MEDICINĂ

HUMAN RACES AND EVOLUTIONARY MEDICINE

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Data from the Human Genome Programme has clearly established thai the human race is unique. Attempts to identify separately Black, Caucasian and Asian, did not establish a biological basis, which is an interesting **socioeconomic** point. Evolutionary medicine takes the view that many contemporary diseases are likely to result **from** the incompatibility between a contemporary lifestyle and dietary habits and the conditions under which the evolutionary pressure had modified our genetic inheritance. The search for gene variants or mutations, which could be associated with arterial hypertension, atherosclerosis and/or cancer, should be directed towards such metabolic genes.

Darwin's intuition is no longer just a theory after the deciphering of the human genome structure - one of the more solid bases of contemporary biology. Evolutionary medicine takes the view that many contemporary diseases are likely to result from an incompatibility between current lifestyle and dietary habits, and the conditions under which the evolutionary pressure had modified our genetic endowment. Human genomes were indeed shaped by millions of year of evolution and adaptation to specific environmental conditions, which have recently been dramatically modified. Both ageing and the mismatches between modern lifestyle and genomic capacities were likely to generate many of the degenerative diseases that characterize medical practice in 2003, including cancer, atherosclerosis and autoimmune diseases. Interestingly, evolutionary medicine generates a more rationale hypothesis for searching new genetic polymorphisms linked to risk factors - a major goal for medical research.

Nevertheless, such views imply that the human race, *Homo sapiens sapiens,* is unique and, from a biological point of view, rather homogeneous, which means that the so-called human races do not have any biological basis, but only a socioeconomic definition, an opinion that is far from being accepted everywhere.
It is our goal both to stress how the current use of 'White', 'Caucasian', 'Black' and 'Asian' in medical literature ' ... is unhelpful to the scientific search for truth and, by casting social reality as biological reality, perpetuates racism ...','

Human races, a social construct, nothing else

For zoologists, an animal race is a subtype of species. Races have been isolated more often by human action than by geographical necessity in order to obtain and isolate a group of individuals with a specific function; for example, a Pointer dog for hunting. Animals of the same species but of different races can reproduce each other while, by definition, animals of different species are not inter-reproductive. Selected pure race animals are fragile, with a short life-span and frequent inherited diseases, and are extremely well-defined in terms of shape, skin colour, etc. By contrast, the 'human race' is an extremely vague concept, with several, and contradictory definitions, mixing geographical (Asians), religious (Jews), and imaginary (Caucasian) origins, together with biologic phenotypes (Black).

Obviously, race, when applied to humankind, has different meanings. Nevertheless, and despite the lack of precision, race is .still currently used throughout medical literature. (Mcdline, under the search term 'negroid race', contained 1301 citations appeared between 1999 and 2000;[2] the Medical Research Council which is funding most medical research in the UK, sent to referees a circular letter to update their records, with a questionnaire including information concerning date of birth, areas of specific research expertise as usual, but also under 'Ethnic origin' whether 'Asian-Indian origin' ...'Black-Caribbean origin', 'Black-African origin' or 'Black-others'. 'White', and even ...'other', whatever that means?)

(i) As emphasized by the founders of the Framingham study (Framingham is a small American city in which a longitudinal prospective epidemiologic study was developed starting

— 50 years ago; the long term follow-up of the entire population of the city had produced evidence that exposure to risk factors, such as high blood pressure or cholesterol, precedes the onset of coronary heart diseases), race is a parameter that cannot be measured accurately and cannot even be defined using objective criteria.[3] Why skin colour? Why not height, which confers a strong evolutionary advantage? Or baldness - which is neutral? How do we classify mulattos? If one drop of black blood is enough to become black, why not the reverse?

(ii) The human race does, in fact, cover socioeconomic conditions that are both crucial determinants and extremely difficult to be quantified,

the socioeconomic status is indeed simultaneously a confounding factor and a determinant of race. Sadly, recent and even contemporary history has provided many examples of the misuse of 'human race'.

