between the interior and exterior plays the biggest part in the exchange of heat from the interior to the exterior and vice versa. A simple metaphor can help explain this statement: if you want to decrease the cost of heating your house in the winter, or cooling it in the summer, you must increase the house's insulation so that the thermal flow between the inside and outside is minimal. Thus, body surface has been largely modified to adapt different people to different environments.

4. We can see only the body's surface, as affected by climate, which distinguishes one relatively homogeneous population from another. We are therefore misled into thinking that races are "pure" (meaning homogeneous) and very different, one from the other. It is difficult to find another reason to explain the enthusiasm of nineteenth-century philosophers and political scientists like Gobineau and his followers for maintaining "racial purity." These men were convinced that the success of whites was due to their racial supremacy. Because only visible traits could be studied then, it was

not absurd to imagine that pure races existed. But today we know that they do not, and that they are practically impossible to create. To achieve even partial "purity" (that is, a genetic homogeneity that is never achieved spontaneously in populations of higher animals) would require at least twenty generations of "inbreeding" (e.g., by brother-sister or parent-children matings repeated many times). Such inbreeding would have severe consequences for the health and fertility of the children, and we can be sure that such an extreme inbreeding process has never been attempted in our history, with a few minor and partial exceptions.

In more recent times, the careful genetic study of hidden variation, unrelated to climate, has confirmed that homogeneous races do not exist. It is not only true that racial purity does not exist in nature: it is entirely unachievable, and would not be desirable. It is true, however, that "cloning," which is now a reality in animals not very remote from us, can generate "pure" races. Identical twins are examples of living human clones. But creating human races artificially by cloning would have potentially very dangerous consequences, both biologically and socially.

We shall also see that the variation between races, defined by their continent of origin or other criteria, is statistically small despite the characteristics that influence our perception that races are different and pure. That perception is truly superficial—being limited to the body surface, which is determined by climate. Most likely only a small bunch of genes are responsible, and little significance is attached to them, especially since we are progressively developing a totally artificial climate.

Hidden Variation: Genetic Polymorphisms

The ABO blood group was the first example of an invisible and completely hereditary trait. Discovered at the beginning of the century, it has been the subject of numerous studies, because the matching of blood types is essential for successful blood transfusions. There

are three major forms of the gene (also called "alleles"): A, B, and O, and they are strictly hereditary. An individual can have one of four possible blood types: O, A, B, and AB.

Although it is not truly essential for the understanding of what follows, it is difficult to resist the opportunity of mentioning at this point a basic rule of inheritance: each of us receives one allele from each parent—one from the father and one from the mother. Therefore AB blood type arises when an individual receives gene A from one parent and gene B from the other. O blood type arises when an individual receives O from both parents. A type, however, can be of two different genetic constitutions, AO and AA: the first receive A from one parent and O from the other, the second receive A from both parents. A similar situation applies to blood group B.

The existence of genetic polymorphism (a situation in which a gene exists in at least two different forms—or alleles) is demonstrated by the reaction of different blood types to specific reagents. To determine a blood type, two reagents are needed (anti-A and anti-B), which react with red blood cells (small oxygen-bearing blood cells invisible to the eye). The reaction is performed by adding two small drops of a patient's blood to a glass slide. A positive reaction occurs if, after adding a reagent, the blood cells clump together. Because blood's color is due to the red blood cells, when they clump together, the remainder of the blood becomes clear. If the reaction is negative, the blood drop remains a consistent red color. Blood group A individuals react positively only to the anti-A, while blood group B reacts only with anti-B. Those with blood group O fail to react with either serum, while AB individuals react with both.

To simplify the statistics, we do not count the number of different individuals or genotypes, but only the number of alleles—two per person. However, we have no way to distinguish between individuals of polymorphic blood group A, who could be either AA or AO. So, too, with B type blood. Luckily, simple mathematical techniques allow us to estimate how many individuals are AA and how many are AO (or BB and BO).

