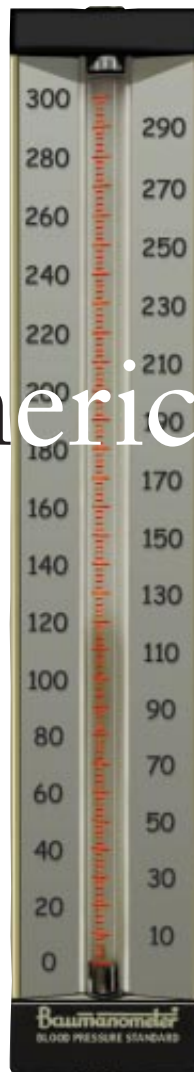


The Puzzle of Hypertension in African-Americans

by Richard S. Cooper, Charles N. Rotimi and Ryk Ward

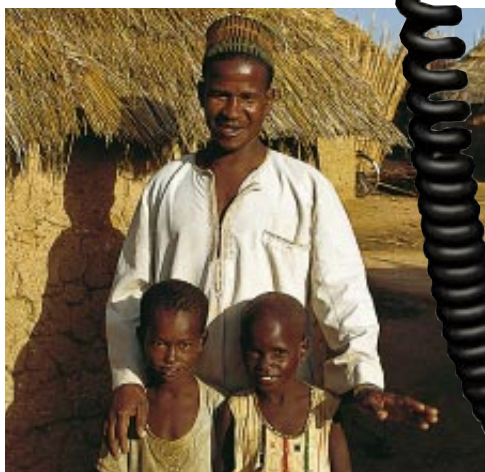
Nearly all Americans undergo a steady rise in blood pressure with age. Almost 25 percent cross the line into hypertension, the technical term for chronically high blood pressure. This condition, in turn, can silently contribute to heart disease, stroke and kidney failure and thus plays a part in some 500,000 deaths every year. For black Americans, the situation is even more dire: 35 percent suffer from hypertension. Worse, the ailment is particularly deadly in this population,



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Genes are often invoked to account for why high blood pressure is so common among African-Americans. Yet the rates are low in Africans. This discrepancy demonstrates how genes and the environment interact

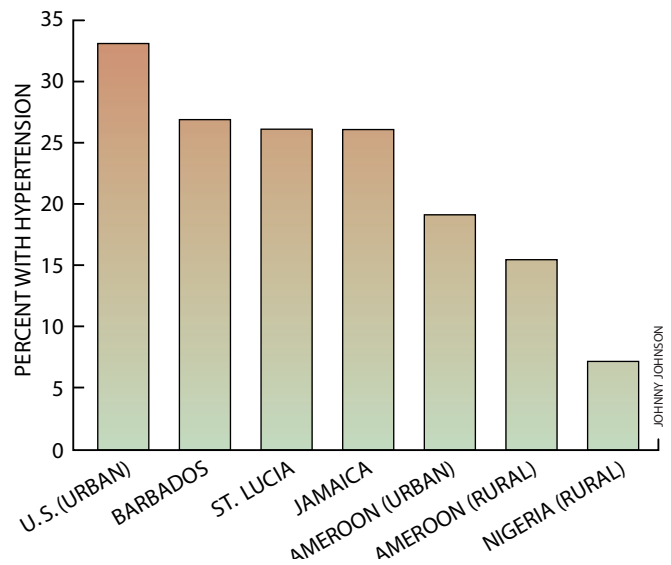
accounting for 20 percent of deaths among blacks in the U.S.—twice the figure for whites.

One popular explanation of this disparity between blacks and whites holds that people of African descent are “intrinsically susceptible” to high blood pressure because of some vaguely defined aspect of their genetic makeup. This conclusion is not satisfying. Indeed, the answer troubles us, for as we will show, it does not reflect the available evidence accurately. Instead such reasoning appears to follow from the racialized character of much public health research, which at times defaults to reductionist interpretations that emphasize the importance of racial or genetic characteristics. Race be-

comes the underlying cause for the presence of a disease, rather than being recognized as a proxy for many other variables (along the lines of, say, socioeconomic status) that influence the course of a disorder.

