Race in a Bottle

Drugmakers are eager to develop medicines targeted at ethnic groups, but so far they have made poor choices based on unsound science

By Jonathan Kahn

KEY CONCEPTS

- BiDil, a drug that combats congestive heart failure by dilating the arteries and veins, was approved in 2005 as a treatment for African-Americans only.
- There is no firm evidence that BiDil works better for African-Americans than for whites.
- BiDil is a combination of two generic pills that are available at one-sixth the cost of the patented drug.
- Although BiDil may delay hospitalization and death for heart failure patients, the race-specific approval of the drug sets an unwise precedent.

—The Editors

Two years ago, on June 23, 2005, the U.S. Food and Drug Administration approved the first "ethnic" drug. Called BiDil (pronounced "bye-dill"), it was intended to treat congestive heart failure—the progressive weakening of the heart muscle to the point where it can no longer pump blood efficiently—in African-Americans only. The approval was widely declared to be a significant step toward a new era of personalized medicine, an era in which pharmaceuticals would be specifically designed to work with an individual's particular genetic makeup. Known as pharmacogenomics, this approach to drug development promises to reduce the cost and increase the safety and efficacy of new therapies. BiDil was also hailed as a means to improve the health of African-Americans, a community woefully underserved by the U.S. medical establishment. Organizations such as the Association of Black Cardiologists and the Congressional Black Caucus strongly supported the drug's approval.

A close inspection of BiDil's history, however, shows that the drug is ethnic in name only. First, BiDil is not a new medicine—it is merely a combination into a single pill of two generic drugs, hydralazine and isosorbide dinitrate, both of which have been used for more than a decade to treat heart failure in people of all races. Second, BiDil is *not* a pharmacogenomic drug. Although studies have shown that the hydralazine/isosorbide dinitrate (H/I) combination can delay hospitalization and death for patients suffering from heart failure, the underlying mechanism for the drug's efficacy is not fully understood and has not been directly connected to any specific genes. Third, and most important, no firm evidence exists that BiDil actually works better or differently in African-Americans than in anyone else. The FDA's approval of BiDil was based primarily on a clinical trial that enrolled only self-identified African-Americans and did not compare their health outcomes with those of other ethnic or racial groups.

So how did BiDil become tagged as an ethnic drug and the harbinger of a new age of medicine? The story of the drug's development is a tangled tale of inconclusive studies, regulatory hurdles and commercial motives. BiDil has had a relatively small impact on the marketplace—over the past two years, only a few million dollars' worth of prescriptions have been sold—but the drug has demonstrated the perils of using racial categories to win approval for new phar-

maceuticals. Although African-Americans are dying from heart disease and other illnesses at younger ages than whites, most researchers believe the premature deaths result from a complex array of social and economic forces [see "Sick of Poverty," by Robert Sapolsky; SCIENTIFIC AMERICAN, December 2005]. Some medical professionals and policy experts, however, have pointed to BiDil as proof that genetic differences can explain the health disparity. Worse, some pharmaceutical companies are now using this unfounded argument to pursue other treatments targeted at various ethnic groups, a trend that may segregate medicine and fatten the profits of drugmakers without addressing the underlying causes that are killing so many African-Americans before their time.

Birth of BiDil

The BiDil saga began more than 20 years ago with a pair of studies designed to gauge the effects of vasodilating drugs—which widen blood vessels—on heart failure, a debilitating and ultimately fatal disease that afflicts millions of Americans. Until then, doctors treated heart failure with diuretics (to reduce the accumulation of fluid that results from inadequate pumping) and digoxin (to increase the contraction of the heart muscle) but had little else at their disposal. In the early 1980s Jay Cohn, a cardiologist at the University of Minnesota, hypothesized that administering two vasodilators, hydralazine and isosorbide dinitrate, might ease the strain on weakened hearts by relaxing both the arteries and veins. Together with the U.S. Veterans Administration, Cohn designed and conducted two trials to assess this theory.

The first Vasodilator Heart Failure Trial (V-HeFT I) tested the H/I combination against a placebo and a drug called prazosin, which is used to treat high blood pressure. The results seemed to show great promise for the combination. The second trial, V-HeFT II, tested H/I against enalapril, a first-generation angiotensin-converting enzyme (ACE) inhibitor. (ACE inhibitors lower blood pressure by curbing the production of vessel-constricting peptides.) As it turned out, enalapril proved more effective than H/I for treating heart failure. From that point forward, ACE inhibitors became the new first-line therapy for heart failure patients. Doctors began recommending hydralazine and isosorbide dinitrate—both available as inexpensive generic pills—for those who did not respond well to ACE inhibitors.