During World War I, Ludwik and Hanka Hirschfeld, two Polish immunologists, examined several different ethnic groups among

the soldiers in the English and French colonial armies and the World War I prisoners, including Vietnamese, Senegalese, and Indians. They discovered that the proportions of individuals belonging to the different blood groups were different in every population. This phenomenon is now known to be universal. We know the number of polymorphisms is extremely high, and each human population is different for most of the other polymorphisms, as well. This early work with ABO gave birth to anthropological genetics.

Genetic Variation between Populations

The following table shows the frequency (in percent) of the ABO alleles by continent.

Region		A	B	O
Europe		27	8	65
	English	25	8	67
	Italian	20	7	73
	Basques	23	2	75
East Asia		20	19	61
Africa		18	13	69
American Natives		1.7	0.3	98
Australian Natives		22	2	76

We immediately notice wide variation among populations in different parts of the earth; each has a distinct gene frequency. The O gene always appears the majority type, varying from 61 to 98 percent. The A gene varies from 1.7 to 27 percent, while the B gene varies from 0.3 to 19 percent. If we consider smaller samples of Native Americans, the A and B genes might be completely absent.

This table suggests two questions: Is this an exceptional situation or does something similar hold true for other genes as well?

Can we explain why there is such great variation? For now, let's explore other genes and save the second question for later.

After World War I, new blood group systems were developed using the same methods that led to the discovery of the ABO system. The most complex group is the RH system, which was found among Europeans during World War II. Its study was quickly extended to several non-European populations. But aside from the ABO and RH systems, very few blood group genes have clinical importance. Anthropological curiosity—the passion to know one's ancestors, relatives, and ultimate origins—has motivated many researchers to continue the search for new genetic polymorphisms, which, performed by new genetic research techniques, is increasingly successful.

Genetics, the study of heritable differences, offers us a window through which to view that past. We know that, with few exceptions, many characteristics such as height and skin, hair, and eye color are genetically determined, but we do not understand precisely how. Moreover, some of them are also influenced by non-genetic factors, for instance, nutrition, in the case of height, and exposure to the sun, in the case of skin tone. Our poor understanding of the hereditary mechanism of these familiar characteristics is due to their interaction with non-genetic, environmental factors, and the general complexity of the mechanisms determining all traits that involve shape. By contrast, we understand clearly the inheritance of blood groups, and of chemical polymorphisms among enzymes and other proteins, because the account of traits determined by relatively simple substances like proteins is chemically simpler and easier to understand and measure. But these traits are not directly visible, and rather sensitive laboratory methods are required to detect them.

Very early on, the American scientist William Boyd showed that by using the first genetic systems discovered—ABO, RH, and MN—one could already differentiate populations from the five continents. Arthur Mourant, a British hematologist, produced the first comprehensive summary of data on human polymorphisms in 1954. The second edition of Mourant's book, appearing in 1976, contained more than one thousand pages, more than doubling the amount of data previously available.

Two major techniques are used to study polymorphisms, or genetic "markers" as they are called because they act as tags on genetic material, on proteins. One, employed for almost all blood group typings, uses biological reagents, often made by humans reacting to foreign substances from bacteria, or from other sources. These reagents are special proteins called immunoglobulins or antibodies. They are made in the course of building immunity, that is, resistance to some external agent, and usually react specifically with substances called antigens, usually other proteins. The other analytical method of genetic analysis, developed in 1948, is a direct study of physical properties of specific protein molecules, usually by measuring their mobility in an electric field. It is called electrophoresis.

Both methods revealed directly or indirectly the variation in structure of specific proteins from individual to individual. The behavior of these variants could be tested in families to confirm the genetic nature of such variation. But the number of polymorphic proteins detected in this way was small and at the beginning of the 1980s only about 250 were known. All proteins are produced by DNA, and therefore behind protein variation there must be a parallel variation of DNA, the chemical substance responsible for biological inheritance. The analytical methods necessary to chemically study DNA were developed later.

