Luigi Luca Cavalli-Sforza

A COMPREHENSIVE OUTLINE OF MY RESEARCH: DRIFT VS. NATURAL SELECTION AS FACTORS OF EVOLUTION AND THE IMPORTANCE OF DEMOGRAPHY

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Luigi Luca Cavalli-Sforza *

A COMPREHENSIVE OUTLINE OF MY RESEARCH: DRIFT VS. NATURAL SELECTION AS FACTORS OF EVOLUTION AND THE IMPORTANCE OF DEMOGRAPHY

Jacques Monod published a great book called *Chance and Necessity* which, given its contents, could also have been named with the less attractive, but more descriptive title of *Mutation and Natural Selection*. In the book, chance was held partly responsible for evolution because of the randomness of mutation, but in reality it plays an even greater role, because of random genetic drift, that is, the effect of statistical fluctuations of the frequencies of genes, due to population size, isolation and poverty of migratory exchanges. At the time I started my research, enthusiasts of selection tended to downplay the importance of drift. My early research proved that you can predict the extent and importance of drift by using demographic information of populations, especially their geographic structure and reciprocal migrations, and that drift is far from negligible. It is clear that human evolution is extremely favorable for the study of drift, because demography, which can predict it quantitatively, is especially easy to study in humans. But demography is also the basis of natural selection, which is the outcome of differential survival and reproduction. It is not surprising that Darwin was greatly influenced by Malthus's insight on the manner of demographic growth of human populations. It is now clear that the understanding of evolution is largely based on the understanding of demography. In his famous book *The Genetical Theory of Natural Selection*, R.A. Fisher adopted Lotka's equation expressing the rate of population growth to define the method of measurement of «Darwinian fitness» in natural selection.

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Thanks to the Japanese population geneticist Motoo Kimura, molecular genetics has played the key role for understanding the major influence of drift in general evolution. Drift is also important when there is natural selection, but in its absence – that is for «selectively neutral» traits – it is almost the only factor, with mutation, of evolutionary change. Many genetic variants discovered at the level of DNA are selectively neutral or nearly so. Kimura introduced the idea of «survival of the luckiest» to emphasize the role of chance as a counterpoint to natural selection, as defined by «survival of the fittest».

Population structure and migratory exchanges between populations are extremely important for understanding human evolution. They are also beginning to play a major role in medical genetics, for a simple reason. It is becoming clear that human population «isolates» are very common. These populations have been through a demographic bottleneck at some stage in their lifetime and have limited migratory exchange with neighbors. They are strongly subject to drift, and the result is that their genetic epidemiology is quite different from that of the general human population. Many hereditary diseases common elsewhere are rare or absent in some of these isolates, while other genetic diseases rare or absent in the general population are common there. Examples of such «isolates» are Ashkenazi Jews, French Canadians, Afrikaners, and many other smaller populations like that of the island of Tristan da Cunha. Most hereditary diseases like schizophrenia or allergies are due to many different genetic causes and are therefore difficult to study in the general population, but responsible genes are easier to identify in these isolates. In fact, it is likely that a single gene is responsible for all of a given disease found in an isolate, or at least it is much easier to dissect a complex causal genetic system there.

Evolutionary Trees

The first approach I tried for reconstructing the history of human evolution was the use of evolutionary trees. Their application relies on the principle that the longer the separation of two populations, the greater is, in probability, the magnitude of the genetic difference between them. This requires measuring a quantity we have called genetic distance. When one examines the genetic distance between species which have been separated for very long times (tens or hundreds of millions of years), one usually examines one individual per species, and finds that species differ for many single genetic differences. The proportion of units of DNA that is different in two species is related in a simple way to their evolutionary separation time. Comparatively speaking, human populations have been separated for a very short time. Archeology shows that modern humans appeared only a little more than 100,000 years ago, in Africa, then spread to Asia, between 100,000 and 50,000 years ago, and from South-East Asia reached Oceania between 60,000 and 40,000 years ago. They reached Europe about 40,000 years ago, from both West Asia and North Africa, and America from Siberia beginning 15,000 years ago.

