Cooper and Kaufman call attention to the difficulty of evaluating racial predisposition to disease. They correctly point out that “racial” predisposition to pathology is usually taken to imply the existence of an inborn genetic flaw and that there are inherent weaknesses in efforts to date to infer genetic effects from observed phenotypes. It is indeed hazardous, and very likely erroneous, to draw etiologic inferences from observational investigation of racial differences in the prevalence of hypertension. This difficulty results in part because the “exposure,” ie, race or ethnicity, is an inherent trait that is extremely difficult to measure or even define and in part because the outcome, hypertension, is a complex phenotype. Furthermore, observational studies only provide clues to pathogenesis (implying “guilt by association”) and not definitive evidence. Observational epidemiology has never claimed to provide definitive information on the “cause” of disease, using instead the term “risk factor” to describe the observed relationship. However, arguments regarding the existence or absence of racial or ethnic differences must also consider the large body of human genetic research in rarer Mendelian forms of diseases, some of which have been described as being largely restricted to single racial or ethnic populations. It also seems fair to note that if it were not for the data suggesting a familial aggregation of hypertension, as well as a “racial” vulnerability to development and sequelae of hypertension, there would be little enthusiasm for testing these hypotheses by the more definitive currently available molecular genetic techniques.

The best that can be inferred from the evidence for black/white differences in hypertension prevalence or adverse hypertension outcome is that the occurrence of hypertension varies in different subgroups of the population. There is no reason to believe that either blacks or whites are genetically homogeneous. Essential hypertension appears to be a complex phenotype, and its mechanism may vary from person to person. Hypertension has been characterized as a “disease of civilization” resulting from an incompatible interaction between a modern affluent lifestyle and Paleolithic genes. Studies of familial aggregation have demonstrated some evidence of assortative mating, but it is also evident from such studies that genetic factors explain a substantial proportion of the interindividual variability in blood pressure. From segregation analyses and other investigations undertaken during the pregenomics era, it has been difficult to draw consistent conclusions regarding the nature of this genetic link, in part as a result of the heterogeneity of the phenotype.

However, while hypertension is a complex phenotype, it is important to recall that a number of rare Mendelian forms of hypertension have been noted in individual pedigrees. Mutations in more than a dozen genes have been shown to alter blood pressure through alterations in common blood pressure homeostatic pathways in the kidneys. Cooper and Kaufman seem to have overlooked the parallel line of reasoning that would apply to both simple Mendelian disorders and complex genetic diseases. It would indeed be inappropriate to generalize for an entire racial or ethnic group on the basis of the existence of single hypertension mutations that confer susceptibility to blood pressure elevation in single or clustered pedigrees. However, it is also worth asking whether the existing experience with other, somewhat more common, Mendelian diseases such as Tay-Sachs disease, sickle cell anemia, or cystic fibrosis can shed light on this discussion. For example, sickle cell anemia has been reported to occur predominantly in black populations, and other hemoglobinopathies have been described as occurring predominantly in other distinct ethnic groups. Specific genetic mutations have been identified for many of these conditions. Do not arguments made by Cooper and Kaufman regarding the difficulty of defining the phenotype of “race” apply equally to sickle cell anemia? From the available evidence, 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.

Cooper and Kaufman raise important underlying concerns regarding the objectives and potential misuses or even abuses of the results of genetic research. Discovery of sequence variations and functional mutations in disease genes holds the promise of increased understanding of pathogenesis, improved diagnosis, and more effective preventive and therapeutic approaches. Again, in the example of sickle cell anemia, the strong evidence of single genotype to phenotype relationships has led to the availability of sensitive and specific screening tests. Unfortunately, as has become commonplace with genetic research, the development of effective treatments based on the genetic research has lagged. The targeted screening...
programs implemented in the 1970s have been aptly criticized for the appearance of a racial motivation to the screening and for misuse of test results. A more reliable screening program for sickle cell anemia is available now that requirements for mandatory testing have been revised and test quality has been improved. More generally, in anticipation of the explosion of information that will result from the Human Genome Project, the National Institutes of Health and other institutions have begun large-scale programs to identify and address potential ethical, legal, and social implications of human genomics research. Nevertheless, it should be apparent that the logical extension of the argument of Cooper and Kaufman appears to be that genetic investigators studying rare, population-wide Mendelian diseases should disregard the possibility of a racial or ethnic susceptibility and that clinicians, patients, and policy makers should disregard racial background in the use of screening tests.

Regarding more common complex diseases such as hypertension, although animal models suggest that a limited number of genes may play the major role in determining hypertension, we are still early in the process of gene discovery. The complexity of the phenotype increases the difficulty of ascertaining genetic effects in subgroups but does not invalidate the possibility that scientific discovery might follow from study of population subgroups, even those defined by “essential” attributes, such as race or gender. Included among the parallel approaches for gene discovery are genome screening as well as the study of candidate gene variants identified from blood pressure discovery. The complexity of the phenotype increases the number of genes that might play a role in most illness, even infectious disease. The human response to any noxious influence is variable, some being exquisitely sensitive and others resistant. Differences in the robustness of universal pathways of blood pressure regulation, rather than uniquely different mechanisms, seem likely. Does this occur in population subgroups as well as individuals? It probably does if there is geographic isolation of population subgroups or inbreeding.

Hypertension appears to be only one component of a more complex syndrome of insulin resistance. It occurs in isolation from other atherogenic traits only approximately 20% of the time. Genetic investigation of this clustering in hypertension also may provide valuable insights for both blacks and whites.

As a population subgroup, blacks appear more prone to hypertension. However, the answer to the question posed by Cooper and Kaufman, “Can available research methods lead to valid inferences when race is regarded as an etiologic quantity, rather than a broad indicator of risk factor status?” is clearly no! Race is only a “risk factor” for the condition and one cannot infer causality. Risk factors are more likely to be causal if they precede the disease, are strong and dose related, lose their impact when corrected, are independent of associated conditions, and are biologically plausible. It is virtually impossible to put race, gender, or age to this test. It is also difficult to study a factor such as race that cannot be measured accurately or even defined. It is true that controlling for socioeconomic status is difficult and even may be inappropriate in evaluating the race/hypertension hypothesis. Adjustment for social and environmental stress, coping practices, diet, pattern of obesity, alcohol intake, and exercise is not only difficult but may not be the right thing to do. Rather, we should be examining whether some blacks (or whites or other population subgroups) are more susceptible to the blood pressure–raising influence of weight gain, salt loading, and insulin resistance.

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