In the early eighties the analysis of variation in DNA had its start. DNA is a very long filament made of a chain combining four different nucleotides, A, C, G, and T. Changes in the sequence of nucleotides of a specific DNA happen rarely, and more or less randomly, when one nucleotide is replaced by another during replication. Thus, if a DNA segment is GCAATGGCCC, it may happen that a copy of it passed by a parent to a child is changed in the fifth nucleotide, T being replaced by C. The DNA generating the child's protein will thus be GCAACGGCCC. This is the smallest change that can happen to DNA, and is called a mutation; as DNA is inherited, descendants of the child will receive the mutated DNA. A change in DNA may cause a change in a protein, and this may cause a change visible to us.

Restriction enzymes provided a simple way to detect differences in the DNA of two individuals. Restriction enzymes are produced by bacteria and break DNA into certain sequences of 4, 6, or 8 nucleotides, for instance GCCG.

A method of multiplying DNA in a test tube with the enzyme DNA polymerase, which nature uses to duplicate DNA when cells divide, was discovered and developed in the second half of the eighties, and is called PCR, or polymerase chain reaction. This new technique has improved the power of genetic analysis in the nineties. We now know that there must exist millions of polymorphisms in DNA, and we can study them all, but the techniques for doing this at a satisfactory pace are only now beginning to be available.

The future of the analysis of genetic variation is clearly in the study of DNA, but results accumulated with the old techniques based on proteins have not lost their value. There are some specific problems, which can be resolved only by DNA techniques. On the other hand, the very rich information generated by protein data on human populations includes almost 100,000 frequencies of polymorphisms. They were studied for over 100 genes in thousands of different populations all over the earth, and many of the conclusions thus made possible and discussed in this book have arisen from studies of proteins. Results with DNA have complemented but never contradicted the protein data. We start having knowledge on thousands of DNA polymorphisms, but they are almost all limited to very few populations. We will summarize the most important ones.

Studying Many Genes Allows Use of the "Law of Large Numbers"

Is it possible to reconstruct human evolution by studying the types of living populations only? We can simplify the process of doing so by concentrating most of our studies to indigenous people, when it is possible to recognize them and differentiate them from recent immigrants to a region. But we learn much about human origins and evolution from a single gene like ABO.

We will introduce here the word "gene." Everybody has heard it, but few know its precise meaning. The old definition, "unit of inheritance," is still difficult to understand—in fact, it was used when we did not know what a gene was in chemical terms. Today we can give a much more concrete definition: a gene is a segment of DNA that has a specified, recognizable biological function (in practice, most frequently that of generating a particular protein). It is, therefore, part of a chromosome, a rod found in the nucleus of a cell that contains an extremely long DNA thread, coiled and organized in a complicated way. A cell usually has many chromosomes, and their distribution to daughter cells is made in such a way that a daughter cell receives a complete copy of the chromosomes of the mother cell. When studying evolution, however, we may, and often must, ignore what a gene is doing, because we don't know. But a gene remains useful for evolutionary studies (and others) if it is present in more than one form, and the more forms of a gene (allele) that exist, the better the gene suits our purposes. With only three alleles, ABO can hardly be very informative. In Africa, the place of origin, one finds all alleles. But this is also true of Asia and Europe. In Asia, however, the B allele is more frequent than in the other continents; group A is somewhat more common in Europe; and Native Americans are almost entirely blood group O. What conclusions can we draw? That A and B genes were probably lost in the majority of Native Americans, but why? Many have speculated about the reason, but it is impossible to provide an entirely satisfactory answer.

The first hypothesis connecting the historical origin of a people and a gene that was subsequently confirmed by independent evidence was made on the basis of the RH gene in the early forties. The simplest genetic analysis recognizes two forms: RH+ and RH−. Globally, RH+ is predominant, but RH− reaches appreciable frequencies in Europe with the Basques having the highest frequency. This suggests that the RH− form arose by mutation from the RH+ allele in western Europe and then spread, for unspecified reasons, toward Asia and Africa, never greatly diminishing the frequency of the RH+ gene. The highest frequencies of the negative type are generally found in the west and northeast of Europe. Frequencies

steadily decline toward the Balkans, as if Europe was once entirely RH− (or at least predominantly so) before a group of RH+ people entered via the Balkans and diffused to the west and north, mixing with indigenous Europeans. This hypothesis would have remained uncertain if it had not been substantiated by the simultaneous study of many other genes. Archeology also lent support to the argument, as we shall see later.

