HYPERTENSION IN AFRICAN AMERICANS

A Challenge for the 21st Century

INTERNAL MEDICINE GRAND ROUNDS

December 10, 1998

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Dr. Victor's basic and clinical research focuses on hypertension in special populations including African-Americans, patients with chronic renal failure, and those with Cyclosporine-induced immunosuppression. Other projects in his laboratory study mechanisms underlying obesity-related hypertension, cocaine-induced hypertensive crisis, and local metabolic modulation of alpha-adrenergic receptor signaling in skeletal muscle.

Disclosure Statement: This is to ackowledge that Ronald Victor, MD has disclosed that he has no financial interests or other relationships with commercial concerns related directly or indirectly to this program.

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A. Introduction

The tradition is to begin grand rounds by presenting an illustrative patient. I am going to begin by presenting the case of an entire community. The community is Harlem, a low-income urban African-American section of New York City. In 1980, a Caucasian male in this country had a >70% chance of surviving to age 65 Y, whereas the chances of an African-American male living in Harlem had only a 35% chance of enjoying the same longevity[1]. The latter was worse than survival statistics in Bangladesh, an impoverished third world country. Similar trends were noted for women. For the entire country, average life expectancies are lower in African-Americans than Caucasians: 63 vs. 72 Y for men and 71 vs. 79 Y for women.[2]

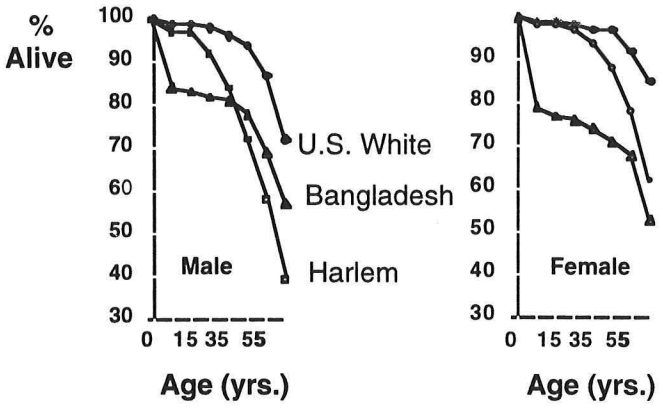

Figure 1. Survival to age 65 in Harlem in 1979-1981. From McCord and Freeman *N EJM* 1990.

The major cause of the excessive mortality in Harlem is not violent crimes but rather cardiovascular disease. This has been confirmed independently ten years later, even after the advent of AIDS.[3] In 1998, cardiovascular disease remains a major cause of death in African-Americans throughout the United States.[4-8]

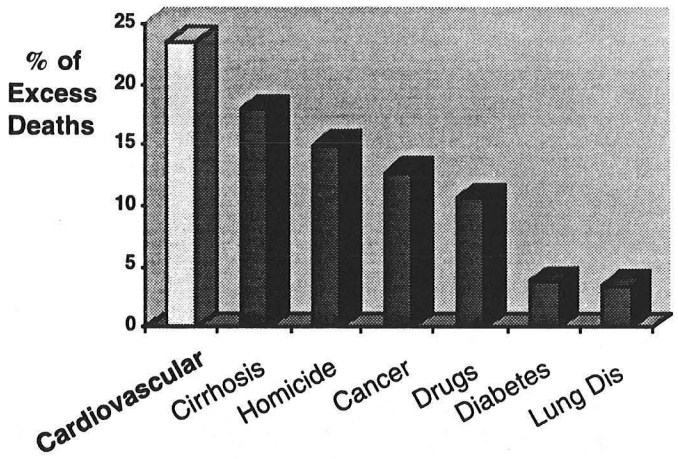

Figure 2. Causes of excess mortality in harlem. From McCord and Freeman, *NEJM* 1990.

Hypertension is by far the number one cause of heart disease and therefore the number one cause of premature death and disability among African-Americans.[4-13] In contrast, coronary artery disease (CAD) is the number one cause of heart disease in Caucasians, and it appears to be less prevalent in African-Americans.[4-8] Consistent with this notion, a recent autopsy study in New York City indicates that hypertension without CAD is the major cause of a non-violent deaths among African-Americans, whereas CAD is the major cause of death among Caucasians.[14]

Hypertension is an enormous public health problem among African Americans. Compared with Caucasians and all other ethnic groups in this country, hypertension is more prevalent in African-Americans, it starts at an earlier age, is more difficult to treat, and causes much more death and disability from heart failure, stroke, and kidney failure. Despite the enormity of this problem, there are large gaps in our scientific understanding at every level, from molecular genetics to clinical practice.

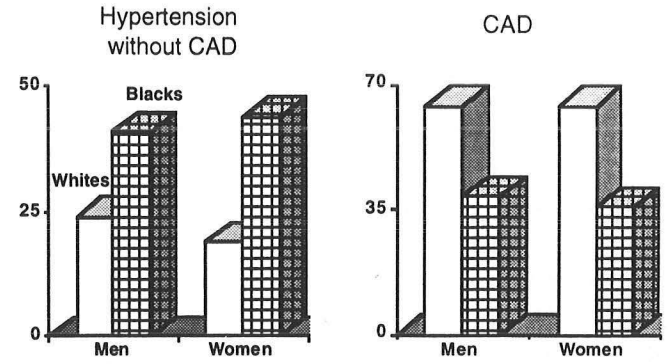

Figure 3. Causes of non-violent death in 586 adults in New York City: an autopsy study. From A Onwuanyi et al., *Hypertension* 1998.

I believe this problem has been understudied for several reasons. First, primary hypertension is a complex polygenic illness with major gene-environment interactions. Second, African-Americans are under-represented both as subjects in clinical investigation and as clinician-investigators in departments of medicine. Third, any discussion of ethnic differences touches on sensitive issues.

The aim of this grand rounds is to critically review what is currently known and what is not known about hypertension in African-Americans and to highlight some of our efforts and plans at UT Southwestern to fill in some of the large gaps in our understanding of this problem. This is a major challenge for the 21st century.

B. Prevalence of Hypertension

In 1932, James M. Adams, an industrial physician in New Orleans, was the first to report ethnic differences in the prevalence of hypertension.[15] He found that blood pressures were higher in African-American compared with Caucasian workmen and that the African-American workmen missed twice as many days from work due to chronic heart disease and kidney disease. In the Bogalusa Heart Study of school-age children, blood pressures of African-American boys and girls were a few mmHg higher at every age group than of white boys and girls, suggesting that ethnic differences begin in childhood.[16] However, the ethnic difference in blood pressure become most apparent after high school.[17]

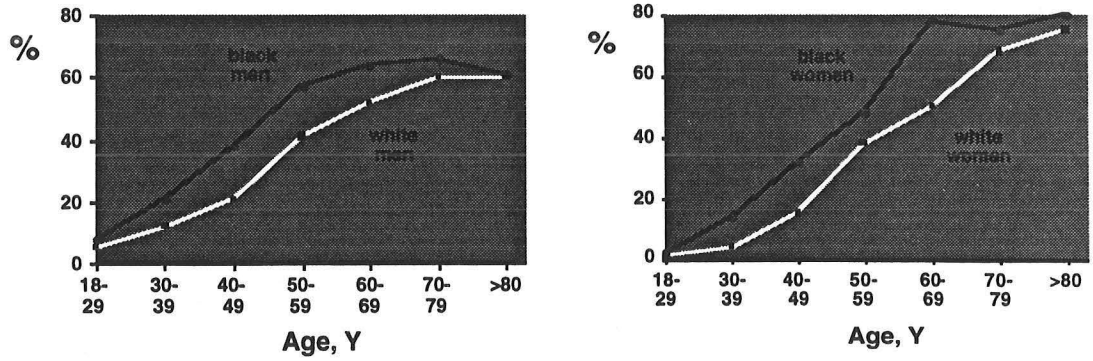

Figure 4. Prevalence of hypertension in African-American and Caucasian men and women(NHANES III: 1989-1991). From Burt et al., *Hypertension* 1995.