Recently, data from the last US census showed that even self-identification of race was problematic, since 7 million people identified themselves as members of more than one race, and about 800,000 respondents said they were both black and white.[4] Investigators began with the social reality of racial difference and gathered unrelated facts based on this hypothesis until they could conclude that the racial groups were indeed different. An enormous variety of data is now available on racial differences, which invariably descend to platitudes about the interplay of genes with environment,[1]

The human race is, and had always been, a social construct reflecting - in a given country, at a given period of time - the status of the society. In addition, in medicine, racial designation opens the door to inequities in medical care [5] and slows down progress in the genetic or behavioural search for risk factors or better therapies. [2]

From a biological point of view, Homo sapiens sapiens is a unique race

Do the results of the Human Genome Programme establish a genetic support for the racial concept? The response is unambiguously no. The genotypes of 'White', 'Black', 'Asians' are remarkably identical, and there are no more than 0.1% variations in the 35 000 genes that have been identified so far in the human genome.*"[8] Furthermore, the differences between human and si mian genomes are also much less important than expected from their respective phenotypes. The reason is that specific traits, which characterize human and simians, such as language or intelligence, did not result from the expression of one gene, but several, and, that, in fact, traits that distinguish a man from a chimpanzee are a result more from the combinatorial and hierarchical character of gene activity and from the influence of environmental factors such as education than from primary gene structures.

Does racial classification have a genetic and taxonomic significance at the scale of populations? The most convincing study based on genetic techniques was the assessment of allele distribution (blood groups, various alleles, which are I alternative versions of a gene) at a given genetic locus to quantify genetic diversity in several groups of people of different geographical origins. [9] The racial classification, which had been selected, was classical with seven 'races', including **Ithe** four usual ones plus South Asian aborigines, Oceanians and Australian I aborigines. The conclusion reached was both clear and simple: the within-popullation diversity i.s much wider than the between-population or the between-races. Diversity, and less than 15% of all human genetic diversity is accounted for by differences between human groups, including populations of diverse geographical origins and races. From a genetic point of view, it is more difficult to distinguish one person from another, than a black from a 'Caucasian'.

Sickle disease and malaria are good examples of how the geographical distribution of a disease could be misused to support the biological foundation of race. Sickle disease is caused by a very specific mutation in the haemoglobin gene. The mutation appeared in, at least, four independent regions of the world, including Central and North Africa, Spain, Arabia and India. In homozygous persons, the mutation is fatal and patients died from severe anaemia and its consequences. In contrast, in heterozygous persons, the mutation provides a selective advantage because patients are resistant to malaria ***(plasmodium falciparum*** does not like mutated haemoglobin), and the contemporary map of sickle disease can be superimposed on thai of malaria. In fact, such an evolutionary advantage was crucial **for** the geographic distribution **of** the disease in three continents (not only in Africa) between black and white Africans, Spanish, Arabs and Indians. Race has nothing to do with such a distribution, and, in no sense, can sickle disease support the assumption that race or even ethnicity has a biological basis. 'It would be entirely unreasonable to argue that race or ethnicity is a

cause of any particular hemoglobinopathy, but a greater prevalence of disease genes does appear to predispose to a greater prevalence of these diseases in these admittedly heterogeneous populations', say **Kannel.**[3] This conclusion can also be easily extended to any inherited trait, or disease or susceptibility gene.

More recently, a model-based clustering method implemented by the computer program STRUCTURE was used to assign individuals to subclusters on the basis of their genotype, ignoring their actual population or racial affiliations.[10] Well-identified DNA mrkers - microsatellites - were genotyped, a clustering analysis was carried out to identify four clusters, stopping when an increase in the number of clusters did not enhance the degree of differentiation. Table 1 shows how these genetic clusters correspond to populations. Interestingly, 62% of Ethiopians belongs to the same cluster as Norwegians, together with 21 % of the Afro-Caribbeans, and the ethnic label 'Asian' inaccurately describe Chinese and Papuans who were placed almost entirely in separate clusters. This genetic-based taxonomy provided evidence thai the 'Black' race is much more heterogeneous than the 'Caucasians', which is confirmed by population genetics. Obviously, this paper showed that the genetic diversity is much more complicated than expected, and that any oversimplification, such as racial classification, muddies the water and inhibits any further scientific analysis. Other studies with a mitochondrial DNA material have supported this conclusion.[11,12]