Reconstructing the history of evolution has proved a daunting task. The accumulation of data on many genes in thousands of people from different populations has produced a dizzying amount of information that describes the frequency of the different forms of more than 100 genes—a body of knowledge that is very useful for testing evolutionary hypotheses. Experience has shown that we can never rely on a single gene for reconstructing human evolution. It might appear that a single system of genes like HLA, which today has hundreds of alleles, would be sufficient. The HLA genes play an important role in fighting infections and recently have become important in matching donors and recipients for tissue and organ transplants. They possess a great diversity of forms, as is necessary for a potential defense against the spread of tumors among unrelated individuals, but they are also subject to extreme natural selection related to their role in fighting infection. If the conclusions we reach about evolution through observations made using HLA are different from those obtained using other genes, we need to explain the reasons, because they may lead to different historical interpretations. It is very useful, and I think essential, to examine all existing information. The broadest synthesis has the greatest chance of answering the questions we ask, and the least chance of being contradicted by later findings.

Therefore, it is also worth gathering information from any discipline that can provide even a partial answer to our problems. Within genetics itself, we want to collect as much information about as many genes as possible, which would allow us to use the "law of large numbers" in the calculation of probabilities: random events are important in evolution, but despite their capriciousness, their behavior can be accounted for through a large number of observations.

Jacques Bernoulli, in his *Ars conjectandi* of 1713, wrote, "Even the stupidest of men, by some instinct of nature, is convinced on his own that with more observations his risk of failure is diminished."

Many studies have been invalidated because of an inadequate number of observations. When we study polymorphisms directly on DNA, there is no dearth of evidence: we can study millions. We may not need to study them all, because at a certain point additional data fail to provide new results or lead to different conclusions. Nevertheless, simply studying a large sample is not always enough. If we observe heterogeneity in our data, so that it can be divided into several categories, each implying a different history, we must further search for the source of these discrepancies. We have seen an important example in the comparison of genes transmitted by the paternal and the maternal line, as we will discuss in another chapter.

Genetic Distances

It is clear that, in order to contrast populations, we must synthesize a vast amount of genetic information. At first, to measure the "genetic distance" between populations, we simply compared pairs of populations. Only much later, when we had a very large number of genes and some new analytical techniques, were we able to study the differences among many populations, or even within individual populations. For most genes, the frequency differences between populations are nil to very slight and their contribution to the global genetic distance between populations is close to zero.

The RH gene provides interesting genetic distances in Europe, but is less useful elsewhere. For example, the frequency of RH negative individuals is 41.1 percent in England, 41.2 percent in France, 40 percent in the former Yugoslavia, and 37 percent in Bulgaria. These differences are slight, but among the Basques the frequency is 50.4 percent and among the Lapps (more appropriately called the Saami) the frequency is 18.7 percent. For this gene the genetic

distance between France and England, calculated simply by taking the difference between the percentages above, is 0.1 percent. The distance between French and Bulgarians (4.2 percent) or between Bulgarians and persons from the former Yugoslavia (3 percent) is greater. But the distance between Basques and English is considerable (9.3 percent) and the difference between Basques and Lapps is dramatic (31.7 percent).

I like to explain the concept of genetic distance in the simple way that I have done above, as a difference between percentage frequencies of the form of a gene. In reality, there are now many methods for calculating genetic distances and all are fairly complicated. When I started this calculation, I asked the advice of my teacher, R. A. Fisher, one of the great geneticists and statisticians, because I could not think of a better consultant. It is pointless to give his formula here, because it is too complex. But it is still essential to average the distance between two populations over many genes if one wants reproducible conclusions.

Among other formulas subsequently proposed, one developed by Masatoshi Nei, a famous Japanese-American mathematical geneticist, has become more popular than the Fisher formula I first used. But more than twenty years after he introduced it, Professor Nei is now convinced that Fisher's approach is better than his own for the study of human populations.

In any case, most of the formulas currently used to calculate genetic distances provide very similar results overall. In fact, if I find substantial disagreement among results using the various distance measures, I tend to suspect there are other problems with the data—usually that the sample of genes is insufficient.