Mutation first appears in one individual, and it spreads to other individuals only in successive generations, when the individual carrying the mutated type has several progeny carrying the mutation. This is because either mutants are favored by selection, and survive easily or have more children, or because they are favored by chance. It usually takes a great number of generations before the mutation is found in many individuals, and even more for it to completely replace the original type. Thus, between the first appearance of a mutation and the replacement of the original type, a very long time will usually elapse. During that period the mutant type is «polymorphic», i.e. there coexist in the population both the original (ancestral) type and the mutant one. It is extremely rare for a mutation to reach 100% in humans living in one part of the world and to be absent in other parts. In fact, we find that genetic variation is enormous in any population, however small. On average, one finds that 85% of the total human variation is within populations, and only 15% between them. Therefore, we cannot use, for the comparison of different human populations, the same measure of genetic distance that proves useful in comparing different species. For instance, we find that the RH-negative type has a frequency of 50% in some populations, e.g., the Basque country, a lower one in England (40%), and 0% in East Asia. Genetic replacement means transition from 0% to 100%. The difference between Basques and English is only 50% – 40% = 10% of a complete replacement, and that between Basques and East Asians, 50%. We actually employ slightly more sophisticated formulas, hopefully proportional to the separation time of two populations, a quantity we badly want to measure. For measurements to be valid, it is also essential to calculate averages over many hereditary characters. When chance is one of the main factors responsible for change, the only way to eliminate the uncertainty it causes is to apply the law of large numbers, that is, use a large number of genetic differences.

With evolutionary trees, we can most usefully study human populations that are widely separated. Geographically close populations are very similar to each other, on average, because migration mixes neighbors. Husband and wife tend to be born at a short distance from each other. As a result, there is a close relationship between the geographic distance of two populations, whether they are camps of hunter-gatherers, or villages, or towns, and their genetic distance. Here, migration acts as a genetic homogenizer and tends to suppress genetic differences caused by natural selection or drift. However, when a group migrates to a great distance – enough to suppress genetic exchange between the original population and the new colony – differentiation will begin and continue at a more or less constant rate, dictated by drift, and if there are important environmental differences, by natural selection. For this reason, trees of populations let us reconstruct their history, and are in very reasonable agreement with archeological observations.

More recently, we have reconstructed genetic trees of individuals, especially for genetic traits that are inherited through one parent only. These are based on mitochondrial DNA, which is transmitted through mothers only, or on Y chromosomes, transmitted only from fathers to sons. These genealogies are sequences of mutations over very long periods, and confirm beautifully the trees made on populations, but are much more detailed and informative.

Genetics and Culture

I find it useful to call culture the patrimony of knowledge accumulating over generations, or, we may also say, what we learn from others and affects our behavior. Most animals have culture, but it is clear that humans are the most cultural animals of all. Culture evolves according to rules that are similar to those of biology, but the substrate is clearly very different, relying on neuronal states, rather than on DNA structure. There are changes that are equivalent to mutations, like inventions or innovations, but they are not as random as biological mutations. On the contrary, they are often directed towards a specific aim. This is a major difference from biological evolution. Another one is that transmission is not, or not only, from parents to children, but can take place between any unrelated individuals. This makes cultural change much faster than biological change. Nevertheless, there are cultural traits which are evolutionarily much more stable than others; not surprisingly, they are usually transmitted from parents to children («vertical» transmission), and therefore imitate to some extent biological transmission, which is known to be very conservative. Children are to some extent malleable, and there are critical periods, too, in which they are especially sensitive to learning specific things, e.g. language (a kind of «imprinting»).

However, most cultural transmission is «horizontal», i.e. not necessarily influenced by the relationship or age difference between transmitter and transmittee. Therefore, the acquisition of cultural novelties is potentially very fast and cultural evolution favors fast assimilation: but what is learnt is not necessarily favorable to survival or reproduction. Still, one can consider culture as a mechanism of adaptation that has developed out of the joint use of communication or observation of others, and of learning skills. It obviously relies on the presence of neural structures that allow these. Cultural change is not necessarily good or bad, but it contributes in an important way to determining our behavior, and, therefore, is subject to natural selection. One can expect that this will keep cultural change being adaptive, on average, although maladaptive cultural aberrations like crime, drugs etc. are to some extent inevitable.

There has been a tendency, in some sociobiological circles and their descendants, to consider cultural traits as dominated by biology, but the reverse is becoming the rule. There is unquestionably a range of new genetic traits introduced by cultural changes. Most of them have to do with acquired cultural traits of new diets, and of customs like dressing. The expansion to northern Asia would have been impossible without clothing. Whether clothing was determined by the previous loss of hair, or it helped the loss of hair is difficult to decide, but it is likely that hair loss was first and made clothing necessary. Is it possible that hair was lost because fire became a major companion of human life, and being hairy is dangerous near a fire? The bleaching of the skin was largely a consequence of the grain diet, which, with dark skin, causes rickets in northern latitudes. The way culture is transmitted makes cultural evolution, and perhaps even culturally determined biological evolution, more Lamarckian than Darwinian – the inheritance of acquired behavioral traits is a reality.

