

Virtual Mentor

American Medical Association Journal of Ethics
June 2003, Volume 5, Number 6: 211-214.

IN THE LITERATURE

Race, Genomics, and Health Care

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The *New England Journal of Medicine's* Sounding Board feature was recently devoted to examining opposing views on the usefulness of race as classification in medical research and treatment.^{1,2} Investigators agree that among the 3 types of factors that influence disease prevalence and response to drugs—genetic, environmental, and cultural—genetic factors play the largest role. But, and here's the specific question the articles debate, are the genetic differences that correlate with disease prevalence and drug response distributed across the human population groups we traditionally call "races" in such a way that knowing a person's race provides useful information about his or her susceptibility to certain diseases or probable response to drug therapy? One group of authors puts the question this way: "To what degree does genetic variability account for medically important differences in disease outcomes among racial and ethnic groups"?³ The exchange of viewpoints on this question is instructive, most strikingly, perhaps, as an example of how researchers in the same field, with access to the same studies and findings, can draw opposing conclusions and support them credibly.

The first Sounding Board article, by Cooper, Kaufman, and Ward, argues that race has not been shown to be helpful in categorizing genetic determinants of disease prevalence and response to drugs and is especially poor in predicting susceptibility of a given, individual member of any race to a specific disease or drug response. The authors of the second article, Burchard, Ziv, Coyle, et al, disagree. They say that the relevance of race and ethnicity is "readily apparent" for mendelian disorders (ie, single gene disorders that behave according to dominant-recessive laws of expression), citing as an example hemochromatosis, "found in all European groups and in especially high frequency . . . in northern Europeans, but . . . virtually absent in nonwhite groups."³ The genetic determinants of non-mendelian, complex disorders are less well understood, but, according to Burchard et al, examples do exist that demonstrate clinically important racial and ethnic differences in the frequency of genes involved in complex disorders.³

The first matter both sets of authors must settle upon is a definition of "race," a definition that is becoming less contentious as time goes on. Most evolutionary biologists now agree that the group of modern day humans (*Homo sapiens*) that began to migrate out of Africa about 100,000 years ago were members of a single, interbreeding group. And, by that time in *Homo sapiens* history, most of the variation present in the human genome of today had already occurred. Because

most genetic variation occurred before the human tribe scattered across the globe, most every genetic variation occurs within every population group that subsequently became known as a race.⁴ Some variation occurred after migration, however, due to the environmental pressures of the climates in which different groups eventually settled. These differences are closely related to climate and environment, which accounts for the fact that the designation "race" is now given, essentially, to 5 groups of humans that adapted to 5 different continental areas and climates: Asia, Africa, Europe (white), Pacific Islands, and the North and South American continents (American Indian and Alaskan native).¹⁻⁴ Hence race can be defined most accurately and succinctly as "a subdivision of the human population that is characterized by specialization to [a] different environment."⁵ To summarize, humankind left Africa having already acquired most of the genetic variation that we see in humans today. Then, climatic pressures (eg, how much or how little sunlight was available) gave advantage to certain genetic mutations (eg, a change in amount of skin pigment), allowing individuals with specific characteristics to thrive in that particular climate and produce offspring that also survived. Eventually, the physical characteristics best adapted to survival on a given continent gained predominance among members of that continental group. According to Burroughs, Maxey, and Levy, those visible physical adaptations that lead us to assign individuals to various races have little relevance to the health effects that are of interest to pharmacogenetics.⁴

This agreed-upon definition of race sets up the research question: Is there a meaningful connection between membership in a continental group known as a race and an individual's susceptibility to given diseases or response to given drugs? And, are these questions worth investigating? Cooper et al say "no" to both questions. "Race," they say, "at the continental level, has not been shown to provide a useful categorization of genetic information about the response to drugs, diagnosis or causes of diseases."⁶ Moreover, they argue, use or misuse of research findings might cause increased bias against members of certain continental population groups (the term Cooper et al prefer to "race"). Past use and common understanding of the term race have connotations that cannot be separated from the narrow way in which the term might properly be applied. Scientists must be mindful of the fact that "science is part of society," and knowledge of the purposes to which their findings might be put must guide their research endeavors. Cooper et al imply, in sum, that the science of genomics should not attempt to trace the distribution of genetic variations in ways that support the "socially defined use of race."⁷ This may be a valid ethical reason for not investigating medically useful connections between genetics and race, but it seems out of place in an argument that claims there are no medically useful connections between the two. It is unlikely that research into these connections would continue for long without the promise of a better (and, hence, more profitable) drug therapy as a goal.

Burchard et al argue strenuously against the view held by Cooper et al. Burchard et al contend that certain "clusters" of genotypes are associated with the major branches of human population known as races and that these race-related genotype

clusters have significance for health and medical treatment.³ In one section of their report, the authors warn of the risks of ignoring race in biomedical research and clinical practice. It is well known, they say, that both disease prevalence and response to drugs differ among racial and ethnic groups. If we do not study genetic differences among these groups, the authors say, we will not be able to identify what contributes to the disparities in prevalence and drug reaction that we know exist. Moreover, they say "if investigators ignored race and ethnic background in research studies and persons were sampled randomly . . . minority populations would never be adequately sampled."⁸ Of course, if Cooper et al are correct, it would not matter that members of minority populations were not adequately sampled.

The work of Burroughs, Maxey, and Levy, also cited above, supports the arguments of Burchard et al. Writing in a special supplement in the *Journal of the National Medical Association* in 2002, these authors conclude that significant genetic differences exist "among racial and ethnic groups in the metabolism, clinical effectiveness, and side-effect profiles of many clinical drugs."⁹ After providing many examples of race- and ethnicity-related differences in response to cardiovascular drugs and nervous system agents, the authors conclude that therapeutic substitution in drug formularies puts members of certain racial and ethnic groups at risk and that significant numbers of patients who are members of these groups should be included in drug metabolism studies and clinical trials.¹⁰

The 3 articles discussed here agree on a couple of points, one being the use of the term "race" to refer to the human population groups that settled in 5 major continental land masses, each remaining isolated from the other 4 groups long enough to develop distinguishing predominant physical characteristics. They also agree that gaining information about the distribution across racial and ethnic groups of gene-related disease prevalence and drug response is an intermediate step. While this information may prompt a physician to ask certain diagnostic questions or begin therapy at a given dosage, the information is not predictive of how an individual patient will react and cannot be applied across the board to all patients who declare themselves members of a given race or ethnicity. When we can routinely and inexpensively obtain each individual's genotype as we now obtain his or her blood type, the biological designation "race" will be of little interest in medicine. Then physicians can concentrate on the cultural and lifestyle differences among patients that interact with genetic contributors to health outcomes.

References

1. The Sounding Board articles are Cooper RS, Kaufman JS, Ward R. Race and genomics. *N Engl J Med*. 2003;348:1166-1170 and Burchard EG, Ziv E, Coyle N, et al. The importance of race and ethnic background in biomedical research and clinical practice. *N Engl J Med*. 2003;348:1170-1175.
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4. Little P. *Genetic Destinies*. Oxford: Oxford University Press; 2002:91.
5. Cooper, 1168.
6. Cooper, 1169.
7. Burchard, 1184.
8. Burroughs, 1.
9. Burroughs, 24.

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