The amount of genetic variation can be estimated in a population on the basis of nucleotide diversity and mutation rate and, despite a much lower census size

Table 1. Proportion (in %)<if members of populations and 'races' in each STRUCTURE-defined clusters {rearranged from Ref. 10). STRUCTURE is a computer programme that defines genetic clusters (see text).

Genetic cluster	A	B	C	D
Population				
'Black"				
Bantu	4	2	93	2
Ethiopia	62	8	24	6
A fro-Caribbean	21	3	73	3
'Caucasian'				
Ashkenazi Jews	96	1	1	2
Norway	96	2	1	1
Armenia	90	4	2	5
"Asians'				
China	9	5	1	84
Papua New Guinea	2	95	I	2

than the human, the genetic diversity of other mammalians, including chimpanzees, is much larger than that of humans. Another important conclusion is that an excess genetic diversity is observed in Africans as compared with non Africans, consistent with the 'out-of-Africa' model of human origins. Of course, the 'out-of-Africa' model is only one hypothesis, and there are other models; one of the main reasons why the genetic origins of humankind are still debatable is that most of the data have come from genetic analysis of mitochondrial DNA, which is both limited in size and maternal in origin.[1213] According to the 'out-of-Africa' model, the root of the human phylogenetic tree falls in Africa and a small, genetically homogeneous group of Africans migrated and radiated in Europe and Asia. Although such a model has to be used with caution, it is, for the moment, the only available tool to analyse human genetic diversity.[1213] A limited genetic diversity is a necessary prerequisite for evolutionary medicine, but the search for a genetic endowment would become nearly impossible if human races were multiple and genetically different.

Evolutionary medicine, a conflict between genetic inheritance and environment

'Nothing in biology makes sense except in the light of evolution'.[14] Our shape and behaviour are consequences of millions years of evolutionary pressure, which selected the genes that best fitted the environmental condilio During millions of years of evolution, mutations occurred that re.su (led in differed proteins with different functions, and, by comparing the DNA sequences* homologous genes in

different animal species, the rate of divergence can I determined. Calculations showed, for example, that replacement divergence in tlis globin genes has an average rate of 0.096% per million years. An evolution^ tree can be constructed for every big family of genes. It shows, for example, that the haemoglobin/myoglobin divergence occurred approximately 1100 million! years ago. This divergence provides to those bearing haemoglobin a strong evolutionary advantage due to the fact that haemoglobin can both bind four! oxygen molecules instead of one for myoglobin and is composed of font I structurally and functionally different subunits that allow the molecule (o adapt! to various oxygen requirements,[15] The evolutionary clock has limitations, and the I rate of divergence may considerably differ from one protein to another." Such I an evolutionary process not only concerns major physiological functions, ii also I occurs in a more subtle way through gene polymorphism and gene duplication which may induce a better adaptation to environmental requirements.

During the last two centuries, life expectancy has nearly doubled fl Western-style countries, partly from public health measures and econonfl prosperity, and partly from improvements in medical care, including vaccination, I antibiotics and prevention medicine. The prime cause of mortality is no longer I infectious disease, but cancer and atherosclerosis, which are multifactorial I diseases resulting from a complex interplay between genetic predisposition and risk factors. Simultaneously, environmental conditions have dramatically I changed, hard exercise is no longer necessary for survival, because we have tractors and cars and aeroplanes. Dietary proteins, fat, carbohydrates and .sail are now fully available, clothes and houses are an efficient protection against temperature variations, and we are efficiently protected against bacteria and j viruses.[16]

Evolutionary medicine is concerned with many aspects of medicine, bul we will | only deal with two examples here: the recent increased incidence of both obesity and essential arterial hypertension, and their relationship with dietary habjt.s. From a dietary point of view, contemporary humans still arc Stone Agers. or even .simians, adapted to pre-agricultural nutritional patterns.