Currently, the overall prevalence of hypertension (BP ≥ 140/90 mmHg) is 40 % higher in African-Americans vs. Caucasians: 34 vs. 21%.[17] In addition, the severity of the hypertension is greater in African-Americans, particularly in African-American women: ~ 1/5 of Caucasian men and women and African-American men have BPs >165/95 mmHg compared with >1/3 of African-American women.[18]

Unlike primary hypertension, renovascular hypertension appears to be less prevalent in African-Americans than in Caucasians.[19,20] An earlier surgical literature in the 1970s suggested that renal artery stenosis is so infrequent among African Americans that there is no need to search for this diagnosis in hypertensive African-Americans.[21] More recent studies indicate that this ethnic difference has been overstated. In patients referred to hypertension specialists for refractory hypertension, renal artery stenosis, the most common secondary cause of the hypertension, is present in about 25% of the Caucasians compared with 12-18% of the African-Americans.[19,20] The important point is that, while renal artery stenosis indeed appears to be less prevalent in African-Americans than Caucasians with refractory hypertension, the prevalence is not zero and the diagnosis must be considered.

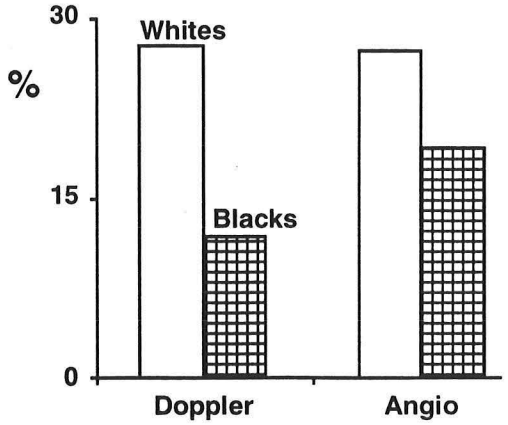

Figure 5. Prevalence of renal artery stneosis in patients with refractory hypertension. From Hansen et al. *Am J Med Sci* 1998;Svetkey et al. *Hypertension* 1991.

C. Control of Hypertension

Currently, there are 50 million Americans with hypertension, and 6 million of these are African-American.[13,17]

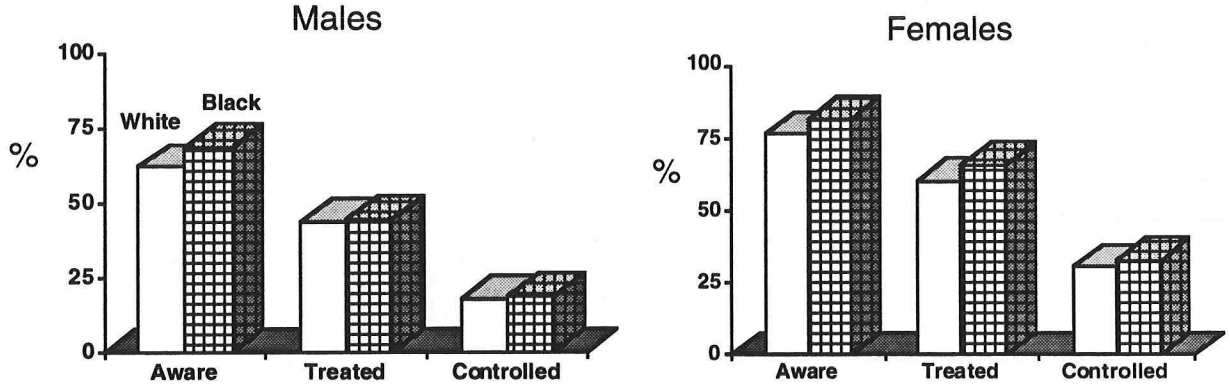

Figure 6. Data from HANES III: 1989-1991. From Burt et al., *Hypertension* 1995.

Of these millions of hypertensives, one-third are unaware of their diagnosis, almost one-half are under no form of treatment, and only one-quarter have there pressures adequately controlled (BP < 140/90 mmHg) with diet and medications.[17] All these figures are worse for men than women. Although there a no clear ethnic differences in these disturbing figures, the consequences of inadequately controlled blood pressure are much worse in African-Americans.

D. Ethnic Gap in Target Organ Disease

While hypertension remains more prevalent in African-Americans than Caucasians,[17] the most striking disparity is the disproportionate hypertensive target organ damage in African Americans. [4-13] The discrepancy is particularly evident in the "expanded stroke belt,"[22,23] which includes the Southeastern United States and Texas. The overall death rates from hypertensive stroke and hypertensive heart disease are 1.8 and 1.5 times greater and the occurrence of hypertensive nephrosclerosis causing end-stage kidney disease is 5 times greater in African-Americans than Caucasians.[5-8]In the MRFIT (Multiple Risk Factor Intervention Trial) Study, in both African-American and Caucasian men the 16-year incidence of end-stage renal disease increased with both blood pressure and socioeconomic status.[24] However, at every level of blood pressure and at every level of socioeconomic status, African-Americans had still had a 2-fold higher risk of developing end-stage renal disease. The AASK (African-American Study of Kidney Disease) Trial, directed at UT Southwestern by Dr. John Middleton, is a large prospective study designed to determine if aggressive treatment of hypertension can halt the progression of renal disease in African-Americans.

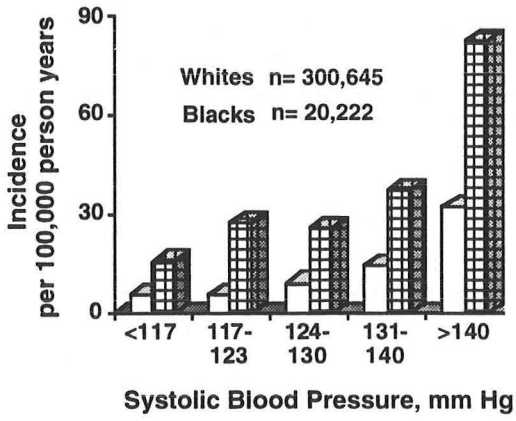

Figure 7. 16-Y incidence of end-stage renal disease in MRFIT. FromMJ Klag et al *JAMA* 1997.

When hypertensive African-Americans and Caucasians are matched for equivalent blood pressures, age, gender, and adiposity, the prevalence of electrocardiographic LVH is consistently several times greater in the African-Americans;[4,5,9] however, EKG criteria may lead to an over-estimation of racial differences in the true prevalence of LVH.[25] In a head-to-head comparison of ECG vs. echocardiographic criteria, the prevalence of LVH was estimated to be 2-6 fold higher in blacks vs. whites by ECG but indistinguishable by echocardiography (26 vs. 20 %).[25] However, another study came to the opposite conclusion, providing echocardiographic evidence for increased left ventricular wall thickness and mass in untreated black vs. white hypertensives.[26] Echocardiographic LVH is one of the most powerful independent risk factors for coronary heart disease events in Caucasian adults;[27] however, there are no such data available in African-Americans. The presence of even EKG-LVH confers a 2-9 fold increased risk of stroke, heart failure, claudication, and fatal and nonfatal myocardial infarction, and overall mortality.[28] LVH is almost certainly part of the explanation why hypertension is a much

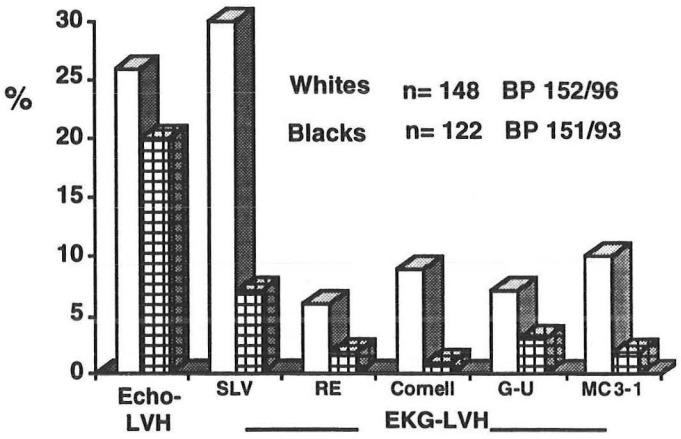

Figure 8. Prevalence of LVH as assessed by echocardiographic and various EKG criteria on the same cohort of hypertensive patients. From DK Lee et al *JAMA* 1992.

more frequent cause of heart failure in African-Americans, accounting for 32% of heart failure cases vs. 4% in Caucasians.[29] While diastolic dysfunction from hypertension is common in all ethnic groups, hypertension leads to much more systolic dysfunction in African-Americans.[4,5 29.]