We suggest that a more fruitful approach to understanding the high levels of hypertension among African-Americans would begin by abandoning conventional hypotheses about

INCIDENCE OF HYPERTENSION, or chronic high blood pressure, was assessed by the authors in Africans as well as in people of African descent in the U.S. and the Caribbean. The rate dropped dramatically from the U.S. across the Atlantic to Africa (*graph*), and the difference was most pronounced between urban African-Americans (*below, right*) and rural Nigerians (*below, left*). The findings suggest that hypertension may largely be a disease of modern life and that genes alone do not account for the high rates of hypertension in African-Americans.



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What Pressure Readings Mean

Blood pressure is measured with a sphygmomanometer, which gives a reading of two numbers: systolic and diastolic pressure. The systolic reading indicates the maximum pressure exerted by the blood on the arterial walls; this high point occurs when the left ventricle of the heart contracts, forcing blood through the arteries. Diastolic pressure is a measure of the lowest pressure on the blood vessel walls and happens when the left ventricle relaxes and refills with blood. Healthy blood pressure is considered to be around 120 millimeters of mercury systolic, 80 millimeters of mercury diastolic (usually presented as 120/80).

Many people can experience temporary increases in blood pressure, particularly under stressful conditions. When blood pressure is consistently above 140/90, however, physicians diagnose hypertension. The disorder can generally be managed with the help of special diets, exercise regimens and medication. —*The Editors*



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race. It would acknowledge that hypertension arises through many different pathways, involving complex interactions among external factors (such as stress or diet), internal physiology (the biological systems that regulate blood pressure) and the genes involved in controlling blood pressure. Only by teasing out the connections among all three tiers of this model will scientists truly comprehend how high blood pressure develops. This knowledge will then enable researchers to return successfully to the questions of why the disorder is so prevalent among African-Americans and how best to intervene for all patients.

One strategy for clarifying the relative significance of different environmental factors would be to hold constant the genetic background of people in distinct environments and focus on the variations in their living conditions or behavior. This kind of experiment is impossible to do perfectly, particularly when vast numbers of Americans have at least one, and frequently several, of the known behavioral risk factors for developing high blood pressure: being overweight, eating a high-salt diet, suffering long-term psychological stress,

being physically inactive and drinking alcohol to excess. In a way, the situation is analogous to trying to identify the causes of lung cancer in a society where everyone smokes; without having nonsmokers for a comparison group, researchers would never know that smoking contributes so profoundly to lung cancer.

Lessons from the Past

Our solution to this dilemma was to turn to Africa. In 1991 we initiated a research project concentrated on the African diaspora, the forced migration of West Africans between the 16th and 19th centuries. In this shameful chapter of world history, European slave traders on the west coast of Africa purchased or captured an estimated 10 million people and transported them to the Caribbean and the Americas, where they gradually mixed with Europeans and Native Americans. Today their descendants live throughout the Western Hemisphere.

Scientists have known for some time that the rate of hypertension in rural West Africa is lower than in any other place in the world, except for some

parts of the Amazon basin and the South Pacific. People of African descent in the U.S. and the U.K., on the other hand, have among the highest rates of hypertension in the world. This shift suggests that something about the surroundings or way of life of European and American blacks—rather than a genetic factor—was the fundamental cause of their altered susceptibility to high blood pressure.

To elucidate what was triggering hypertension among these people, we established research facilities in communities in Nigeria, Cameroon, Zimbabwe, St. Lucia, Barbados, Jamaica and the U.S. As the project progressed, we focused our attention on Nigeria, Jamaica and the U.S. as the three countries that allow us, in a sense, to capture the medical effects of the westward movement of Africans from their native lands. We conducted testing of randomly sampled people at each location to determine the general prevalence of both hypertension and its common risk factors, such as eating a high-salt diet or being obese or physically inactive.

As might be expected, the differences between the three societies are vast. The Nigerian community we surveyed, with the help of colleagues at the University of Ibadan Medical School, is a rural one in the district of Igbo-Ora. Polygamy is a common practice there, so families tend to be complex and large; on average, women raise five children. The residents of Igbo-Ora are typically lean, engage in physically demanding subsistence farming and eat the traditional Nigerian diet of rice, tubers and fruit.