The dietary habits of our ancestors is not easy to assess (Table 2).[UIJ] During the Miocene era (5 to 24 million years ago), fruits were likely to be the main dietary constituent of hominids. After the divergence of the simian and human line j (around 4 to 7 million years ago) the feeding pattern of *Homo HabUis* and *Erectus* progressively included meat. Several carefully performed studies on archaeological sites have provided data showing that meat provided over *50°/r* of the diel at that time. Meat from bunted game contains a high level of polyunsaturated fatty

Table 2. Comparisons between Palaeolithic and current American diet. For Palaeolithic diet, data were averaged from .studies made both on fossilized material and on contemporary hunter-gatherer population (data were rearranged from Refs 16-18, see Ref. 16 for the detailed references).

	Palaeolithic diet	Current American diet
Protein	34%*	I2%*
Carbohydrate	45#[J]	4'6%[S]
Fat	21?c[5]	42%*
Fibre*	45 **g/day**	19 g/day
Po l v u n s a t urated/sat urate d **fatty** acids[ws]	1.41	0.44
Sodium	0.69 g/day	2.30-6.90 g/dav
Vitamin C	392 mg/day	87 mg/day

in % tola! energy expenditure. Several sludies had suggested that the fibre content of food (leaves are rich in fibres, not bread or rice) have a **protective** effect against colon cancer. ™ A high level of polyun saturated fatty acids is presently known to have a protective effects against atherosclerosis, game meat and fish contain more of this type of fatty acids than cow or pork.

acids, just as high as that now recommended to prevent atherosclerosis. Over 50 studies on different existing hunter-gatiiercr societies[6] showed thai, despite several limitations, the range and content of foods were similar to those **of** our ancestors. Stone Age populations consumed more animal protein, micronutrienls, and vitamin C, less salt, and saturated **fatty** acids than do current Western people. In addition, the contribution of fruit and vegetables in contemporary human diet *K* reduced as compared with our simian predecessors wilh wheat, rice and corn now providing 40-90% *of* our energy requirements.

One of the consequences of such a change is a diminution **of** the fibre content, which could facilitate colon cancer. Nutritionists are beginning to identify a generally preventive diet, which could prevent or at leasl attenuate the incidence of nol only atherosclerosis, but also Alzheimer's disease and cancer. Such a diet, in many aspects, resembles the diet of our ancestors. Such views may explain the increasing incidence of obesity, diabetes and hypertension in our society, as resulting from incompatibilities between modern diets and our inappropriate genetic endowment. Recent studies have given evidence that when hunter-gather populations - such as Australian **aborigines—leave** their reserves[16] and are introduced into a contemporary urban milieu, they soon develop obesity and diabetes. A current aim of evolutionary nutritionism is to improve the search for metabolic genes.

In Western countries, the incidence of essential arterial hypertension (RAH) in the over 65s is around 30%. and the disease results from complex interactions between genetics and environmental factors. EAH is known to reduce fitness by increasing perinatal and maternal mortality, so it is not *a priori* an evolutionary trait (a trait, to be evolutionary, has to be inherited, variable, and to increase fitness - fitness **is** measured in terms of the number of offspring surviving to sexual maturity and subsequently reproducing themselves).[1]" Why is the incidence of EAH increasing despile such a negative evolutionary pressure? There are several explanations that stress the difficulty in studying multifactorial common diseases such as hypertension.