Blood pressure normally falls during sleep, but, in some hypertensives the nocturnal dip in blood pressure is attenuated or lost.[30] Non-dippers are predisposed to LVH, presumably because of the more prolonged exposure of the cardiovascular system to high blood pressure over each 24 hour period. Several but by no means all studies have suggested that the greater prevalence of LVH in black hypertensives is related to a greater prevalence of "non-dipping."[31-34] Blood pressure reactivity to stressors (e.g., cold pressor test) also is said to be greater in African-Americans;[9,33] however, this may be related more to a family history of hypertension rather than ethnicity.[34]

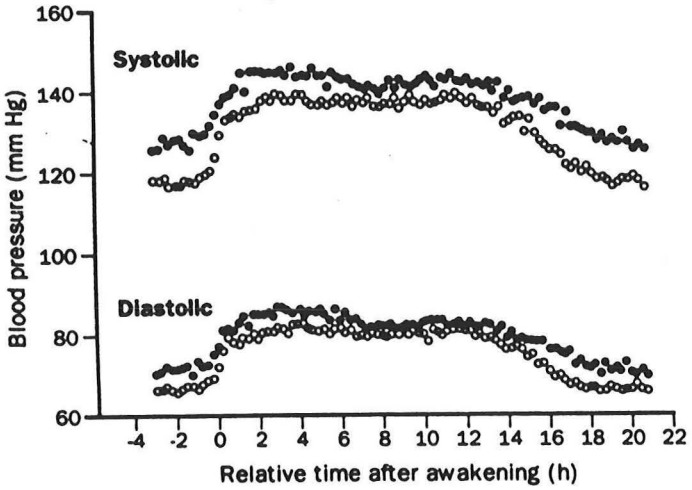

Figure 9. Smaller nocturnal dip in blood pressure in untreated hypertensive African-Americans compared with Caucasians. From DD Gretler et al., *Am J Hypertens* 1994.

III. Candidate Genes

To explain the higher blood pressures and greater target organ damage in African-Americans, the question of whether the underlying mechanism involves mainly genes or environment has been the subject of considerable debate.[35,36] Some academicians, have called into question the entire issue of racial differences as a valid topic for scientific inquiry.[35,37] The issue is not "black or "white," and a more useful paradigm is to view primary hypertension as a polygenic disorder with major gene-environment interactions.[38] Investigations focusing on certain segments of the population with the greatest risk of developing hypertension and its consequences is a valid strategy for improving our understanding of the pathogenesis of primary hypertension in the general population.[39]

Defn of +FHX	% with +FHX	20-39 Y	60-69 Y
≥ 1 Affected	53	2.5	1.2
≥ 1 Before age 55 Y	32	2.8	1.1
≥ 2 Affected	24	3.8	1.2
≥ 2 Before age 55 Y	11	4.1	1.0

Figure 10. Definitions of "positive family history" and the prevlance of hypertension. Data are from a 13-year follow up in a restrospective cohort of 94,292 persons in 15,200 Utah families. From Hunt and Williams, In Hypertension Primer, 1998

Blood pressure aggregates in families in a "dose-dependent" manner: the stronger a person's the family history of hypertension the greater the risk of developing the disease.[39,40] Thus, a thorough family history is important is estimating a person's risk. The Utah group estimates that genetics accounts for ~ 70% of the familial aggregation of blood pressure, which fuels the search for hypertension candidate genes.[39]

Blood pressure is the product of cardiac output times systemic vascular resistance. Hypertension could be caused by both (a) an increase in the gain of mechanisms causing increased plasma volume and increased peripheral vasomotor tone, and (b) a decrease in the gain of mechanisms causing decreased plasma volume and decreased vasomotor tone. To explain the greater prevalence and severity of hypertension in African-Americans include, putative candidate genes include those encoding components of epithelial sodium channels,[41,42] the renin-angiotensin system,[43-48]alpha-adrenergic receptors,[49] endothelin and endothelin receptors, kallikrein,[50] natriuretic peptides and their receptors,[51] beta-adrenergic receptors,[52] and the nitric oxide pathway.[53] This work is in its infancy and I will discuss only the two best candidate genes for hypertension in African-Americans.

BP = CO x SVR

↑ Plasma Volume / Vasoconstriction	↓ Plasma Volume / Vasodilation
■ Endothelial Sodium Channel (ENAC)	■ Kallikrein
■ Renin-Angiotensin	■ Prostaglandins
■ α-Adrenergic	■ Natriuretic peptides
■ Endothelin	■ β-Adrenergic
	■ Nitric Oxide

Figure 11. A current list of hypertension candidate genes in African-Americans.

1. Epithelial Sodium Channel Genes: T594M Mutation

One theory holds that Africans living near the Sahara desert evolved extremely efficient mechanisms for renal reabsorption of sodium.[54] While this trait confers a survival advantage in the desert, it provides a genetic susceptibility to hypertension when such individuals were exposed to a high salt Western diet. Regardless of the veracity of this theory,[55] most investigators have found a greater percentage of salt-sensitivity (usually defined as an increase in blood pressure of 5-10 mmHg over baseline after brief salt loading) among African-Americans than among Caucasians matched for age, gender, and blood pressure[4,5,9, 10, 56] I want to emphasize two points. First, for both ethnic groups, salt-sensitivity is more prevalent among hypertensives than among normotensives.[56] So, some of the salt-sensitivity appears to be the consequence rather than the cause of the hypertension. Second, while salt-sensitivity is twice as prevalent among African-Americans than Caucasians, the situation is not all-or-none: about 40% of hypertensive African-Americans and 60% of normotensive African-Americans are not "salt-sensitive." [56]

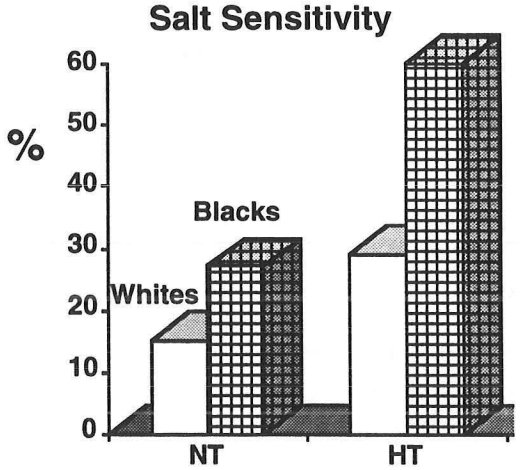

Figure 12. Prevalence of salt sensitivity. From JM Sullivan et al. *Am J Med Sci* 1988.