Nations in sub-Saharan Africa do not keep formal records on mortality and life expectancy, but based on local studies, we assume that infection, especially malaria, is the major killer. Our research revealed that adults in Igbo-Ora have an annual mortality risk of between 1 and 2 percent—high by any Western standard. Those who do survive to older ages tend to be quite healthy. In particular, blood pressure does not rise with age, and even though hypertension does occur, it is rare. (We were pleased that we could coordinate with the established medical personnel in the region to treat those patients who did suffer from hypertension.)

Jamaica, in contrast, is an emerging industrial economy in which the risk of infectious disease is very low but the levels of chronic disease are higher than

in Nigeria. The base of operations for our team was Spanish Town, the original colonial capital of Jamaica. A bustling city of 90,000 people, Spanish Town features a cross section of Jamaican society. Investigators at the Tropical Metabolism Research Unit of the University of the West Indies, Mona Campus, led the project.

The family structure in Jamaica has evolved away from the patriarchy of Africa. Women head a significant number of households, which are generally small and often fragmented. Chronic unemployment has tended to marginalize men and lower their social position. Farming and other physically demanding occupations are common; residents' diets include a blend of local foodstuffs and modern commercial products. Despite widespread poverty, life expectancy in Jamaica is six years longer than it is for blacks in the U.S. because of lower rates of cardiovascular disease and cancer.

In the metropolitan Chicago area, we worked in the primarily African-American city of Maywood. Many of the older adults in this community were born in the southern U.S., primarily in Mississippi, Alabama or Arkansas. Interestingly, the northern migration seems to have greatly improved both the health and the economic standing of these people. Unionized jobs in heavy industry provide the best opportunities for men, whereas women have been integrated into the workforce across a range of job categories. The prevailing diet is typical American fare: high in fat and salt. The generation now reaching late adulthood has enjoyed substantial increases in life expectancy, although progress has been uneven in the past decade.

Similarities and Differences

Even as we sought out these examples of contrasting cultures, we were careful to make sure the people we studied had similar genetic backgrounds. We found that the American and Jamaican blacks who participated shared, on average, 75 percent of their genetic heritage with the Nigerians. Against this common genetic background, a number of important differences stood out.

First, the rates of hypertension: just 7 percent of the group in rural Nigeria had high blood pressure, with increased rates noted in urban areas. Around 26 percent of the black Jamaicans and 33

percent of the black Americans surveyed were either suffering from hypertension or already taking medication to lower their blood pressure. In addition, certain risk factors for high blood pressure became more common as we moved across the Atlantic. Body mass index, a measure of weight relative to height, went up steadily from Africa to Jamaica to the U.S., as did average salt intake. Our analysis of these data suggests that being overweight, and the associated lack of exercise and poor diet, explains between 40 and 50 percent of the increased risk for hypertension that African-Americans face compared with Nigerians. Variations in dietary salt intake are likely to contribute to the excess risk as well.

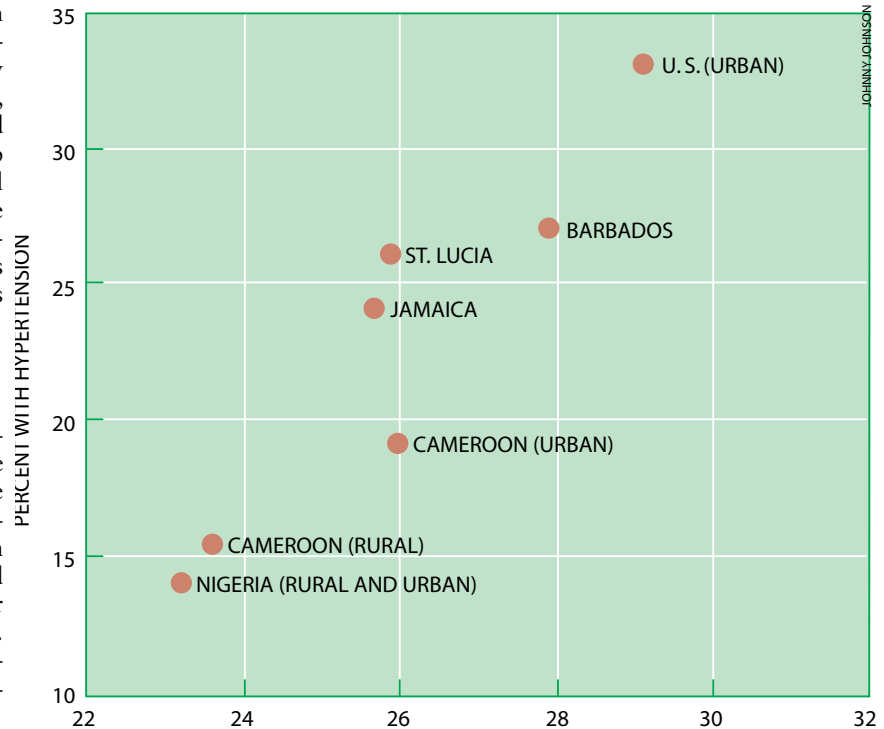
The African diaspora has turned out to be a powerful tool for evaluating the effects of a changing society and environment on a relatively stable gene pool. Our study also raises the question of whether rising blood pressure is a nearly unavoidable hazard of modern