The genetic study of human evolution has shown with extreme clarity that the genetic success of a population, as proved by its expansion in numbers and across vast regions, has been practically every time the result of a major technological innovation. Typically, this has regarded food production (as with agriculture and animal breeding, and their various developments), or transportation (cattle, horses, camels, llamas, boats, oceanic navigation), or military power (bronze, iron, the horse and camel, war chariots) and, in more recent times, communication (writing, roads, and again the horse, telephone, radio, television, and so on), mathematics (agronomy, geography, astronomy, computers), the experimental method (engineering, chemistry, modern physics).

With the modern triumph of communication, cultural evolution is becoming ever more the directional force of human evolution, and genetic evolution may eventually be completely under its control.

Racism

I don't like the word «race» because it corresponds to old subdivisions that are inconsistent with genetic reality and unjustifiable by a rational classification. Moreover, there is no real use of such classifications and, what is worse, there is always an associated racist flavour. Darwin had already recognized the difficulty of a rational classification of races in what is almost a perfect continuum, and noted the futility of racial classifications, given the enormous variety of numbers and definitions of races that different taxonomists have traditionally offered, from two to more than one hundred. The current trend to increased admixture can only make races even less clear.

It is important, however, to note that current classifications depend on external appearance, which is due to very few genes (hereditary factors) affecting skin, hair and eye colour. Body and face size and shape may involve a few more genes but, like the former, are the result of an adaptation to climate (including diet and customs, which obviously also depend largely on climate). Common belief in the «existence» of races must depend on local uniformity of skin color in different environments: dark in tropical climate, brown at some distance from the equator, light brown in south Europe, reaching the highest degree of whiteness in the southern Baltic. To a very superficial examination, races exist, in the sense that some groups of individuals are distinguishable and relatively uniform for a few superficial traits. That there exist «pure» races is pure myth, generated by the fact that most Europeans are white, sub-Saharan Africans black, many Asians brown, and a few further traits may help to distinguish more finely the geographic origins of individuals. There is no equal uniformity under the skin. Genetic differences among populations or races, however defined, are small or trivial compared with those within populations. Below the superficially uniform veneer, there are no «pure races». Moreover, cultural differences among ethnic groups have been frequently believed to be of genetic origin, but the reality is that most of them disappear after two or three generations of assimilation in another culture, and if some last longer, it is because some cultural traits are more highly conserved than others are. Distinguishing nature from culture is extremely difficult for most behavioral traits, but cultural differences are often strong in appearance and labile at the test of time. Some students of twins have been betrayed by their enthusiasm for genetics, I think, beginning with the classic example of Sir Cyril Burt, whose aberrations were exposed. I am not pressing a blanket condemnation of all students of twins, but I think the marvel some of them have expressed at the fact that a few identical twins reared apart prefer the same brand of cigarettes should not be taken very seriously. Another myth, which dominated nineteenth-century Europe and continued in the present century, is that interracial hybrids are inferior, and that race admixture is to be avoided at all costs. The degree of genetic differentiation in the human species is so small that it is impossible that racial admixture is genetically dangerous. One might expect, on the contrary, that its absolute opposite, hybrid vigor, is likely to hold, but a greater degree of genetic differentiation might be necessary for hybrid vigor to be manifest, except for outcrosses of individuals from highly inbred populations. There are, however, a few recent examples of very successful interracial hybrids. They cannot be too many, because there still is a real social handicap confronting interracial hybrids in most societies, which limits their numbers and success.

I consider racism one of the scourges of humanity. There are very few social environments in which it is absent, and racism is certainly not only a European or white social disease. My beloved African Pygmies are considered animals by most of their Bantu neighbors, who think themselves superior because of the superiority of their agricultural economy, however primitive, compared with that of hunter-gatherers. The Saami should not be called Lapps, as they usually are, because the name «Lapps» means «no good», and they are so called by their proximate neighbors because they do not practice agriculture. I find that culture, not genetics, distinguishes people. Every culture has merits, but they give very different chances of economic and educational success. Is racism innate in humans? I do not know, but I believe a strong educational effort to eradicate racism is one of our most urgent needs. It may be impossible to eliminate it, but it should be possible to reduce the criminality with which it is constantly associated.

Political Difficulties Encountered by Genetics

There is today great disagreement on practical applications of molecular genetics to plants and animals. It is good that these discussions take place. Every innovation is associated with potential benefits and costs. The latter are more difficult to evaluate in advance, leaving room for pessimists to overworry, and optimists to be careless. It is good that different countries take different strategies, so that the overcautious can wait as much as they like, and the overconfident take the loss, if there is one.