Sodium absorption in the distal nephron is mediated by the epithelial sodium channel (ENaC).[57] This ion channel is sensitive to inhibition by amiloride and, as explained in detail by Dr. Alpern's grand rounds earlier this year, a polymorphism of this ion

channel is the molecular basis of Liddle's Syndrome, one of the first monogenic forms of hypertension described by Richard Lifton and colleagues.[58,59]

Mutations that truncate the C-terminus of the β and γ subunits of ENaC lead both to constituitive activation of the channel and to an increase in the number of channels expressed in the distal nephron, thereby causing to excessive Na+ absorption.[58,59,60] Much of the credit for elucidating the latter mechanism goes to Dr. Peter Snyder,[60] a former Parkland Medical House Officer who recently completed his cardiology fellowship at the University of Iowa. This is a very rare mutation, accounting for tiny fraction all hypertension and there is only a single case described in an African-American.[61]

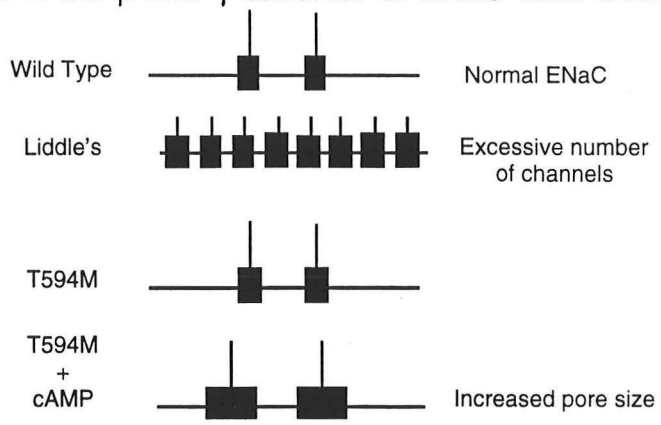

Figure 13. Molecularvariants of the epithelial sodium channel. T594M is present only in people of African descent. From VR Su et al. *J Am Soc Nephrol* 1996.

The race is on to determine whether other specific mutations could contribute to the more severe cases of primary hypertension, such as in African-Americans. The first positive result was recently described by Su and colleagues at the University of Cincinnati.[41] They identified a missense mutation in which methionine is replaced by threonine at residue 594 (T594M) in the carboxyl terminus of the β-subunit of ENaC in 6% of African-Americans. When patch clamp experiments were performed on the subjects' lymphocytes, the channel at first seemed to function normally. However, it opens excessively, as if the sodium pore were too large, in response to exogenous cAMP, which is the second messenger for beta-adrenergic signaling. This is important because, the renal sympathetic nerves play a major role in modulating channel activity in vivo.[62] What's known is that this mutation is only present in the lymphocytes of individuals of African descent. What's not know is whether the mutant channel protein is expressed in the kidney and other relevant target tissues to such an extent that it is a cause of hypertension. The original paper in from Cincinnati found comparable prevalence in normotensive and hypertensive African-Americans (7 vs. 6%),[41] however, a subsequent paper published this year from London indicates a greater prevalence in hypertensive vs. normotensive Jamaicans living in London: 8 vs. 2 %.[42] Of note, all the individuals possessing the T594M variant were heterozygotes.

	# T594M / # tested	%
U.S. Blacks - **HTN**[a]	7 / 126	5.6
U.S. Blacks - **NT**[a]	7 / 105	6.7
U.S. **Whites**[a]	0 / 192	**0**
London Blacks - **HTN**[b]	17 / 206	8.3
London Blacks - **NT**[b]	3 / 142	2.1

Figure 14. T594M variant of ENaC as a candidate gene for hypertension in African-Americans. From [a] Su et al. *J Am Soc Nephrol* 1996; [b] Baker et al. *Lancet* 1998.

The jury is still out because these are cross-sectional comparisons between a hypertensive clinic population, a non-random sample, and non-random sample of normotensive volunteers. There are other limitations to this work: (1) a polymorphism

that is present only in people of African descent is an unlikely candidate gene for salt-sensitivity, which is present in 1/3 of hypertensive Caucasians and not present in 1/3 of hypertensive African-Americans. Second, these studies did not assess salt-sensitivity, which varies not only with ethnicity but also with body mass and stage of hypertension.[56,63]

What is needed are: (1) better genetic epidemiology, (2) better phenotyping, and (3) interventional studies. Clinic blood pressure should not be the only endpoint. Other important intermediate phenotypes are (a) blood pressure reactivity to environmental stressors and (b) the rate of progression of target organ damage (e.g., renal insufficiency, LVH) caused by a given ambient level of blood pressure.

2. Angiotensinogen Gene: M235T Variant in African-Americans.

Angiotensinogen (AGT), or renin substrate, is cleaved by renin to form Angiotensin-I which is the precursor of Angiotensin II (A-II). The concentration of AGT is rate-limiting for the generation of A-II.[64]

Figure 15. The plasma concentration of angiotensinogen is rate-limiting for formation of angiotensin-II.

Transgenic mice over-expressing the rat AGT gene in liver and brain develop captopril-sensitive hypertension.[65] Manipulation of the number of AGT genes in the mouse by targeted gene duplication has provided direct evidence that a modest increase in gene expression leads to both elevated plasma AGT levels and elevated blood pressures .[66,67]

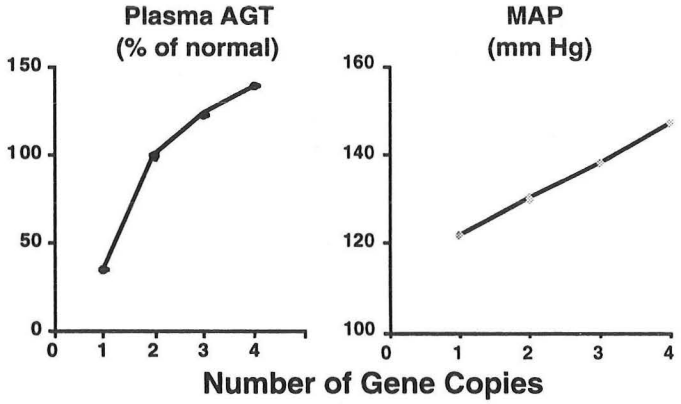

Figure 16. Gene-dose effect of angiotensinogen (AGT) on plasma AGT levels and mean arterial pressure (MAP) in transgenic mice. From O. Smithies and H-S Kim *PNAS* 1994; H-S Kim et al. *PNAS* 1995.

While these experiments do not conclusively prove that the elevated AGT caused the elevated blood pressure, they set the stage for an elegant series of studies in humans. Jeunemaitre et al.[68] established genetic linkage between AGT and essential hypertension in 215 Caucasian sibships. They identified 15 distinct molecular variants of the AGT gene and compared the prevalence of each one between hypertensive cases and normotensive controls. Only 2 of the 15 variants showed any relation to blood pressure, M235T (methionine is replace by threonine at residue 235) and T174M, but only M235T correlated with serum AGT concentrations (r=0.38). The best

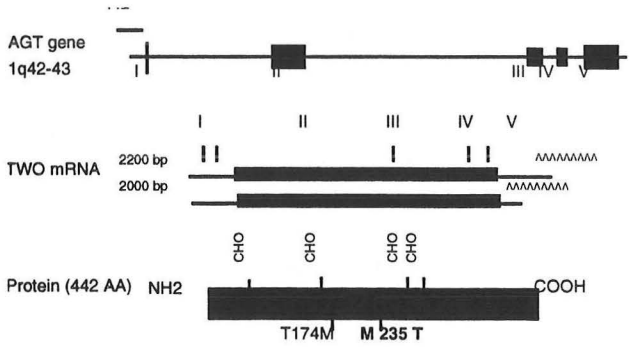

Figure 17. Variants of theAGT gene. From X Jeunemaitre et al. *Cell* 1992.

correlation was in women: M235T was present in 50% of the hypertensive women vs. 38% of their normotensive controls (all heterozygotes).

This mutation is present in 20-38% of Caucasians but 80% of African-Americans and > 90% of Africans living in Africa, the higher value being due to lack of admixture of African and Caucasian genes.[45-48] To date, small cross-sectional studies have not revealed an association between the prevalence of M235T with blood pressure any people of African descent.[46,48] Sibship studies in African-Americans have not been reported, so the jury is still out.