life for people of all skin colors. The human cardiovascular system evolved in the geographic setting of rural Africa in which obesity was uncommon, salt intake was moderate, the diet was low in fat, and high levels of physical activity were required. The life of subsistence farmers in Africa today has not, at least in these respects, changed all that much. We see that for people living this

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way, blood pressure hardly rises with age and atherosclerosis is virtually unknown. As a result, the African farmers provide epidemiologists with a revealing control group that can be compared with populations living in more modernized societies.

It is disquieting to recognize that a modest shift from these baseline conditions leads to sizable changes in the risk for hypertension. For instance, blood pressures are substantially higher in the



BODY MASS INDEX, or BMI, measures a person's weight-to-height ratio; a BMI over 25 is generally considered a sign of being overweight. In the authors' study of people of African descent, a low average BMI in a population corresponded to a low rate of hypertension in that community. As average BMI increased, so did the prevalence of hypertension. The findings support the view that obesity contributes to high blood pressure.

city of Ibadan, Nigeria, than in nearby rural areas, despite small differences in the groups' overall levels of obesity and sodium intake. Other variables, such as psychological stress and lack of physical activity, may help account for this increase.

Psychological and social stresses are extremely difficult to measure, especially across cultures. Yet there is little dispute that blacks in North America and Europe face a unique kind of stress—racial discrimination. The long-term effects of racism on blood pressure remain unknown; however, it is worth noting that blacks in certain parts of the Caribbean, including Trinidad, Cuba and rural Puerto Rico, have average blood pressures that are nearly the same as those of other racial groups. Although this is no more than con-

jecture, perhaps the relationships among races in those societies impose fewer insults on the cardiovascular system than those in the continental U.S. do.