Once a genetic distance is calculated between populations for each of several genes, we can average all the distance values thus obtained. We thus synthesize the information from all the genes studied. The more genes we have, the more likely it is that conclusions will be correct. When we have enough genes, we can subdivide them into two or more classes and use each class to test our conclusions, which should, if everything is fine, be independent of the genes employed.

Isolation by Geographic Distance

Interesting theories developed by three mathematicians—Sewall Wright in the United States, Gustave Malécot in France, and Motoo Kimura in Japan—led, with minor differences, to the conclusion that the genetic distance between two populations generally increases in direct correlation with geographic distance separating them. This expectation derives from the observation that while most spouses are selected from within their own village or town, or part of a city, a small proportion are chosen from neighboring ones. This proportion reflects the migration that goes on all the time everywhere because of marriage. In the simplest model, equal numbers of migrants are exchanged between neighboring villages. The first measurements of migration arising from marriage were performed by Jean Sutter and Tran Ngoc Toan, and independently by myself in collaboration with Antonio Moroni and Gianna Zei, using church wedding records, which noted the spouses' birthplaces. They confirmed the tendency of people to find spouses from a short distance away, as expected. The first verification of the theory that genetic distance increases with geographic distance between populations was provided by Newton Morton, who studied small, homogeneous regions. Menozzi, Piazza, and I extended them to the entire world in our book *The History and Geography of Human Genes,* from which figure 1 was taken.

The increase of genetic distance with geographic distance may be linear at first, but over a greater geographic distance, the increase in genetic distance slows sharply. The two characteristics of the curve—the rate (i.e., the slope) of the initial increase, and the maximal value reached by the genetic distance over a great geographic distance—are different for the various continents. They are greatest for indigenous Americans and Australians, and slightest in Europe, which is the most homogeneous continent. The maximal genetic distance (in Europe) is three times smaller than on the least homogeneous continents. Despite political fragmentation, migration within Europe has been sufficient to create a greater genetic homogeneity than elsewhere. The curve has not reached a maximum value (and therefore
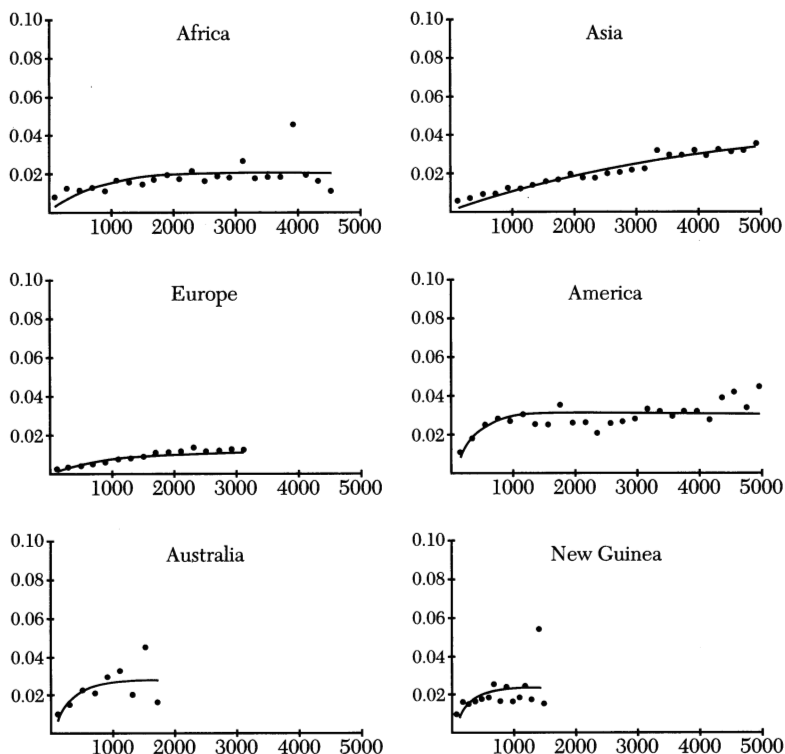
Figure 1. Relationship of geographic distance (in miles, on the horizontal axis) to genetic distance (on a scale between 0 and 1, vertical axis) in the various continents. Genetic distances among pairs of populations were averaged for all available data on 110 genes tested by methods of protein analysis (blood groups, electrophoresis, etc.). Robust averages of genetic distances were calculated for all possible pairs of tribes, towns, or other human communities that share a geographic distance class. (Cavalli-Sforza, Menozzi, and Piazza 1994)