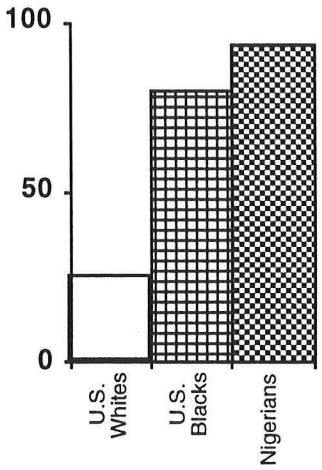

Figure 18. From C Rotimi et al . *Hypertension* 1994 and 1996.

Furthermore, the thinking about the molecular genetics of AGT has evolved in several ways. First, the 235 residue is far from the putative renin cleavage site, and in subsequent experiments, no functional difference could be assigned with respect to substitutions at residue 235. AGT encoding M235 or T235 (i.e., "M235T") were cloned and expressed transiently in mammalian cells.[69] In numerous experiments, the substitutions had no effect on the kinetics of enzymatic cleavage of AGT by human recombinant renin. Correlation does not equal causality. Second, the causal factor is a molecular variant of the AGT promoter which is in tight linkage disequilibrium with T235. In human lymphocytes, an adenine, instead of guanine, six residues upstream from the transcription initiation site was found in >97% of AGT alleles carrying T235, but in <5% of those carrying M235. Both markers, A(-6) and T235, were present in 38% of normotensive Caucasians, 74% of normotensive Japanese, and 82% of normotensive African-Carribeans. Third, the A(-6) variant promoter leads to a 20-70% higher basal rate of transcription compared with A(6). Although these are all in vitro experiments, at least a faster rate of transcription constitutes a plausible explanation for the higher plasma AGT levels seen in humans with this genotype, which could predispose to hypertension. Fourth, the A(-6)/T235 markers were found in all of six primates species studied, raising the fascinating conclusion that A (-6) and T235 mark the original form of the gene and M235 represents the mutation.

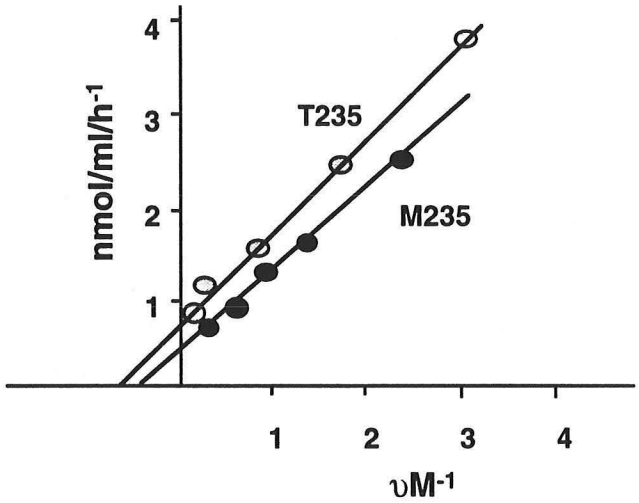

Figure 19. Double reciprocal plot of the cleavage reaction of the two molecular variants of AGT. The AGT was concentrated from media of transfected COS-1 cells and incubated with purified human renin. From Inoue et al. *J Clin Invest* 1997.

Although African-Americans typically have "low-renin-hypertension," a role for increased AGT gene expression is by no means excluded for the following reason. Baseline plasma renin activity (PRA) typically is much lower in hypertensive African-Americans vs. hypertensive Caucasians.[9,10] This phenotype has been generally interpreted to suggest that PRA is being suppressed by an expanded plasma volume due to greater salt-sensitivity in African-Americans.[9] If so, PRA should increase excessively when the inhibitory stimulus is removed. However, in 1976, Dr. Norman Kaplan showed that 40 mg of intravenous lasix evoked a blunted maximal rise in PRA in normotensive and hypertensive African-Americans vs. Caucasians.[70] More recently, He et al.[71] reported that one week of a low salt diet evoked a blunted increase in PRA and plasma A-II despite a greater fall in blood pressure in African-American than in Caucasian hypertensives.

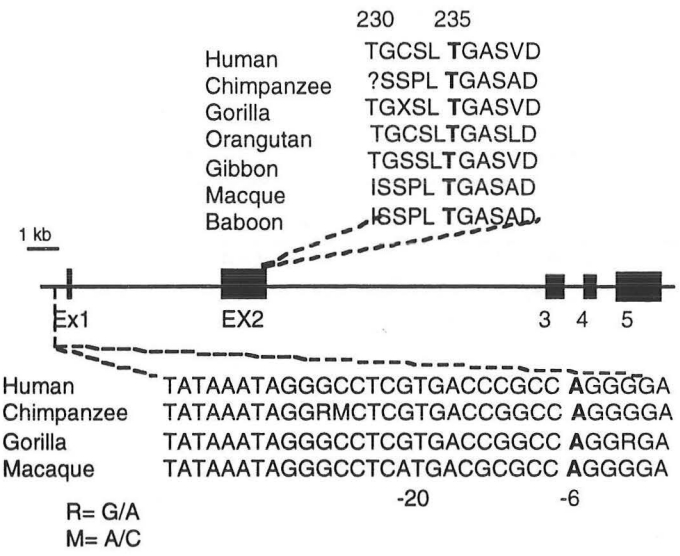

Figure 20. From I Inoue et al. *J Clin Invest* 1997

These findings such an alternative hypothesis that some cases of low renin hypertension may be caused by a fundamental down-regulation of renin release which is independent of volume status. In this regard, recent data from Oliver Smithies laboratory indicates that in transgenic mice over-or under-expression of the AGT gene induced an unexpected compensation characterized by alteration in the number of renin producing cells in the juxtaglomerular apparatus.[72] Perhaps, some cases of low renin-hypertension in African Americans reflect a primary up-regulation in AGT gene expression.

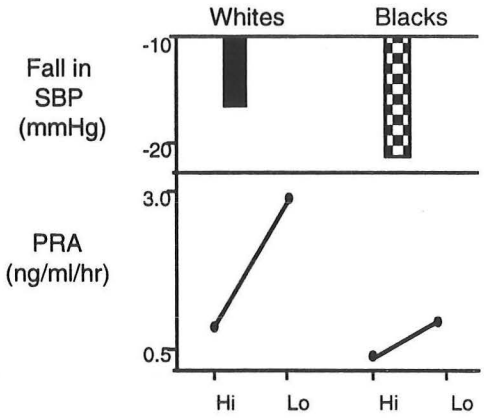

Figure 21. Changes in systolic blood pressure (SBP) and plasma renin activity (PRA) on transition from a high to low salt diet. From FJ He et al. *Hypertension* 1998.

III. Obesity-Related Hypertension in African-Americans: A Gene- Environment Interaction

African-Americans experience much higher death rates not only from hypertension but also from other diseases such as breast and prostate cancer.[73,74] These poorer outcomes from such diverse disease processes emphasize the importance of environmental factors that contributing to the excessive hypertension and target-organ

disease among African-Americans. These factors include access to health care, socioeconomic status, education, psychosocial stress, diet, and obesity, the latter being the topic of our Specialized Center of Research on Ischemic Heart Disease in Blacks, which is one of two centers funded by the National Institutes of Health.