▲ APPROVAL of BiDil as a treatment for congestive heart failure in African-Americans has encouraged drugmakers to consider developing other medicines targeted at racial or ethnic groups. But most scientists agree that these categories are not useful for predicting drug responses, because the genetic variation among individuals in the same race is much greater than the variation between races.

PHOTOILLUSTRATION BY AARON GOODMAN; JEN CHRISTIANSEN (pills)

[BUYING TIME]

Milestones in the Development of BiDil

1986 The results of the first Vasodilator Heart Failure Trial (V-HeFT I) are published. The combination of hydralazine and isosorbide dinitrate (H/I) shows promise.

1987 Jay Cohn of the University of Minnesota applies for a patent on the method of using hydralazine and isosorbide dinitrate together. BiDil is born.

1991 A second trial, V-HeFT II, shows that enalapril, an ACE inhibitor, is more effective than H/I for treating heart failure.

1996 Cohn and Medco, which holds the patent rights to BiDil, bring the drug to the FDA for approval.

FIRST PATENT

Cohn, however, remained committed to developing a treatment that combined hydralazine and isosorbide dinitrate because he believed in its effectiveness. In 1987 he applied for a patent on the *method* of using the drugs together to treat heart failure in all people, regardless of race. (He could not get a patent on the drug combination itself because both medicines were already available in generic form.) He then licensed the patent rights to Medco, a small pharmaceutical firm in North Carolina, which took steps in the early 1990s to put the H/I combination into a single pill—and BiDil was born.

Medco and Cohn brought BiDil to the FDA for approval in 1996. In early 1997 the agency refused to approve the drug. Ironically, most of the doctors on the FDA's review panel thought BiDil did in fact work and said they would consider prescribing it. The problem was not with the drug but with the statistical data from the V-HeFT trials, which were designed not to meet the regulatory standards for FDA approval but to test the hypothesis that vasodilators could treat heart failure. After the rejection, Medco's stock plummeted by more than 20 percent, and the company let the patent rights revert to Cohn. By 1997 half of the 20-year life of the original BiDil patent had already passed, which may explain Medco's reluctance to sink more money into the drug.

BiDil's Racial Rebirth

It was only at this point that race entered the story. After the FDA's rejection of BiDil, Cohn went back to the V-HeFT results from the 1980s and broke down the data by race, examining how well African-Americans had responded to the competing treatments. Such retrospective "data dredging" can yield useful insights for further investigations, but it is also fraught with statistical peril; if the number of research subjects in each category is too small, the results for the subgroups may be meaningless. Cohn argued that H/I worked particularly well in the African-Americans enrolled in the V-HeFT studies. The clearest support for this claim came from V-HeFT I, which placed only 49 African-Americans on H/I—a tiny number considering that new drug trials typically enroll thousands of subjects. In 1999 Cohn published a paper in the *Journal of Cardiac Failure* on this hypothesized racial difference and filed a new patent application. This second patent was almost identical to the first except for specifying the use of H/I to treat heart failure in black patients. Issued in 2000, the new patent lasts until 2020, 13 years after the original patent was set to expire. Thus was BiDil reinvented as an ethnic drug.

Race-specific patent in hand, Cohn relicensed the intellectual-property rights to NitroMed, a small Massachusetts firm. The FDA then gave NitroMed the go-ahead to conduct the African-American Heart Failure Trial (A-HeFT), a relatively small study involving 1,050 self-identified African-Americans. In A-HeFT, half the heart failure patients took BiDil while the other half received a placebo; at the same time, the patients in both groups continued taking their already prescribed treatments for heart failure (for example, about 70 percent of the subjects in both groups were on ACE inhibitors). The results were strikingly positive: the mortality rate in the BiDil subjects was 43 percent lower than that in the placebo group. In fact, BiDil appeared so effective that A-HeFT's Data Safety Monitoring Board suspended the trial early, in July 2004, so that the drug could be offered to the subjects in the placebo group as well. NitroMed's stock surged on the news, more than tripling in value in the following days. The next June the FDA formally approved BiDil with a race-specific label, indicating that it was for use in black patients.