The study of human evolution has had its share of political difficulties, coming out of religious attitudes in primitive cultures and from some political arenas. At the beginning, the Human Genome Project avoided the study of variation, mostly, I believe, because it was felt that dealing with one single genome was already ambitious enough. I was asked by the international branch of the Human Genome Project (the Human Genome Organization, HUGO) to help study human genetic variation. The Human Genome Diversity Project (HGDP) – unrelated to the Human Genome Project – has been the outcome. Its aim is to accumulate samples of DNA from the human world population, make them available to researchers working on human population genetics, and put their results in a data bank available to the research community. Coordination of efforts could bring substantial advantages. It is also timely, given that the new developments of medical genetics make this type of research very useful. Pharmaceutical and biotechnological firms have promptly understood their interest in genetic variation and have started working on genetic isolates and patenting polymorphisms. Our work has been made particularly difficult by totally unjustified attacks, full of lies, by a special interest group, a Canadian NGO, which has an established network among some indigenous populations of America and Oceania. It accused the Human Genome Diversity Project of being behind totally unrelated efforts of patenting cell lines by the U.S. National Institute of Health, of being interested in profit, consorting with pharmaceutical industries, and various other lies. The truth is that the HGDP is a non-profit institution, and has always been against patenting DNA.

Fortunately, several countries and regions, including the European Union, China, some Moslem countries and Israel have started efforts to systematically study human variation. The Human Genome Project has begun to reverse its policy of avoiding the study of human variation, and a consortium of pharmaceutical firms has been formed for this purpose, but so far they have simplified their task both by totally avoiding the issue of ethnic variation and by exploring it in an ethnicity-blind way.

One of the unsolved problems is that a few indigenous populations that are politically organized are asking to have a share in the possible profits of research from ethnic variation. This is a reasonable request, especially considering the poverty of indigenous peoples, but these profits are difficult to predict and ascertain, and can only come on a very long-term basis from medical research, which is very expensive. Some journalists have spread rumours that knowledge of ethnic variation might be used for new forms of biological warfare, directed against specific ethnic groups. This is a hypothetical form of warfare, very unlikely to be ever possible or effective, given the extremely mixed and complex structure of human populations. We witness daily heinous examples of ethnic warfare very effectively delivered with conventional or even traditional weapons, between peoples among whom there cannot exist any, or almost any genetic difference. Unfortunately, there already exists a very dangerous biological arsenal, but the weapons developed so far have fortunately no connection whatsoever with ethnic differences.

The Genetic Future of Humans

There are a few signs of directions which human evolution may take. There has been, especially in the last five hundred years, an increasing migration across countries and continents, which had already some effects in increasing overall admixture. Le Comte de Gobineau, who feared that admixture would ruin the qualities of human races (especially of the white race, of course), could feel reassured today. There is absolutely no danger, and possibly even some advantage, from increased admixture. Human individual variation is a major insurance against future challenges from parasites or other environmental dangers, and the genetic structure of populations guarantees that it will not change. The global variation will not change, but the distribution of variation between and within continents or «races» may change, with a decrease of the variation between, and an increase of that within populations. Today there is, however, a major difference between the net reproductive rates of different countries and continents. Europeans grew in numbers in the last millennium but went through a demographic transition in the last two centuries, which is almost completed, and are practically not increasing any more in numbers, except through immigration. The rest of the world, with the exception of North America and part of Oceania, is increasing at maximum rate. This is the result of the arrival in the third world of western hygiene and medicine, even if still very limited. Unaccompanied by birth limitations, it has been causing a very worrying jump in population numbers. With white people of European origin being demographically stationary and the rest of the world with an average darker skin multiplying actively, the consequence will be an average darkening of the skin at world level. This change may chagrin white racists, but is not worrying at all from a genetic point of view.

What is more worrying is that medicine has a dysgenic effect, because it has become successful in curing diseases which have a genetic component, and therefore these diseases will increase in frequency in the future. In truth, there has been very little progress so far in curing hardcore hereditary diseases. The main hope seems to be gene therapy, which is due in a not necessarily close future. Progress of medicine has been more common in surgical treatment of many diseases, and in that of infectious ones, where the genetic component is less dramatic, but is not absent. As diseases that will increase in frequency are those which are curable, there will be no worsening of general health, but there will be an increase in the global cost of medical treatment that will be compounded with the increase due to the greater expense of modern medical treatment, independently of the augmented frequency of disease. This cost increase is already wrecking present systems of social medicine. A third cause of increase is the extension of medical treatment to developing countries.

