

Comment

Color blind

Gregory A Petsko

Address: Rosenstiel Basic Medical Sciences Research Center, Brandeis University, Waltham, MA 02454-9110, USA.
E-mail: petsko@brandeis.edu

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By the time you read this, the result of the 2004 US Presidential election will be known - assuming, of course, that there isn't a repeat of the travesty of 2000, when the Supreme Court of the United States, by a vote that split along the lines of which political party had appointed which particular judge, awarded the election to George W. Bush by the slimmest of margins (less than 1,000 votes) in the state of which his brother was governor. Contested ballots notwithstanding, I never cease to be amazed when I cast my vote on election day. After the cacophony of the seemingly endless campaign, on election day a curious quiet descends on the country. No bands play. No troops march. People waiting in line to vote tend to speak in hushed tones, almost as though they were in church. I didn't see a single cell phone in use. The transfer of power in what is arguably the most powerful nation in the history of the world happens softly, like a whisper in the dark. That's the wonder of democracy.

Contrary to what many Americans think, democracy wasn't invented here. It has a long history, going back at least to ancient Greece. And, especially if we have another disputed election this time, I would have trouble arguing that it was perfected here either. But if not the practice of democracy, I think the concept of democracy may have reached its zenith on these shores, in the city of Philadelphia, in the month of June, in the year 1776. At that time and place, Thomas Jefferson composed these words for the document in which the thirteen former British colonies declared their independence: "all men are created equal". As a weapon in a war, which it was, that phrase was powerful. It was meant to convince and to confound, and it did both. Then it developed a life of its own, and began to reverberate around the world like the sound of an exploding volcano. It echoed in the French Revolution thirteen years later. It could be heard in 1848, the year of revolutions in Europe. It was still echoing more than a hundred years later when India broke from Britain. It can still be heard today, as loud and potent as ever. Not bad for an idea that is biological nonsense.

Basketball star Michael Jordan could jump through the roof of a building; I never could. Footballer David Beckham can bend a corner kick around a goalpost; I can barely kick a soccer ball straight. I can't run a marathon in under three hours and I never would be able to no matter how hard and long I trained. Neither could most people, nor do they expect to. Implicit in the meritocracy of sport is the idea that, although practice and coaching are important, there are vast differences in talent among individuals. Such limitations are understood in other areas as well: most people cannot do high-level mathematics and probably never could no matter how long they studied. I took piano lessons for five years, but Horowitz is a pianist; I'm not, and never will be. We all know these things, and accept them. But taken literally, "all men are created equal" could imply that such facts aren't true. Of course, the phrase was never meant to refer to physical abilities, or talent for music or abstract reasoning. It meant that all men (alas, the Founding Fathers probably really did mean only men - there were no Founding Mothers to set them straight) should be equal in the eyes of the law, and the government. Since I live in a country where the wealthy and influential often receive preferential treatment by both, I understand that this is an ideal not always achieved in practice.

But the extreme interpretation is always there, in any democracy. It's responsible for the contempt of 'the elite' or 'intellectuals' that one hears, especially around election time. It underlies our iconoclastic tendencies. Somewhere, in some inner place that is hard to reach, a lot of us harbor the secret belief that we're just as good as anybody, in just about everything. Maybe this delusion is harmless, but I doubt it. I think it contributes to the streak of anti-intellectualism that has a foothold in Western culture right now. I think it also makes it easier for populists and demagogues to coax people into voting against their self-interests. But even if I'm wrong about these consequences, there is one area in which the notion of absolute equality is certainly dangerous: the area of medicine.

This month, a report appeared in *The New England Journal of Medicine* (351:2049-2055; issue of 11 November 2004) entitled "Combination of Isosorbide Dinitrate and Hydralazine in Blacks with Heart Failure". The article was written by Anne L. Taylor MD, Susan Ziesche RN, and a number of other authors, on behalf of the African-American Heart Failure Trial Investigators. The paper presents the results of a study of 1,050 black patients with advanced heart failure. Half received a placebo, while the other half received BiDil, a combination of two generic drugs (isosorbide dinitrate, which stimulates the production of nitric oxide, and hydralazine, an antioxidant and vasodilator that appears to prevent the nitric oxide from deactivating). The results were so striking that the study was terminated prematurely so that all remaining patients could be given BiDil. Over the two years of the study, 6.2% of the patients given the drug died, compared with 10.2% of those given the standard treatment, a 43% improvement. First hospitalizations were also reduced by 33%. Ray Gibbons, a cardiologist at the Mayo Clinic and spokesman for the American Heart Association, says "When you have this level of risk reduction in a high-stakes disease like heart failure, it's at least a home run." The study was initiated by NitroMed, Inc., a biotechnology company in Lexington, Massachusetts. Combined use of the two generic drugs would allow NitroMed to receive a new patent for the joint formulation. An earlier trial of the mixture, by Dr Jay Cohn of the University of Minnesota in the 1980s, had been disappointing: in a test against the general population, the drugs fared worse than angiotensin-converting enzyme (ACE) inhibitors. But Dr Cohn reanalyzed the data when it became clear years later that one reason African-Americans die from heart failure at 2.5 times the rate of Caucasians was because ACE inhibitors appear to be much less effective in black patients than in non-blacks. Sure enough, in the 395 black patients in the original study, the drug combination appeared better than the standard therapy. The new trial, exclusively in African-Americans, was begun as a consequence.