But researchers have good reason to believe

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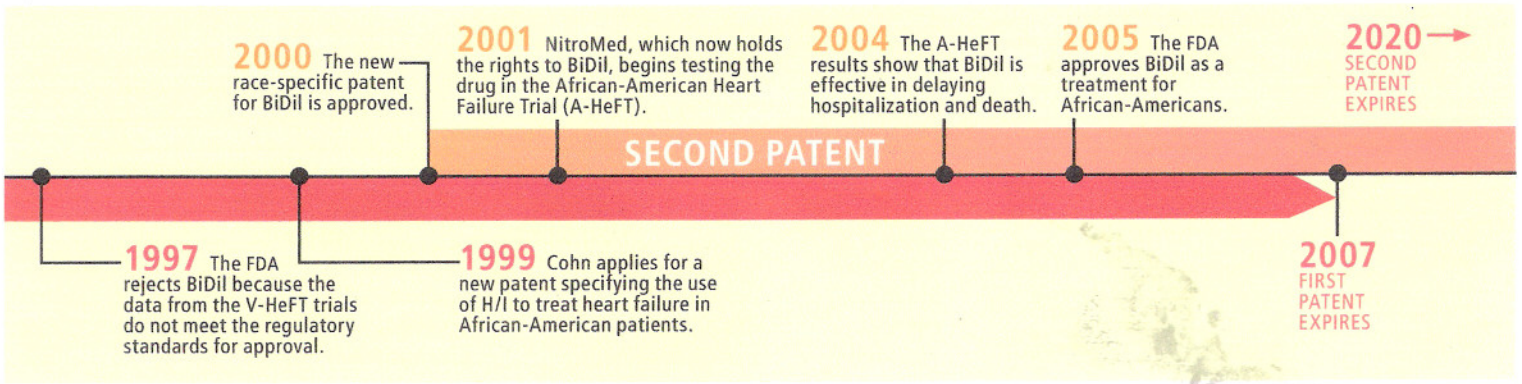
COURTESY OF HAMLINE UNIVERSITY (Kahn); JEN CHRISTIANSEN (pills)



that BiDil would also be effective in nonblack patients. Indeed, Cohn himself has said he believes the drug should work in people of all races. So why did the developers of the drug test it in only one ethnic group? The answer seems to be driven more by commerce than by science. If the FDA had approved BiDil for the general population, the patent protection for the drug's manufacturer would have expired in 2007. Restricting the clinical trial to African-Americans maximized the chances that the FDA would approve the race-specific use of BiDil, giving NitroMed an additional 13 years to sell the H/I combination without competition.