Obesity is epidemic in the United States, and it clearly is one of the strongest risk factors for hypertension.[75] In the Frahmingham Study of Caucasian men and women followed for over 4 decades, obesity is estimated to account for over 50% all the hypertension.[76] In both experimental animals and human subjects, overfeeding elevates blood pressure and in obese subjects weight loss decreases blood pressure even when dietary salt intake is maintained at a high level.[77] There is ample evidence that the antihypertensive effect of weight loss is not explained on the basis of inappropriate sphygmomanometer cuff size or familiarity with the procedure used to measure blood pressure. There also is ample evidence that the frequent clustering of obesity, insulin-resistance, hyperlipidemia, and hypertension -- the "deadly quartet" places such individuals at very high cardiovascular risk.[78-80]

Obesity is known to be even more prevalent in African-Americans than Caucasians, particularly in African-American women: 50% vs. 30% prevalence in African-American men and Caucasian men and women.[77] It is therefore surprising how little is known about the role played by obesity in contributing to hypertension and target organ disease in African-Americans. In a much-cited study of an obese normotensive sample, Saad et al.[81] detected a correlation between obesity and insulin resistance with blood pressure in Caucasians but not in Pima Indians or African-Americans. More recently, however, obesity and fasting insulin levels were found to correlate with blood pressures in the CARDIA (Coronary Artery Risk Development in Young Adults) Study of young adult African-American and Caucasian men and women.[82] Hypertension prevalence correlates closely with body mass index in multiple populations throughout the African diaspora.[83]

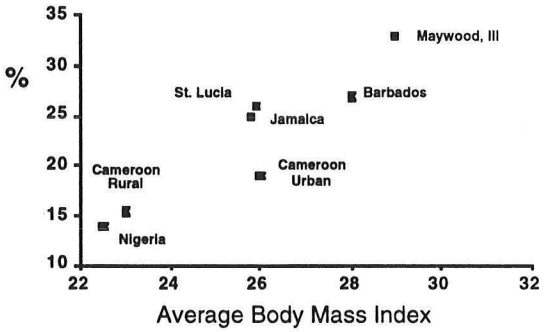

Figure 22. Prevalence of hypertension by body mass index in 7 populations throught the African diaspora. Cooper et al. *Am J Public Health* 1997.

An increasing body of experimental data implicates a pivotal role for the sympathetic nervous system in explaining the frequent coexistence of obesity, insulin-resistance, hyperlipidemia, and hypertension, but the vast majority of that work has been performed on Caucasians.[84-87] Indeed, the prevailing view is that neither obesity nor neurogenic factors contribute much to hypertension in blacks, which is assumed to be mainly salt (i.e., volume)-dependent.[4,5,9,10]

The importance minority inclusion in clinical investigation is underscored by the following study. Spraul and colleagues[87] examined the relation between body fat (assessed by underwater weighing) and sympathetic nerve activity to the skeletal muscle bed (assessed directly with intraneural microelectrodes in a peripheral nerve).

[86]In humans, the skeletal muscle is the major site of non-shivering thermogenesis and skeletal muscle sympathetic activity is a major determinant of energy expenditure, presumably via oxidation of skeletal muscle fat.[86,87] Experiments were performed in Caucasians who have a high prevalence of obesity and hypertension and Pima Indians who have a lot of obesity but very little hypertension. The subjects were all normotensive males. In the Caucasians, sympathetic nerve activity increased with increasing adiposity. This finding has been confirmed[88,89] and the notion is that the increased sympathetic activity constitutes a compensatory mechanism to burn more fat, but at the expense of sympathetic overactivity to vascular smooth muscle, leading to vasoconstriction and remodeling which sets the stage for hypertension.[87,90] In Pima Indians, however, the basal levels of sympathetic nerve activity are much lower and do not track with body fat. The consistently low levels of sympathetic activity in the Pimas is thought to be a permissive mechanism contributing to weight gain but without hypertension. [87]

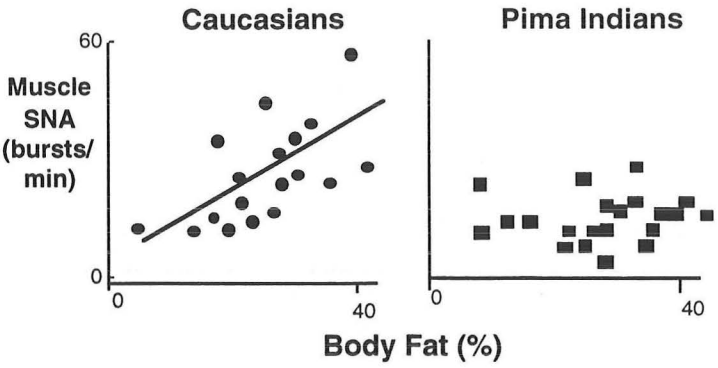

Figure 23. From M Spraul et al., *J Clin Invest* 1993.

B. Preliminary Results from the UT Southwestern Specialized Center of Resesarch on Ischemic Heart Disease in Blacks

We asked whether the phenotype in African-Americans more closely resembles that in Caucasians or Pima Indians. The subsequent figures contain data that have been presented only in abstract form. [91-93]

Accordingly, we performed the same type of experiments in young adult African-American men (n=29) and women (n=31). Because we wanted to define a phenotype that predates the onset of hypertension, we studied only normotensive healthy subjects 18-39 years of age with body mass indexes ranging from lean to obese. Blood pressures were measured with 24-hour ambulatory monitoring, body fat with calipers and underwater weighing, and sympathetic nerve activity with microelectrodes inserted into the peroneal nerve. Subjects were placed on an isocaloric 4 gram sodium diet for 4 days prior to study, and all experiments were performed with the subject supine and resting quietly for one hour. For the group as a whole, we found only a weak relation between body mass index and blood pressure. In contrast, examination of the sympathetic traffic provided a stronger phenotype.

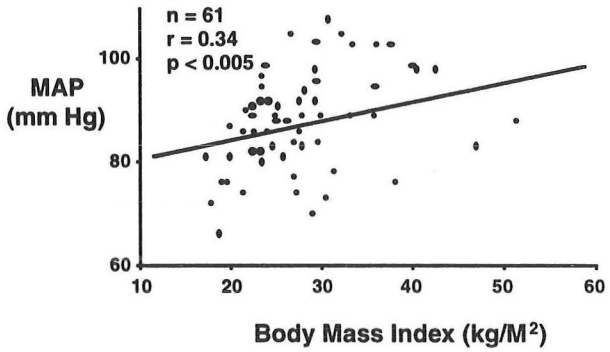

Figure 24. Weak relation bewteen body mass index and mean arterial pressure(MAP) in overtly healthy normotensive young adult African-American men and women.

These are illustrative recordings of sympathetic nerve activity from these young African-American women are lean, obese, and very obese. On these neurograms, the peaks represent spontaneous bursts of sympathetic discharge targeted to the skeletal muscle of the leg. The rate of sympathetic discharge increases with increasing adiposity.

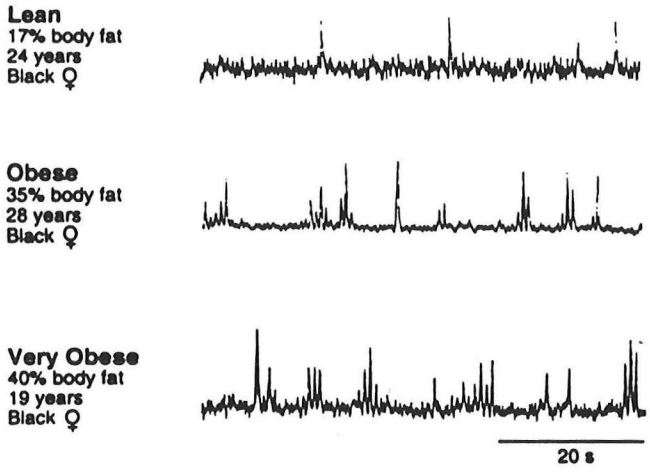

Figure 25. Illustrative recordings of sympathetic nerve activity.