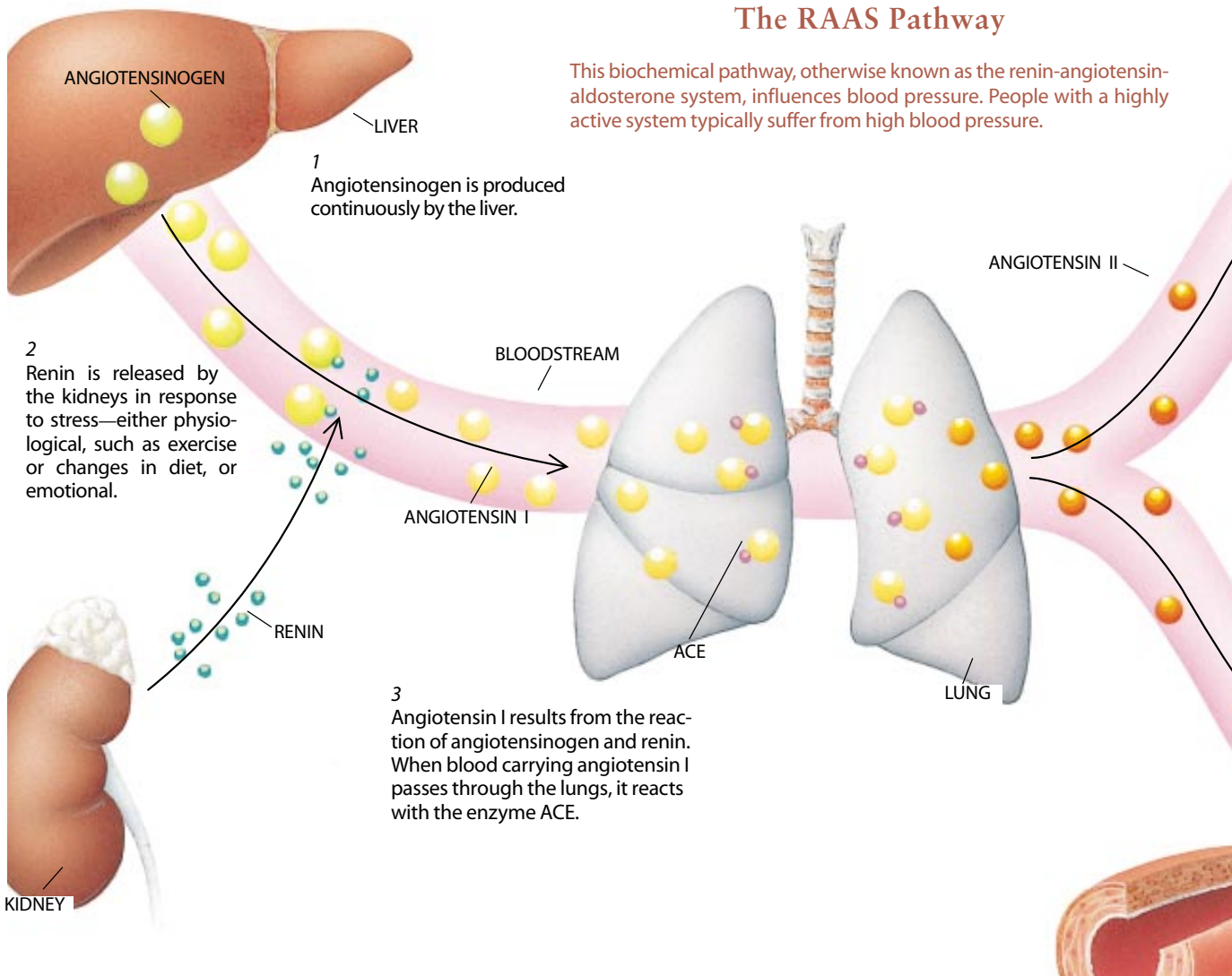
Environment at Work

As epidemiologists, we want to move beyond these descriptive findings of what might increase people's risk for hypertension and examine more closely how environmental and biological risk factors interact to produce the disease. Physiologists have not yet uncovered every detail of how the body regulates blood pressure. Nevertheless, they know that the kidneys play a key role, by controlling the concentration in the bloodstream of sodium ions (derived from table salt—sodium chloride—in the diet), which in turn influ-

ences blood volume and blood pressure.

Having evolved when the human diet was habitually low in sodium, the kidneys developed an enormous capacity to retain this vital ion. As these organs filter waste from the blood, they routinely hold on to as much as 98 percent of the sodium that passes through, then eventually return the ion to the bloodstream. When doused with sodium, however, the kidneys will excrete excessive amounts into the blood, thereby elevating blood pressure. Too much salt in the kidneys can also harm their internal filtering mechanism, leading to a sustained rise in pressure.

As a gauge of how well the organs were modulating the body's sodium balance in our patients, we decided to measure the activity of an important biochemical pathway that helps to reg-



TOMO NARASHIMA

ulate blood pressure. Known as the renin-angiotensin-aldosterone system, or RAAS, this intricate series of chemical reactions (named for three of the compounds involved) has the net effect of controlling the amount of the protein angiotensin II present in the bloodstream. Angiotensin II performs a range of functions, such as prompting the constriction of blood vessels, which causes a rise in blood pressure, and triggering the release of another crucial chemical, aldosterone, which induces an increase in the reuptake of sodium by the kidneys. In short, a highly active RAAS pathway should correlate with elevated blood pressure.

As a convenient method for tracing the activity of RAAS in our patients, we measured the amount of the compound angiotensinogen—one of the chemicals

involved in the first step of RAAS [*see illustration below*]*—*present in blood samples. One advantage to measuring angiotensinogen is that unlike other, short-lived compounds in the pathway, it circulates at a relatively constant level in the bloodstream.