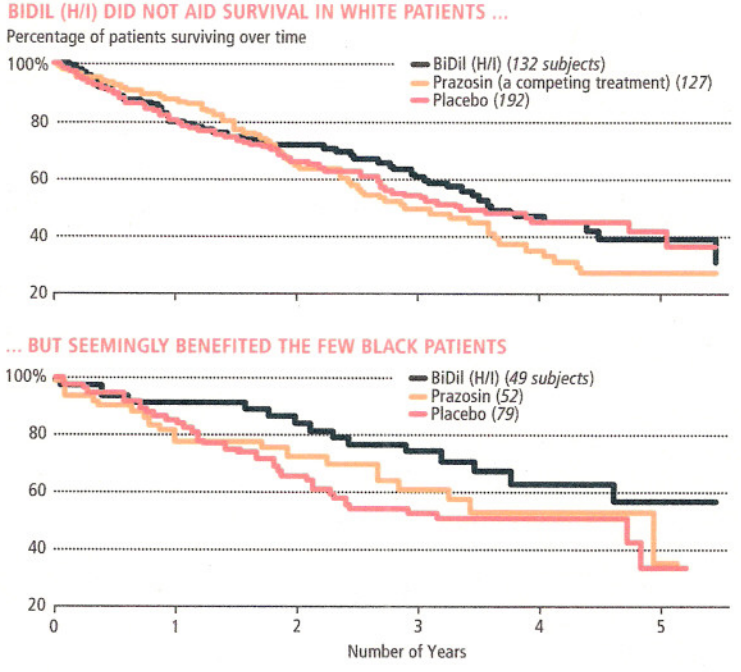
Segregated Medicine

Science and commerce have always proceeded together in advancing medicine, but in the case of BiDil the balance seems to have gotten out of whack. There can be no doubt that Cohn and the other medical professionals behind the drug's development sincerely want to improve the lives of the many people suffering from heart failure. In this respect, the approval of BiDil is certainly a good thing. But Cohn and NitroMed have also used race to obtain commercial advantage. The patented drug costs about six times as much as the readily available generic equivalents. The high cost has already made many insurers reluctant to cover BiDil and may place it beyond the reach of the millions of Americans without health insurance. Moreover, the unprecedented media attention to the race-specific character of the drug may lead many doctors and patients alike to think that non-African-Americans should not get the drug, when, in fact, it might help prolong their lives.

Perhaps most problematically, the patent award and FDA approval of BiDil have given the imprimatur of the federal government to using race as a genetic category. Since the inception of the Human Genome Project, scientists have worked hard to ensure that the biological knowledge emerging from advances in genetic research is not used inappropriately to make socially constructed racial categories appear biologically given or natural. As a 2001 editorial in the journal *Nature Genetics* put it, "scientists have long been saying that at the genetic level there is more variation between two individuals in the same population than between populations and that there is no biological basis for 'race.'" More recently, an editorial in *Nature Biotechnology* asserted that "race is simply a poor proxy for the environmental and genetic causes of disease or

LOOKING FOR A TREND

After the FDA's rejection of BiDil in 1997, the drug's developers examined the trial results by race. They spotted a small positive effect among black patients, but because only 49 blacks were taking the drug in the trial, the results may not be meaningful.



LUCY READING-IKKANDA (timeline and graphic); SOURCE FOR GRAPHS: "RACIAL DIFFERENCES IN RESPONSE TO THERAPY FOR HEART FAILURE: ANALYSIS OF THE VASODILATOR–HEART FAILURE TRIALS," BY PETER CARSON, SUSAN BESCHE, GARY JOHNSON AND JAY N. COHN, IN *JOURNAL OF CARDIAC FAILURE*, VOL. 5, NO. 3, SEPTEMBER 1999

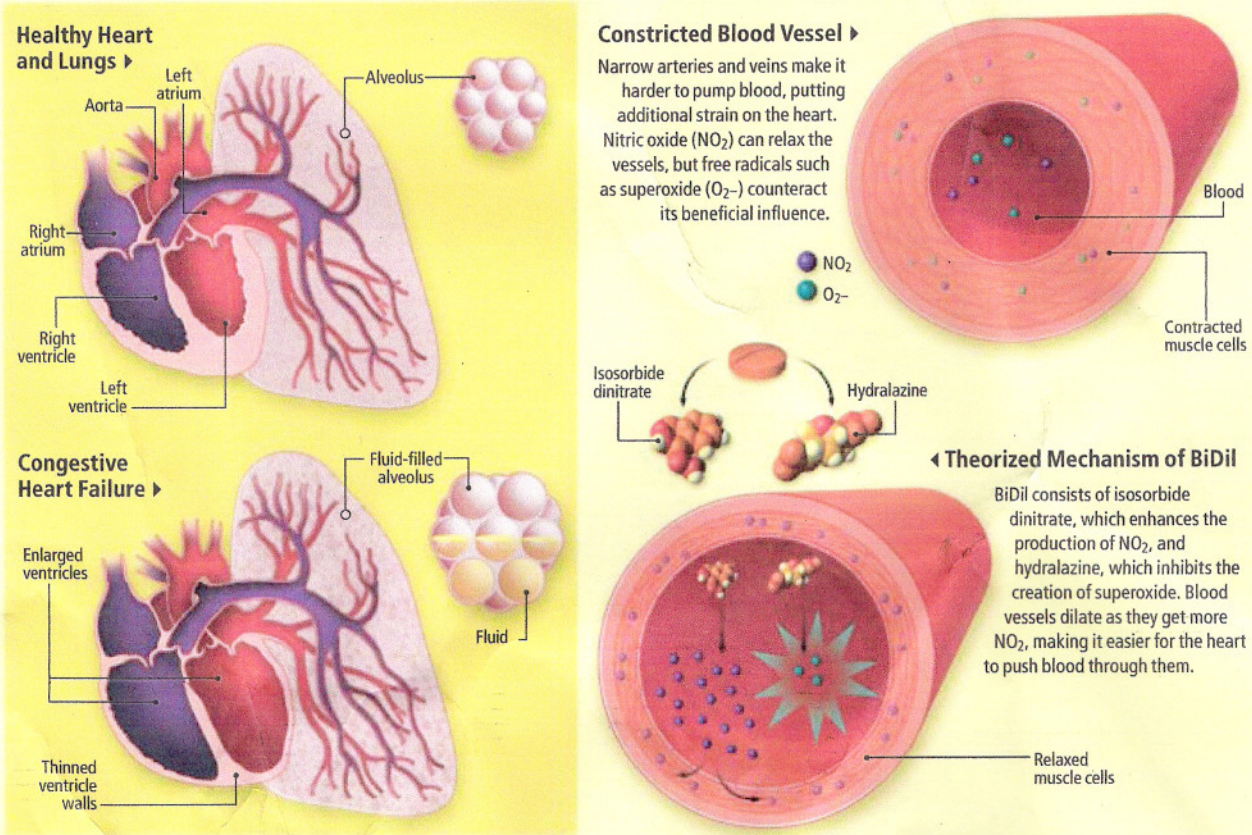
drug response.... Pooling people in race silos is akin to zoologists grouping raccoons, tigers and okapis on the basis that they are all stripey."