The graphs show summary data plotting skeletal muscle sympathetic nerve activity against body fat. The major new finding is that the nerve activity increases linearly with increasing adiposity in the African-American women but not in the men. From these data, we do not yet know what the mechanism is for this unexpected gender difference nor do we know whether the increased nerve discharge identifies a group at high risk for future development of hypertension. However, I believe we have excluded suppressed sympathetic nerve activity as a mechanism of increased weight gain in African-American women, and we hypothesize that the sympathetic nervous system plays a greater role in the early pathogenesis of obesity-related hypertension in African-American women than men.

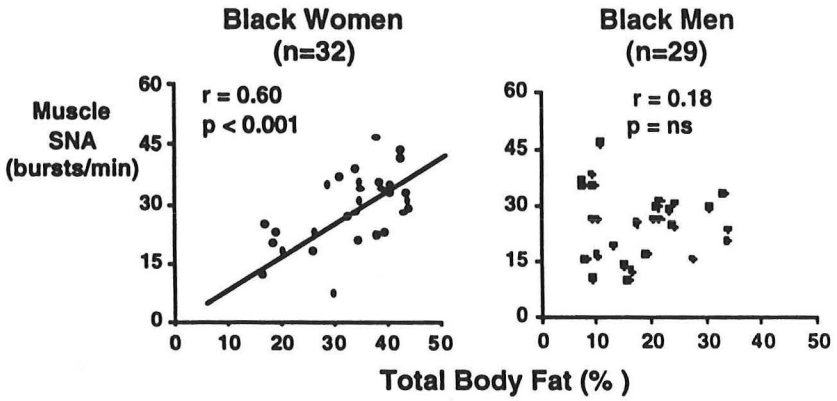

Figure 26. Summary data.

We then asked if obesity also begets cardiac and vascular hypertrophy that precedes the onset of hypertension. Our initial rationale for these experiments was that sympathetic neural stimulation of alpha-adrenergic receptors is a potent stimulus to vascular remodeling and hypertrophy.[86] Beginning with our normotensive female subjects, we used phase-contrast magnetic resonance imaging to measure the wall thickness and geometry of the left ventricle and ascending aorta.

We found that adiposity is a strong predictor of left ventricular mass (indexed for height) in these young African-American women.[94] In these normotensive subjects, the increased cardiac was directly related to body fat but unrelated to blood pressure (as measured by 24 hour ambulatory monitoring). One-third of our sample exceeded the Framingham criteria for LVH (≥102 g/m).

Similar findings were made for aortic wall thickness.

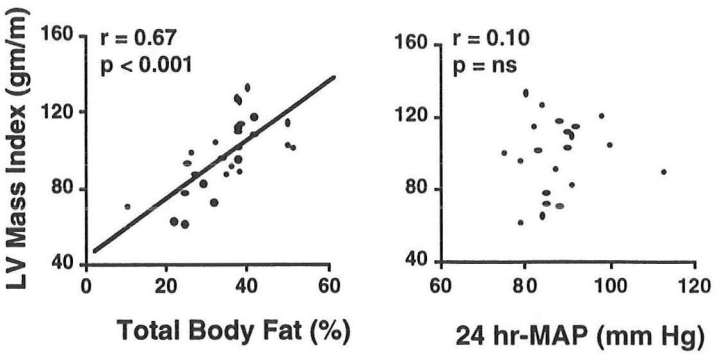

Figure 27. Relation between adiposity and left ventricular mass index in normotensive African-American women.

We usually think of LVH as the long-term consequence of years of inadequately controlled hypertension. Here we show that in 20- and 30-year old women obesity-related LVH predates the onset of hypertension. Such individuals have a head start to the hypertrophic process which presumably is greatly accelerated with the advent of hypertension in the subsequent decades of life.

Because of the strength of this correlation, we performed the same experiments in a cohort of Caucasian women matched for age and body mass index. We found that LV mass index tracks with body fat in Caucasian as well as African-American women, however, the relation is half as steep and not so tight in the Caucasians.[93] These apparently large ethnic differences would seem to provide the footprints of an important gene-environment interaction. The next phase of this research will be to identify the causes of the hypertrophy and, in particular, polymorphisms of candidate genes in the outliers and their immediate family members.

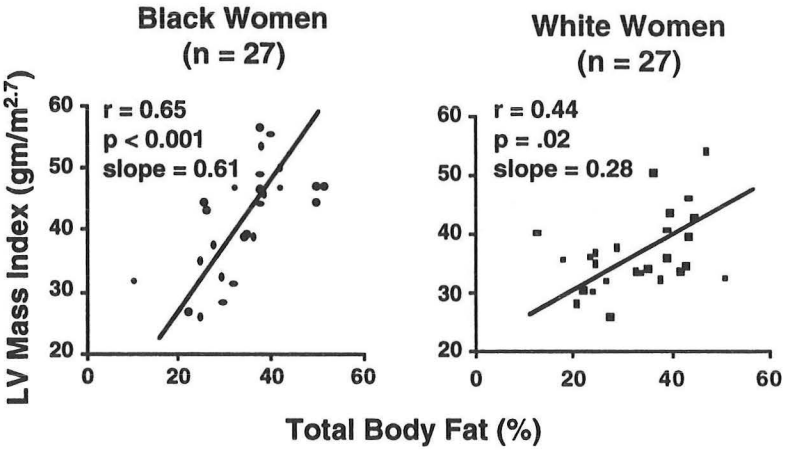

Figure 28. The relation between adiposity and left ventricualr mass index is steeper in the African-American women.

IV. Controlling Blood Pressure in African-Americans

A. Access to Health Care

For over 25 years, we have known that if, appropriate treatment can be provided and utilized, most of the excessive morbidity and mortality caused by hypertension can be prevented.[9,95,96] The most recent evidence suggests that 19% of the coronary heart disease in African-American women and 34% in African-American men could be prevented if systolic blood pressures were maintained below 140 mmHg.[97] Despite this knowledge, of the currently 6 million African-Americans with hypertension, 26% are unaware, 43 % remain untreated, and only 25% have their pressures adequately

controlled (blood pressure < 140/90 mmHg).[17] All these figures are worse for African American men than women.

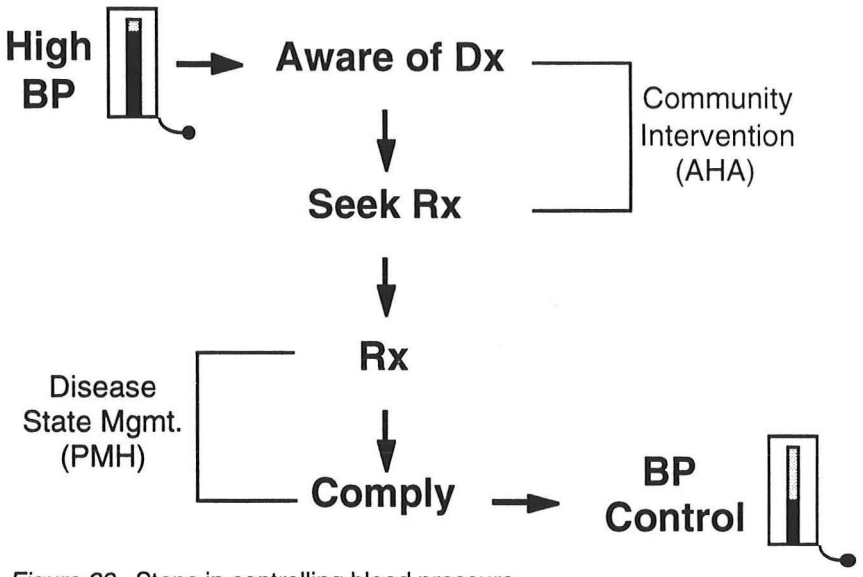

Figure 29. Steps in controlling blood pressure.