the point of genetic equilibrium) in Asia (and clearly even less in the whole world) in spite of the extensive migrations of the past millennia. Mongols, for example, began important expansions east, south, and west around 300 B.C. The Turkish advance, halted near Vienna in the eighteenth century, was their last exploit.

Figure 1 shows the remarkable precision with which the data support the theory. Naturally, individual pairs of populations would

vary substantially from the theoretical curve, but the points in figure 1 are the averages of many population pairs, calculated from over a hundred genes. We observed that it matters little which genes are chosen. Only one genetic system shows a major deviation from the others—the immunoglobulin genes. These genes code for our antibodies, and the greater variation found in them is probably a response to the great geographic variation in the array of infectious diseases we encounter.

What Is a Race, Then?

A race is a group of individuals that we can recognize as biologically different from others. To be scientifically "recognized," the differences between a population that we would like to call a race and neighboring populations must be statistically significant according to some defined criteria. The threshold of statistical significance is arbitrary. The probability of reaching significance for a given distance increases steadily with the number of individuals and genes tested.

Our experiments have shown that even neighboring populations (villages or towns) can often be quite different from each other. There is a limit to the number of individuals in a given village population who can be tested. But the maximum number of testable genes is so high that we could in principle detect, and prove to be statistically significant, a difference between any two populations however close geographically or genetically. If we look at enough genes, the genetic distance between Ithaca and Albany in New York or Pisa and Florence in Italy is most likely to be significant, and therefore scientifically proven. The inhabitants of Ithaca and Albany might be disappointed to discover that they belong to separate races. People in Pisa and Florence might be pleased that science had validated their ancient mutual distrust by demonstrating their genetic differences. In his *Divine Comedy,* Dante, a Florentine, expressed

his dislike of people from Pisa by wishing that God would move two islands situated at the mouth of the river Arno, thereby flooding Pisa and drowning all its people.

Classifying the world's population into several hundreds of thousands or a million different races would, of course, be completely impractical. But what level of genetic divergence would be necessary to determine boundaries for a definition of racial difference? Because genetic divergence increases in a continuous manner, it is obvious that any definition or threshold would be completely arbitrary.

It has been suggested that one might define race by the analysis of discontinuities in the surface of gene frequencies generated on a geographic map. Introduced by Guido Barbujani and Robert Sokal (1990), the method looks for local increases in the rate of change of gene frequencies, per unit of geographic distance. Obstacles to migration or marriage could create these local increases. If proved for many genes, such barriers could help distinguish races. But a true discontinuity is difficult if not impossible to establish for gene frequencies, so they would rather look for regions where gene frequencies change rapidly. The particular rapidity of genetic change that could suffice as a "genetic barrier" would naturally be chosen in an arbitrary manner.

This procedure illustrates the theoretical difficulties classification by race poses. Gene frequencies are not geographic features like altitude or compass direction, which can be measured precisely at any point on the earth's surface; rather, they are properties of a population that occupies an area of finite extent. One possible solution would be to use villages and small cities as "points" in geographic space. Large cities could be subdivided into several points to take account of residential segregation. But the available data on gene frequency in villages or small cities are insufficient and they would provide an extremely detailed clustering.

In any case, this method is still useful for identifying the geographic location of genetic "boundaries," however arbitrary these are. In Europe, for example, Barbujani and Sokal found 33 genetic boundaries that corresponded in 22 cases to geographic features

(mountains, rivers, seas) and almost always (in 31 cases) to linguistic or dialectic boundaries. In a country with a homogeneous language, like Italy, family names provided better results than genes. Because they're inherited, surnames can give almost the same information as genes, but are more informative because surnames are readily available in large numbers.