The FDA's approval of BiDil was based on accepting NitroMed's argument that the drug should be indicated only for African-Americans because the trial population was African-American. This labeling sends the scientifically unproved message that the subject population's race was somehow a relevant biological variable in assessing the safety and efficacy of BiDil. Most drugs on the market today were tested in overwhelmingly white populations, but we do not call these medicines "white," nor should we. The FDA's unstated assumption is that a drug that proves effective for white people is good enough for everyone; the same assumption should apply when the trial population happens to be black. Otherwise, the FDA is implying that African-Americans are somehow less fully representative of humanity than whites are.

In November 2004 *Nature Genetics* published an article by Sarah K. Tate and David B. Goldstein of University College London entitled "Will Tomorrow's Medicines Work for Everyone?" The paper noted that "29 medicines (or combinations of medicines) have been claimed, in peer-reviewed scientific or medical journals, to have differences in either safety or, more commonly, efficacy among racial or ethnic groups." Journalists immediately quoted the study as providing further evidence of biological differences among races; for example, an article in the *Los Angeles Times*, after discussing BiDil, referred to "a report in the journal *Nature Genetics* last month [that] listed 29 drugs that are *known* to have different efficacies in the two races." (The italics are mine.) Similarly, a story in the *Times of London* asserted that "only last week, *Nature Genetics* revealed research from University College London *showing* that 29 medicines have safety or efficacy profiles that vary between ethnic or racial groups." (Again, the italics are mine.) And a *New York Times* editorial entitled

HOW BIDIL TREATS HEART FAILURE

Unlike a healthy person's heart, a failing heart gets larger as it struggles to pump blood and causes fluid to accumulate in the lungs' alveoli. BiDil is thought to slow the progress of the disorder by dilating narrow blood vessels, which can ease the burden on the heart.



TAMI TOLPA

"Toward the First Racial Medicine" began with a discussion of BiDil and went on to note that "by one count, some 29 medicines show evidence of being safer or more effective in one racial group or another, suggesting that more targeted medicines may be coming."

One small problem: these newspaper stories totally misrepresented the *Nature Genetics* piece. Tate and Goldstein asserted that the racial differences in drug safety or efficacy have only been claimed, not proved, and in the next sentence they go on to say, "But these claims are universally controversial, and there is *no consensus* on how important race or ethnicity is in determining drug response." (My italics again.)

In only four of the 29 medicines identified, Tate and Goldstein found evidence that genetic variations between races could possibly be related to the different responses to the drugs. (All four are beta blockers used for treating high blood pressure and other cardiovascular ills; some research indicates that these drugs work better in individuals carrying a gene variant that is more common in people of European ancestry than in African-Americans.) For nine of the medicines, the authors found "a reasonable underlying physiological basis" to explain why blacks and whites may respond differently to the drugs; for example, some scientists have speculated that ACE inhibitors may be more effective in people of European descent than in African-Americans because of variations in enzyme activity. (Other researchers have contested this hypothesis.) For five of the drugs, Tate and Goldstein found no physiological reasons to explain the varying responses; for the remaining 11 they concluded that the reports of differing responses may not be valid.