As expected, we found that in general the higher angiotensinogen levels are, the higher blood pressure is likely to be, although this association is not as strong for women (variations in estrogen also appear to affect a woman's blood pressure). Further, the average level of angiotensinogen for each group we studied increased substantially as we moved from Nigeria to Jamaica to the U.S., just as the rate of hypertension did; that pattern was found in both men and women.

Our results suggest that some of the risk factors for hypertension might promote the disorder by elevating levels of angiotensinogen in the blood. Obesity, in particular, may contribute to chronic high blood pressure in this way. Excessive body fat, for instance, has been shown to correspond to an elevation in an individual's circulating level of angiotensinogen. And the incidence of obesity rose more or less in parallel with levels of hypertension and angiotensinogen in our study groups. Correlations do not necessarily prove causality, of course, but the collected findings do hint that obesity promotes hypertension at least in part by leading to enhanced angiotensinogen production.

Clues in the Genes

Genetic findings seem to lend some support to a role for excess angiotensinogen in the development of hypertension. Scientists have found that some people carry certain variations of the gene for producing angiotensinogen (these variations in genes are known as alleles) that give rise to elevated levels of the protein. Intriguingly, people with these alleles tend to have a higher risk of developing high blood pressure.

Several years ago researchers at the University of Utah and the Collège de France in Paris reported that two alleles of the angiotensinogen gene, known as 235T and 174M, correlated with high levels of circulating angiotensinogen—as well as with hypertension—among people of European descent. The scientists do not know, however, whether these

alleles themselves play a part in controlling angiotensinogen levels or are merely markers inherited along with other alleles that have more of an effect.

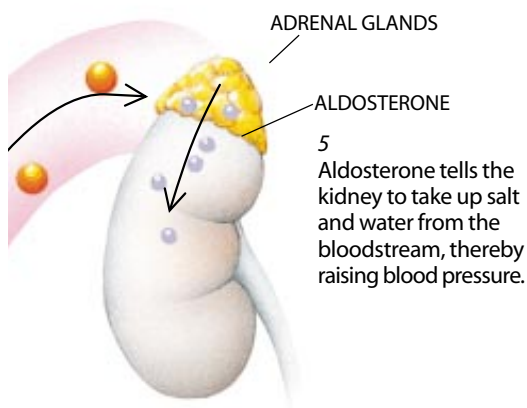
We must emphasize that identification of a gene associated with greater susceptibility to hypertension is not equivalent to finding the cause of the condition. Nor is it equivalent to saying that

The destructive effects of racism complicate any study of how a disease such as hypertension affects minority groups.

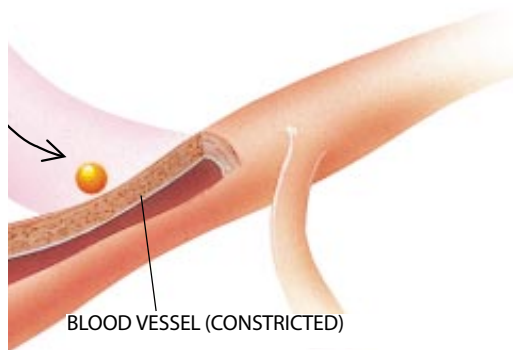
certain groups with the gene are fated to become hypertensive. Investigators have determined that genetic factors account for 25 to 40 percent of the variability in blood pressure between people and that many genes—perhaps as many as 10 or 15—can play a part in this variation. Those numbers indicate, then, that an isolated gene contributes only about 2 to 4 percent of the differences in blood pressure among people. And whether genes promote the development of hypertension depends considerably on whether the environmental influences needed to “express” those hypertension-causing traits are present.

Our own genetic findings seem to illustrate this point. In a quite perplexing discovery, we found that the 235T allele is twice as common among African-Americans as it is among European-Americans but that blacks with this form of the gene do not seem to be at an increased risk for hypertension compared with other blacks who do not carry the gene. Among the Nigerians in our study, we did see a modest elevation in levels of angiotensinogen in those with the 235T gene variant; again, however, this factor did not translate into a higher risk for hypertension. Furthermore, 90 percent of the Africans we tested carried the 235T allele, yet the rate of hypertension in this community is, as noted earlier, extremely low. (The frequency of the 174M allele was equivalent in all groups.)