So why isn't everybody cheering? Many are, including the Association of Black Cardiologists, who cosponsored the trial. But others are not. In a perspective in the same issue of *The New England Journal of Medicine*, Dr M Gregg Bloche of Georgetown University Law Center asks, "Are we moving into a new era of race-based therapeutics?" He believes the answer is yes, especially since the US Food and Drug Administration has already indicated that if the drug is approved, it will be labeled as indicated for patients of African-American descent, an unprecedented situation. (Although at least 29 drugs are known to have different efficacies between blacks and Caucasians, none of them is labeled in this way.) JudyAnn Bigby, director of the Office for Women, Family and Community Programs at Brigham and Women's Hospital in Boston, fears that "if people get one little inkling that there's a biological basis to race, we could potentially lose ground in understanding racial differences in disease.

Biology could be an excuse for not looking at the social basis" of diseases like heart disease, which is known to be affected by stress, income, diet and access to health care, among other non-genetic factors. "You have the federal government giving its imprimatur, its stamp of approval, to using race as a biological category," warns Jonathan Kahn, of Hamline University, who wrote a paper in the *Yale Journal of Health Policy, Law, and Ethics* on the danger of approving BiDil. "To my mind, it's the road to hell being paved with good intentions."

This concern is understandable given the sorry history of the US when it comes to matters of race. Yet we have known for half a century that sickle-cell anemia is overwhelmingly a disease of blacks, that Tay-Sachs Disease is overwhelmingly a disease of Ashkenazi Jews, and that cystic fibrosis is overwhelmingly a disease of Caucasians. Somehow that knowledge has not set us on the road to hell. Why not? I think that main reason is that 'race' in these diseases is only a surrogate marker: in each case the specific genetic abnormality is known. Blacks do not suffer disproportionately from sickle-cell anemia because they are genetically inferior to whites, they suffer from it because the sickle cell mutation is more commonly found in people of African origin, and because the presence of the mutation in such individuals appears to confer protection against infection by the malaria parasite. But there are 'non-blacks' who have the same mutation and suffer from the same disease. Race isn't the issue; the issue is who has the relevant genetic trait. Once the affected gene is known, anybody can be tested for the disease-causing mutation. Race becomes irrelevant.

BiDil works in African-Americans because there is some gene - possibly more than one, but probably no more than a few - that differs between most people of African-American descent and those of, say, Indo-European descent. The tools of genomics can be used to find that gene or genes, and when that is done it will be possible to test everyone who suffers from heart failure for the mutations that confer susceptibility to BiDil therapy. When that happens, it will certainly become clear that many non-blacks would also benefit from BiDil. Since this would increase the market for the drug considerably above, say, the 375,000 African-Americans who suffer from moderate to severe heart failure, it would be in the interest of NitroMed to support the search for those genetic differences. Then the drug could be labeled the right way: according to its molecular targets, not the color of the patient's skin.

Last spring, The Magic Theater in San Francisco presented a play by Cassandra Medley entitled *'Relativity'*. It concerns an African-American woman scientist who is asked by her mother to disprove that all racial groups are genetically similar (you can read a synopsis of it in Sandra Soo-Jin Lee's thoughtful review in *PloS Biology* 2004, 2:1263-1264). The play raises the question: does identifying genetic differences

between groups itself constitute an act of racism? Obviously I don't think so, but I do realize that any statement of differences between races can never be neutral. That is why we must shift the discussion away from color and towards those things that make us different as individuals, not as members of some group.

Genomic data indicate that all humans share about 99.9% of our genetic make-up. As more data accumulate and it becomes clear that the concept of race is meaningless biologically, we should be able to agree that all 'men' are almost equal biologically, and to shift our focus once and for all to those genetic differences that are meaningful, such as those that determine our susceptibility to disease and our responses - beneficial and adverse - to therapy. One of the great future benefits of the Human Genome Project may be that, in years to come, when someone is described as being a credit to their race, it will be understood by everyone that what is meant is the human race.