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## Pharmacogenetics and ethnically targeted therapies

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secondary prevention of coronary heart disease. In terms of primary prevention, development and testing of combination pills aimed at reducing more than one risk factor seems entirely logical, particularly in the context of assessment of global cardiovascular risk. Funding bodies and the NHS need to support the necessary trials and cost effectiveness studies to further examine the polypill strategy in comparison with non-pharmacological alternatives.

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## Pharmacogenetics and ethnically targeted therapies

*New drug BiDil marks the return of biology to the debate about race and ethnicity*

In modern conceptions of race and ethnicity, biology has been relegated to a minor underlying factor.<sup>1</sup> Instead, these concepts have been cast as largely social constructions.<sup>2</sup> For example, race traditionally distinguishes between groups according to a mixture of physical characteristics (including skin colour), which reflect ancestry and hence biology. A modern conception of race would place the emphasis on a common social and political heritage. Similarly, ethnicity puts emphasis on distinguishing between groups by using a mixture of cultural factors, including language and religion.<sup>2</sup> Recent developments in pharmacogenetics, however, renew the historical emphasis on biology in concepts of race and ethnicity. Pharmacogeneticists examine whether different responses to drug treatment may be attributable to genetic differences. They are focusing on race and ethnicity as a means to this end. A recent international conference, the 8th world congress on clinical pharmacology and therapeutics, in Brisbane, Australia, had an afternoon on ethnopharmacology, showing how seriously this new subject is being taken.<sup>3</sup>

In the middle of this resurgence of the role of biology in concepts of race and ethnicity comes BiDil, a new drug treatment for heart failure tested solely in one particular racial group. In 2001 NitroMed began the African-American heart failure trial (A-HeFT), the first heart failure trial conducted exclusively in African-American patients, claiming that "observed racial disparities in mortality and therapeutic response rates in Black heart failure patients may be due in part to ethnic differences in the underlying pathophysiology of heart failure."<sup>4,5</sup> The study found that BiDil (a

fixed dose of isosorbide dinitrate and hydralazine, designed to restore low or depleted nitric oxide concentrations to the blood) combined with standard therapy for heart failure reduced mortality by 43% among black patients.<sup>5</sup> Hailed by the media as the first ethnic drug, BiDil is reported to be on the way to becoming the first drug approved by the US Food and Drug Administration to treat heart failure in African-American patients only.<sup>6</sup>

The major implication of BiDil is that differential responses to treatment between racial groups, defined by using ostensibly social categories (here, patients self reported to be African-Americans), are attributed primarily to genetic differences. If this is shown to be true it will undermine a postwar consensus emphasising the social construction of race and ethnicity. Largely social categories of race and ethnicity may be useful indicators of genetic variations because they are at least partly based on biological characteristics. If everyone were the same physically—skin colour and so on—racial and ethnic categories would not exist. This raises fundamental and controversial questions. Do important genetic differences exist between ethnic and racial groups as defined by current classifications? If they do, how good are current racial labels as an indicator of these genetic differences? Should such classifications be used in this way? If so, will race science see a resurgence?<sup>1</sup>

Many researchers and policy makers argue against the use of racial or ethnic categories in medicine, saying that classifying people according to race and ethnicity reinforces existing social divisions in society or leads to discriminatory practices.<sup>7</sup> Others cite

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research showing that genetic differences are greater within socially defined racial groups than between groups.<sup>8</sup> The relation between features that traditionally define race and contribute to ethnicity, such as skin colour, and genetic differences has been found to be inconsistent.<sup>9</sup> In addition, by focusing on biological factors as the explanation for differences in response to drugs, researchers risk ignoring other possible environmental, psychosocial, and economic factors, and lifestyle factors such as diet, that are important in producing illness.<sup>7</sup> If important genetic variations exist between currently defined racial and ethnic groups, drug treatments may be tailored for greater effect.

In a review of the research on the effects of cardiovascular therapies carried out by Taylor and Ellis,<sup>10</sup> the evidence for ethnic variations in response to such drugs seems modest—a conclusion we reached in our own review in July 2004 and presented at the conference in Brisbane.<sup>3</sup> Diuretics were found to be beneficial for both black and white patients with heart failure. Black patients were found to respond equally well to angiotensin receptor blockers, spironolactone, digoxin, and carvedilol ( $\beta$ -adrenoceptor antagonists). Compared with white patients, black patients were found to respond less well to angiotensin converting enzyme inhibitors (enalapril),<sup>10</sup> though this conclusion has been contested. Yu et al showed that Chinese patients required lower dosages of heparin and warfarin than those usually recommended for white patients.<sup>11 12</sup>

The new genetics has reopened the debate on the biological basis of race and ethnicity. Pharmacogenetics is growing fast, and it will lead to a more refined understanding of ethnic and racial differences in drug response. Many claims and counterclaims will be made. Doctors need to take an open minded but critical stance. A historical perspective is likely to be helpful—

claims of a biological basis to racial or ethnic variations in health and disease, including therapeutics, have proved to be overstated.<sup>1</sup>

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Competing interests: RSB was an invited speaker at the 8th world congress on clinical pharmacology and therapeutics, giving a presentation on concepts of ethnicity and race, and his expenses were met by both the congress and the James Lance GlaxoSmithKline Medicines Research Unit in Sydney.

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## Prevalence of asthma

*Is no longer increasing in some countries, but the reasons for this are unclear*

A broad consensus exists that in most Western countries the prevalence of asthma increased over the last four decades of the 20th century. This is based largely on repeat studies of school age children. Evidence is emerging that in recent years this trend has flattened or fallen in some countries. For example, as part of the UK arm of the international study of asthma and allergies in childhood (ISAAC), repeat studies found that self reported symptoms of asthma in 13-14 year old children had fallen by about 20% in the United Kingdom between 1995 and 2002.<sup>1</sup> This trend was also observed in the health survey for England between 1996 and 2001.<sup>2</sup> Over the same period a similar fall in symptoms of asthma in 6-7 year old children reported by parents was seen in Melbourne.<sup>3</sup> On the other hand, the only available repeat survey of preschool children noted a major increase in prevalence between 1990 and 1998.<sup>4</sup> A global picture of recent trends in children will soon be provided by the results of ISAAC phase 3, which has obtained trends in prevalence between 1995 and 2002 in more than 100 centres in 58

countries.<sup>5</sup> Little information exists about long term trends in adults, but recent trends in the UK seem to be flat.<sup>2 6</sup>

These data are limited by the lack of an objective measure of asthma in large populations and the reliance on surveys to elicit symptoms of wheezy breathlessness, which are likely to represent a heterogeneous group of disorders.<sup>7</sup> Questions about lifetime prevalence are subject to serious recall bias, and the usual compromise is to rely on the 12 month period of prevalence in an attempt to capture the intermittent nature of symptoms experienced by most people with asthma, while limiting the recall entailed and avoiding problems with labelling. Trends in the cultural perception and naming of symptoms might explain the trends observed in prevalence studies,<sup>8</sup> and while it remains true that without objective measures we cannot be certain how much is real and how much is artefact it seems unlikely that artefact would completely explain the observed trends.

If the trend is indeed flattening or decreasing, might it be explained by trends in health care? The use