It may well be that high angiotensinogen levels are not sufficient to trigger hypertension in people of African descent; rather other factors—genetic, physiological or environmental—may also be needed to induce the disorder. Alterna-



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Angiotensin II results from the reaction of angiotensin I and ACE. Angiotensin II has two primary effects. It prompts the adrenal glands to release aldosterone, and it causes smooth muscle in blood vessels to contract, which raises blood pressure.



tively, this particular allele may not be equally important in the development of hypertension for all ethnic groups.

Pieces of the Puzzle

Although our results reveal at least one aspect of how nurture may interact with nature to alter a person's physiology and thereby produce hypertension, the findings also highlight the pitfalls of making sweeping generalizations. Clearly, no single allele and no single environmental factor can explain why hypertension occurs and why it is so common in African-Americans. An individual with a given mix of alleles may be susceptible to high blood pressure, but as our research on the African diaspora emphasizes, that person will develop hypertension only in a certain setting. The continuing challenge for researchers is to isolate specific genetic and environmental effects on hypertension and then put the pieces back together to determine the myriad ways these factors can conspire to cause chronic elevations of blood pressure.

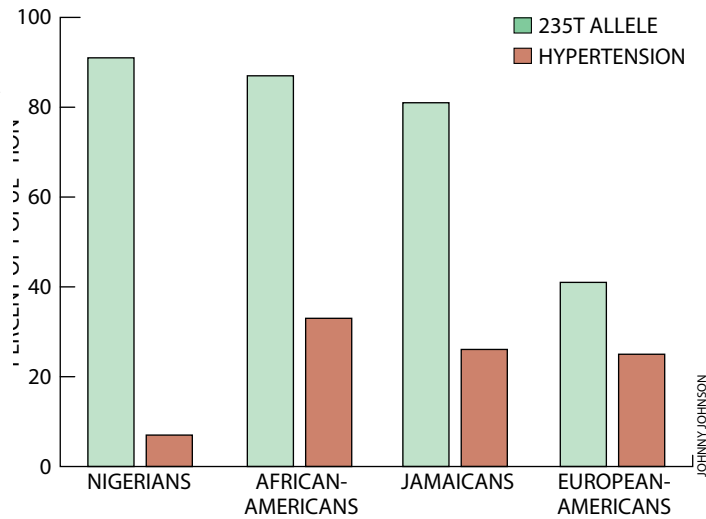
Hypertension currently accounts for approximately 7 percent of all deaths worldwide, and this figure will no doubt increase as more societies adopt the habits and lifestyle of industrial nations. There is no returning to our evolutionary home-

land, so science must lead us forward to another solution. The sanitary revolution was born of the awareness of contagion. Heart disease became a tractable problem when researchers recognized the importance of lifetime dietary habits on cholesterol metabolism. Prevention and treatment of hypertension will require a fuller appreciation of how genes and the environment join forces to disrupt blood pressure regulation.

We also believe that to understand hypertension in African-Americans better, the scientific community should reevaluate what the ethnic and racial divisions of our species mean. Many disci-

plines hold that there is no biological basis to the concept of race; instead they view it as a reflection of societal distinctions rather than readily defined scientific ones. Physical anthropologists, for instance, long ago ceased their attempts to classify *Homo sapiens* into various races, or subspecies. The disciplines of medicine and epidemiology, however, continue to ascribe biological meaning to racial designations, arguing that race is useful not only for distinguishing between groups of people but also for explaining the prevalence of certain disorders. Yet the racial classifications they incorporate in their studies are not based on rigorous scientific criteria but instead on bureaucratic categories, such as those used in the U.S. census.

As researchers grapple with the scientific import of race, its societal meaning must not be forgotten. We live in a world in which racial designations assume unfortunate significance. The destructive effects of racism complicate any study of how a disease such as hypertension affects minority groups. But as we continue to explore the complex interactions between external risk factors, such as stress and obesity, and the genes associated with the regulation of blood pressure, the results should offer guidance for all of us, regardless of skin color.



RATES OF A PARTICULAR GENE VARIANT—235T—and of hypertension in different ethnic groups yield a puzzling picture. Scientists expected that people who carried 235T would have a high incidence of hypertension. Yet that association has not held true universally. For instance, 235T is very common in Nigerians, in whom high blood pressure is rare. The findings suggest that a single gene cannot control the development of high blood pressure.

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