A more significant difficulty resulting from racial classification is that the barriers found by the method described above have rarely defined a closed space inhabited by a population enclave, even when aided by geographical features such as the Alps. Islands may be the only exceptions. The population of each island could be classified as a race, because it would be different from other islands and the nearest mainland, if there were sufficient genetic information. But would that be useful for practical purposes, like for instance taking a census in the United States? The answer is certainly no. A third problem is that a huge number of genes must be studied to distinguish closely related populations.

Scientific attempts to classify races continued through the end of the nineteenth century. The results often contradicted each other, a good indication of the difficulty of such efforts. Darwin understood that geographic continuity would frustrate any attempt at classifying human races. He noted a phenomenon that repeated itself many times in the course of history: different anthropologists come to completely different tallies of races, from 3 to over 100. But why does this compulsion to classify human races exist? The question is extremely important. Maybe it would be more useful to answer a more general question: why classify?

Why Classify Things?

When we are presented with a great number of things, we feel compelled to impose some order on potential chaos. Such is the goal of classification. It allows us to describe a complex array of objects with simple words or concepts, even at the cost of oversimplification.

Zoologists and botanists have classified thousands or even millions of species, and their work is not close to being finished. If variation were not important and complex, it would not be necessary to categorize at all. One could simply recognize the level of difference relevant to one's needs.

Humans are not alone in their tendency to classify. Chimpanzees, for example, and probably most other animals, can separate several hundred leaves and fruits into edible and non-edible categories. Depending on their appetite, other categories may be used, although edibility is fundamental since many plants are potentially toxic. Chimpanzees have even been observed teaching their offspring which foods can be eaten and which cannot.

Unlike animals, humans use language to differentiate between objects. We assign a name to each object we wish to distinguish. African Pygmies recognize hundreds of tree species (Western botanists identify a similar number) and several hundred animals; but such diversity is still too little to require a terribly high order of classification.

Classification and some accompanying oversimplification become necessary when variation is very high. Naturalists such as Georges Louis Leclerc Buffon and Carolus Linnaeus established valid systems of classification for the extraordinary diversity of plant and animal species. Similar systems can be found in some so-called "primitive" populations who have an undeveloped (or non-monetary) economy.

Why can classifying human races be useful? Demographers and sociologists undoubtedly have some opinion on the subject. Most practical classifications are extremely simplistic. The U.S. census recognizes Whites, Blacks (African Americans), Native Americans, Asians, and Hispanics. This last category has almost no biological meaning. In practice it refers to Mexicans, but more generally, a large number of Spanish-speaking people are assigned to it.

Proposing an improved classification can only end in failure. Observing the variation between ethnic groups should convince us of that. Visible differences lead us to believe in the existence

of "pure" races, but we have seen that these are very narrow, essentially incorrect criteria. And when measured and plotted carefully, visible traits are actually far less discontinuous than is usually believed. Classification based on continental origin could furnish a first approximation of racial division, until we realize that Asia and even Africa and the Americas are very heterogeneous. Even in Europe, where the population is much more homogeneous, several subdivisions have been proposed. But it is immediately clear that all systems lack clear and satisfactory criteria for classifying. The more we pay attention to questions of statistical adequacy, the more hopeless the effort becomes. It is true that strictly inherited characteristics are more satisfactory than anthropometric measurements or observations of colors and morphology. But above all it is true that one encounters near total genetic continuity between all regions while attempting to select even the most homogeneous races.

The observation has been made that almost any human group—from a village in the Pyrenees or the Alps, to a Pygmy camp in Africa—displays almost the same average distance between individuals, although gene frequencies typically differ from village to village by some small amount. Any small village typically contains about the same amount of genetic variation as another village located on any other continent. Each population is a microcosm that recapitulates the entire human macrocosm even if the precise genetic compositions vary slightly. Naturally, a small village in the Alps, or a Pygmy camp of 30 people, is somewhat less heterogeneous genetically than a large country, for example, China, but perhaps only by a factor of two. On average, these populations have a heterogeneity among individuals only slightly less than that in evidence in the whole world. Regardless of the type of genetic markers used (selected from a very wide range), the variation between two random individuals within any one population is 85 percent as large as that between two individuals randomly selected from the world's population.