In the last century and in the first part of the present one there was great confidence in eugenics, a movement which recommended improvement of the human species by encouraging the multiplication of people endowed with successful characters (positive eugenics), and discouraging that of antisocial and medically unfit individuals (negative eugenics). Fundamentally, this was inspired by the practice of animal and plant breeders, who try to improve breeds by artificial selection, i.e. the choice of the best reproducers. However, there are serious traps in eugenic policies: it is very difficult to tell «good» genes from «bad genes», or even good people from bad people. It has been noted that selecting against serious psychiatric diseases like schizophrenia and manic-depressive psychosis might destroy major sources of entertainment and pleasure like the theatre, literature, and the arts, given that there is a significant association between these diseases and artistic creativity. A very good geneticist, H.J. Muller, involuntarily gave another famous example. He was in favor of conserving sperm from famous people for insemination of female volunteers, and formed a list of examples of men whose sperm should be conserved to propagate their genes. He was a communist and went to the USSR before the Second World War in the hope of convincing the Soviet authorities to try out his program. He was not successful and, on his return to the free world, he decided to cancel Lenin and Stalin from his list of great men who should donate their sperm for his eugenic program.

We can now predict the birth of children with major genetic diseases in time for early and safe pregnancy interruption. This practice, which avoids many pains and expenses to families and potential patients of very serious diseases, has met with considerable success even in traditionally Roman Catholic countries, where religious views are still contrary to it. There is often confusion between it and eugenics, but this practice is neither eugenic nor dysgenic. It does almost exactly what natural selection does, by removing from reproduction individuals who would not ordinarily reproduce. With very few exceptions, it simply removes them before they are born and die, usually avoiding extreme pains to them and to their relatives. It therefore does not, in practice, change the incidence of the disease, but it wipes out the disease before it appears, in the unborn.

Multidisciplinarity and Historical Studies

The research on human origins has made it useful or necessary to study parallel events and phenomena in a number of related disciplines, ranging from genetics to paleoanthropology, archeology, ecology, history, demography, sociology, cultural and physical anthropology, linguistics, toponomastics and anthroponymy, and this list will probably increase in the future. This has been made possible by many collaborators whom I have tried to thank in my other speech given today. There are definite advantages in this multidisciplinarity. A major one is the intellectual pleasure of finding so many similarities between disparate fields of study, some of which belong traditionally to the two opposite sides of culture: science and the humanities. The unity of scientific method comes out very clearly from such an exercise. It is also clear that many basic paradigms, especially mathematical ones, are extremely useful in many different disciplines, including both sciences and humanities, and are sufficiently few and simple that they can be easily exported from one field to the other. The book on *The Two Cultures* by C.P. Snow has already given reasons for not maintaining the hiatus existing between the two cultures, but little has happened since it was published.

There is also a specific advantage in multidisciplinarity when studying evolution. Evolution, like all history, suffers from a major handicap: one cannot use the experimental method, because one cannot hope to replicate history. For this reason, some philosophers of science have denied that the study of evolution is a science. However, historical events rarely have restricted meaning or influence. One repeatedly finds consequences of the same events in profoundly different areas of life. To give an example, the history of the settlement of geographic areas by populations expanding demographically has similar consequences in genetics and in linguistics, so that their evolutionary trees are similar, in spite of the profound difference of the physical substrate evolving in biology and language. There is much fear among some scientists of the possible superficiality of conclusions drawn based on analogies between different sciences. Still, one of the great scientists, Darwin, noted, in chapter 14 of the *Origin of Species*, that if we knew the genealogical tree of humanity we could predict that of languages. We are now very close to this aim. Many researchers have noted independently the similarities between the evolution of genes, of languages, and, more generally, of culture. Without the study of demography, that of genetic evolution, especially of the human species, would be fruitless. One could continue with these parallels, reciprocal interactions, and cross-fertilizations of different disciplines, but naturally, no two cases where the same model can apply are truly identical. Analogies, metaphors, and models are powerful instruments for novel ideas, but critical thinking remains our best protection against possible superficiality of conclusions derived from them. The increase of knowledge today demands extreme specialization, but, in my experience, the cooperation between scientists of different disciplines can give that degree of generality without which research would be penalized. Multidisciplinarity is a major enrichment especially in those sciences in which, as in history, repetition of the experiment is impossible, and may provide a sort of analogue of it.

Abstract – Luigi Luca Cavalli-Sforza offers a comprehensive overview of his life's work, touching on such topics as drift vs. natural selection as factors of evolution; the importance of demography for understanding evolution; the use of evolutionary trees in reconstructing human evolution; genetics and culture; racism and problems in developing a rational classification of races; and the political difficulties encountered by genetics and the study of human evolution. He concludes with considerations on the future direction of human genetics and the importance of multidisciplinarity in studying evolution.

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