(i) Salt is a major determinant of intracellular homeostasis. For millions of years, salt was scarce and our genetic inheritance selected salt-retaining genes. Our contemporary diet contains approximately | ten limes more sodium chloride than the palaeolithic diet (Table 2). Nevertheless, the salt-retaining genes are still there, which results in an increasing epidemic incidence of salt-sensitive arterial hyperten-**sion** (Table 3). Such an evolutionary mechanism also supports the survival hypothesis during black slavery. [2U2] The Intcrsalt Cooperative Research Group obtained clear evidence that Ihe greatest variation in blood pressure in the world was in Blacks, with the highest prevalence of high pressure in Mississippi and the lowest in Kenya.[21] Black American are descendants of slaves who were transported under inhuman conditions during the slavery period of history. On-board ship conditions resulted in severe sodium depletion and high mortality, and the survivors were selected on the basis of their genetic ability to store sodium.[23]

(ii) Arterial hypertension is multifactorial, and the genes that regulate blood pressure are pleiotropic, which means that they may have several different and sometimes contradictory effects. For example, the activation of the renin-angiotensin system increases blood pressure (blocking this system is a major pharmacological target), but, in addition, it also reduces the incidence of renal abnormalities during development.[21] Another example is obesity. Evolutionary pressure was directed towards the seleclion of fat-retaining genes,[22] but at present fatty foods are easily available, the result is anj increasing incidence of obesity, and obesity is a major cause of EAH.[24]

There is substantial evidence coming from different sources, for example the (European) MONICA register, that a lower socio-economic status is associated with a much greater incidence of hypertension and also coronary diseases.[25] The

Table 3. The origin of the high incidence of arterial hypertension in Americans of I African origin.[11]

The lirst human appeared in Africa, the so-called cradle of humankind

During 20(1 (1(1(1 years (and more) in Africa

I Salt was rare and the evolutionary pressure had selected salt-retaining genes or alleles, which arc more capable of retaining salt.

Over three centuries, around 48 million slaves were imported into the Americas

On-board ship conditions result in severe salt-depletion. I Survivors were selected on the basis of their genetic ability to store salt.

Present status

Sail is available easily and is present in excess in most foods. I Salt-retaining genes, although useless, are still present and active. The incidence of hypertension has dramatically increased.
Unresolved problems
Salt-sensitivity is not easy to diagnose.
Salt-retaining genes are not the only genes responsible for hypertension.
The selection procedure also occurs in non-Africans.
Genetics is far from being the unique factor involved in hypertension.
average annual household income of the Black American community is $23 697, that of the White is $31 738; 30% of the White households have at least a high-school diploma, versus 41% for the Black.[2fi] Is this due to genetic or environmental factors? Would clinicians modify their treatment because someone is a rich Black and another a poor White? Racial classification does indeed induce confusion, and does not clarify the debate nor help us to decipher pathogenesis. The human race is unique, and, from a genetic point of view, rather homogeneous, which provides us with the basis for evolutionary medicine. A search for gene variants or mutations that could explain the increasing incidence of arterial hypertension, atherosclerosis and cancer is a major goal for pathophysiologists. It should consider metabolic genes, which have been selected over millions years of evolution and are not compatible with the contemporary lifestyle.

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INCIDENȚA NEOPLAZIILOR ONCO-HEMATOLOGICE DIN JUDEȚUL ARAD

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Abstract

The authors of the study „The Incidence of Neoplastic Oncology – Hematology in Arad Country" presents some scientific conclusions based on the clinical experience in what concerns the types of neoplastic processes foe the registred patients. It also highlights the administrations of the therapies accepted by the European and American medicine.

ARADUL este primul oraş important la intrarea în România dinspre Europa Centrală

Este situat în Câmpia de Vest, pe malurile râului Mureş la 46º12' longitudine nordică şi 21º19' latitudine estică, la altitudinea de 116,5 metri. Clima este temperată, temperatura medie fiind de 21º vara şi -1º iarna.

Suprafața județului este de aproximativ 7654 kmp, ceea ce reprezintă 3,2% din teritoriul României.

Populația județului, conform datelor din 1996, este de aproximativ 477.700 locuitori, iar a Municipiului Arad de 185.470 locuitori.

Municipiul Arad este, din punct de vedere administrativ, oraşul de reşedință al județului Arad.