It seems wise to me, therefore, to abandon any attempt at racial classification along the traditional lines. There is, however, one practical reason for keeping an interest in genetic differences.

Can the Study of Genetic Differences Be Useful in Practice?

The intellectual interest of a rational classification of races clashes with the absurdity of imposing an artificial discontinuity on a phenomenon that is very nearly continuous. But is there a practical reason that justifies it? It clearly must be sought where a real discontinuity exists, if any. Here, it happens, we are closer to practical reasons that justify some sort of classification on the basis of genetic differences.

Humans live in social communities. The social group is evolving rapidly, its size increases and its internal structure becomes more complicated. The majority of the world is still, however, formed by groups that are at the lower end of the complexity scale. The industrialized countries are at the opposite end. Most people like to identify with their social group, and therefore give it a name. For obvious reasons, this tends to be the same as the name of the language, and of the tribe, although in many cases the tribe has grown enough that it is no more a simple social group. Within the larger groups there tend to be further subdivisions. This helps to give a lower bound of the number of social human groups existing on Earth. The number of languages existing today is 5,000–6,000, and the number of social groups that may exist today in the world must be greater than 10,000, or even 100,000.

If we want to fix an upper bound we must be more precise about the meaning of social group. From a genetic point of view, the most meaningful social group is the one in which one is likely to find a spouse. The minimum size of such a group to avoid deleterious effects of inbreeding is five hundred. This is also a "magic number" that many anthropologists, not without some factual support, indicate as the average size of a tribe, especially for the more economically primitive ones. This would mean that there exist on Earth at most ten million social groups. On the basis of some other considerations, perhaps one million may be a reasonable upper bound of the number of social groups that are worth being considered as distinct from a genetic point of view. The average group would consist of 5,000–500,000 individuals. These numbers may have to be some-

what modified and I reserve the right to do it. But the principle remains valid.

Clearly no anthropologist would accept a classification into a million races, and probably not even into 10,000 ones. But this is a "genetic" classification that might be useful, and will probably exist, with some further complication, a day not too far ahead. Individuals belonging to a group of this kind would have genetic similarity greater than two random individuals, because they would share significantly more ancestry. In fact, the group will have been defined on the basis of endogamous behavior (a tendency to marry within the group). Endogamy tends to generate, gradually, both genetic and cultural differentiation between groups. We have seen that the genetic differentiation of populations, even if real, is small, but stable in time. In contrast to this, cultural differentiation can be surprisingly high, and fast to reach, but also more easily reversible, and hence less stable. But there is no question that genetic differences can be important from a very practical point of view: namely the chances of having specific diseases, and responding similarly to the same drugs.

To skeptical readers, an example of the application of this principle can already be seen in Iceland, where medical research of all Icelanders has begun with Parliamentary approval by a foreign pharmaceutical firm. Here the population is of 250,000 individuals, and therefore within the upper and lower bounds defined before. But current research may show that the Icelandic population is not as homogeneous as might be expected.

Weakness and Strength of Historical Research

We have begun a survey of human diversity, and it is inevitable to ask oneself a number of questions: How are such diversities produced? What are the forces at work? What has been the course of these events? In short, what has been the history of human evolution, and which factors have caused and directed it?

Any attempt at reconstructing human evolution presents the same problems we encounter in historical research. Experimental science allows us to test any hypothesis, no matter how unlikely, but history cannot be repeated at will—even if it sometimes gives the appearance of repeating itself. Nevertheless, historical and anthropological analogies are often useful. When these offer independent confirmation or supplementary evidence, they allow us to eliminate or support a hypothesis. Multidisciplinary research provides, in a way, a sort of replication of an event, which is generally possible only in experimental science.

Exploring related disciplines can lead to rich discoveries. It was with this intent that I have searched for, and often found, support from fields such as linguistics, archeology, and demography. Just as this approach yields positive results, it is also a source of great intellectual satisfaction. The researcher sees the fundamental unity of the sciences and their procedures.