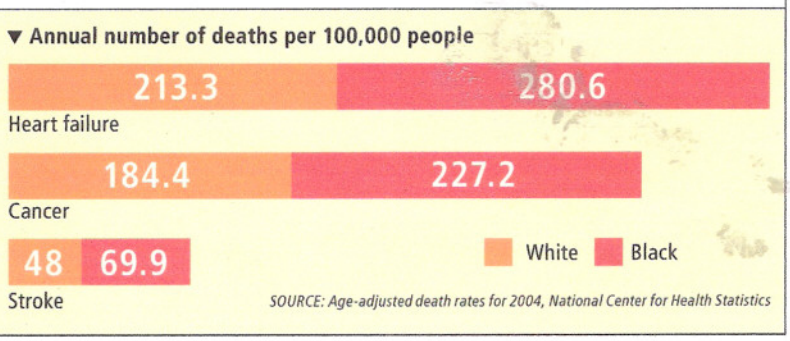
Racial Injustice

Nevertheless, the appeal of race-specific drugs is growing. In 2003 VaxGen, a California biopharmaceutical company, made an abortive attempt to use a retrospective analysis of racial subgroups to salvage a proposed AIDS vaccine called AIDSVAX. Although the clinical trial for AIDSVAX showed no decrease in HIV infection rates in the study population as a whole, VaxGen claimed a significant reduction in infection among the black and Asian participants. But only a few hundred blacks and Asians were involved in the study, meaning that a handful of infections could have skewed the results. The claim of race-specific response was undercut later that year when another trial in Thailand showed that AIDSVAX was ineffective there as well. In a similar case, AstraZeneca, the British pharmaceutical firm, argued that its lung cancer drug, Iressa, worked better in the Asians enrolled in a 2004 clinical trial, which showed that the medicine did not improve survival rates overall. (Unconvinced, the FDA changed the labeling for Iressa, disallowing its use in any new patients.) More recently, AstraZeneca has conducted trials of Crestor, the company's multibillion-dollar cholesterol-lowering drug, in African-Americans, South Asians and Hispanics. Consumer groups have claimed that Crestor is less safe than other cholesterol-lowering drugs, but AstraZeneca says the race-specific studies demonstrate the safety and efficacy of the medicine.

Researchers using race to develop drugs may be motivated by good intentions, but such efforts are also driven by the dictates of an increasingly competitive medical marketplace. The example of BiDil indicates that researchers and regulators alike have not fully appreciated that race is a powerful and volatile category. When used to bolster the commercial value of a drug, it can lead to haphazard regulation, substandard medical treatment and other unfortunate unintended consequences. The FDA should not grant race-specific approvals without clear and convincing evidence of a genetic or biological basis for any observed racial differences in safety or efficacy. Approving more drugs such as BiDil will not alleviate the very serious health disparities between races in the U.S. We need social and political will, not mislabeled medicines, to redress that injustice. ■

HEALTH IN BLACK AND WHITE

In the U.S., heart disease, cancer and stroke exact a greater toll on blacks than on whites. Although these diseases are the leading causes of death for both races, the age-adjusted death rates are much higher among African-Americans, meaning that they die at younger ages from the illnesses. Researchers have proposed several theories to explain the health disparity: whereas some experts put the blame on a lack of access to health care, others say the culprit is stress caused by low socioeconomic status.



SOURCE: Age-adjusted death rates for 2004, National Center for Health Statistics

MORE TO EXPLORE

The Meanings of "'Race" in the New Genomics: Implications for Health Disparities Research. Sandra Soo-Jin Lee et al. in *Yale Journal of Health Policy, Law, and Ethics*, Vol. 1, pages 33–75; 2001.

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From Disparity to Difference: How Race-Specific Medicines May Undermine Policies to Address Inequalities in Health Care. Jonathan Kahn in *Southern California Interdisciplinary Law Journal*, Vol. 15, pages 105–129; 2005.

Enhanced: Race and Reification in Science. Troy Duster in *Science*, Vol. 307, pages 1050–1051; February 18, 2005.

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LUCY READING-IKKANDA