These statistics are reinforced every day at Parkland Hospital, where we treat large numbers of African-American men and women whose first presentation of hypertension is severe target organ damage before the age of 40 Y. The only way I know to make an impact here is to begin a proactive approach aimed at the community. To control blood pressure, a person must first be aware of his or her diagnosis. They must seek treatment, receive good treatment, and be good patients. Understanding how to change the behavior of lay people and physicians at first seems infinitely more difficult, but no less important, than elucidating hypertension candidate genes. We have initiated two nascent programs. First, with funding from the American Heart Association,[98] we will start a community-based intervention to improve the awareness and treatment of hypertension in Oak Cliff. I will say more about this later. Second, with the support and collaboration of the Parkland administration, we will establish a Disease State Management program designed to enhance the access to first rate hypertension treatment throughout the Parkland System. We need to improve both physician compliance with current standards of practice and patient compliance with treatment. Dr. Nina Radford is heading this program.

In the early 1970s, Dr. Michael Alderman hypothesized that equal access to health care at the worksite would isolate the impact of ethnicity on hypertension and its consequences.[99] Between 1973-1985, he conducted a prospective study of thousands of African-American and Caucasian municipal workers.[95,99] The two groups were well matched for age, gender, entry blood pressures, socioeconomic status, and other risk factors. Health care was provided mainly by nurses and paraprofessionals. The endpoints were blood pressure and cardiovascular events.

The major new findings were two-fold: First, when provided equal access to care, equivalent degrees of blood pressure control could be achieved in both ethnic groups. Second, controlling hypertension was associated with an equivalent or even lower incidence of cardiovascular morbidity and mortality in African-Americans. The greatest benefit was reduction in fatal myocardial infarctions in the African-American men over the age of 55Y.

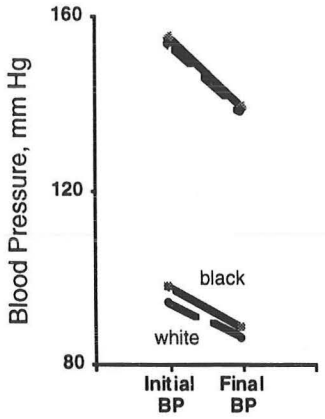

Figure 30. Equivalent degree of blood pressure control in 2962 Caucasians and 1807 African-Americans at a worksite. From Ooi et al. *Hypertension* 1989.

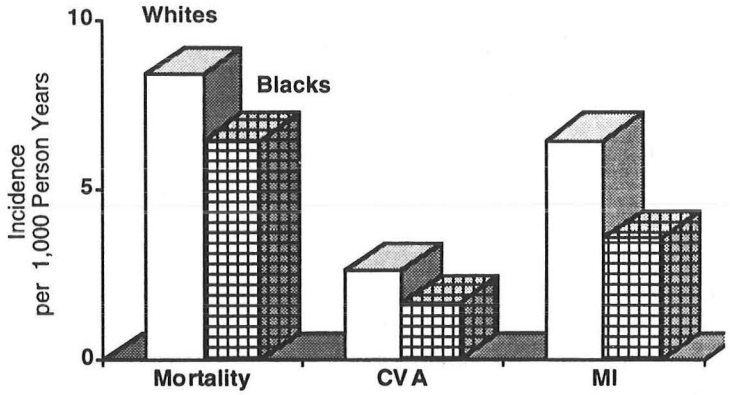

Figure 31. Major endpoints. From Ooi et al. *Hypertension* 1989.

Similar findings were obtained in the much larger Hypertension Detection and Follow-up Program that compared usual referred care to intensive stepped care.[96] The intensive stepped care reduced the risk of stroke in African-Americans to a level almost equivalent to that in Caucasians. Taken together, these data demonstrate the power of an interventional study. **Access to care is more important than ethnicity.**

One possible exception to this interpretation is hypertensive nephrosclerosis.

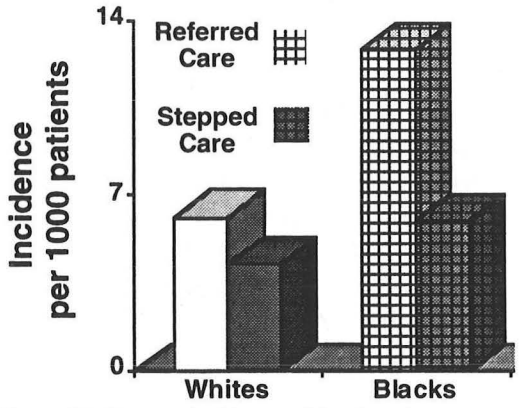

Figure 32. Six-year incidence of fatal stroke. 10,940 hypertensives were randomized (44% black). From HDFP *JAMA* 1982.

When equivalently good degrees of blood pressure control were achieved in a huge multi-ethnic cohort followed prospectively for six years in the MRFIT study, serum creatinines decreased in non-blacks but increased in African-Americans, although the absolute magnitude of these changes was small (a serum creatinine of 88.4 υmol/L = 1.0 mg/dl).[100]

The aim of the AASK Trial is to determine if even tighter control of blood pressure and other risk factors is required to halt the progression of hypertensive renal disease in African-Americans.

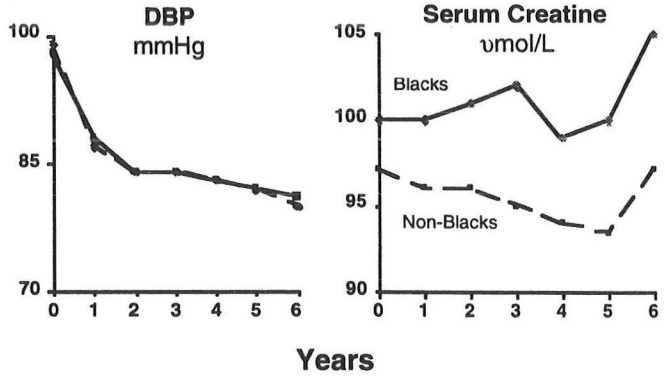

Figure 33. Blood pressure control and serum creatinine in MRFIT (n= 463 blacks and 5061 non-blacks). FromG Walker et al., *JAMA* 1992.

B. Knowledge and Cultural Beliefs About High Blood Pressure

A major factor in the positive outcomes from the NYC project is that all the patients were employed, and their labor union ensured their compliance.[95,99]

In a low income urban African-American community such as ours, how do we encourage people to seek medical treatment early enough so that target organ disease can be prevented? This topic is the focus of our new community intervention program that we are about to start in Oak Cliff.

	Medical	Folk	%
Symptoms	none "silent kiler"	universal	51
Terminology	HBP = HTN	HBP ≠ HTN	43
Stress	?	HTN = stress	25
Home Remedies	ineffective	effective	50
Rel. Importance	major: #1	minor	95

Figure 34. From R Wilson Stanford University Press 1986

Dr. Ruth Wilson, who is a Professor of Medical Anthropology at Southern Methodist University and our collaborator, conducted a study of cultural beliefs and misbeliefs about hypertension among 104 African Americans residing in a housing project in Oakland, California. Ages ranged from 18-80 years and 62% of the respondents were female. Her study was performed in the mid 1980s as part of her doctoral dissertation from Stanford University.[101]

She found that a considerable number of these indigent urban African Americans held a conceptual framework about high blood pressure that differed substantially from the modern biomedical view in 5 important ways: ***Symptoms:*** 51% of her sample believed that high blood pressure is frequently accompanied by symptoms such as headache and dizziness. In contrast, the biomedical view holds that high blood pressure is asymptomatic for years, hence the name "the silent killer." ***Terminology:*** 43% of her sample thought that high blood pressure and hypertension were different diseases, whereas medical professionals use these terms interchangeably. ***Stress:*** Those who thought that high blood pressure and hypertension were different diseases equated "hypertension" with stress. In contrast, the current biomedical view is that psychosocial stress seems to be a rather minor factor in causing hypertension. ***Home Remedies:*** 50% of her sample knew about at least one of 83 total home remedies for high blood pressure. ***Relative Importance:*** A surprising number of respondents (95%) believed that many illnesses -- ranging from multiple sclerosis to the flu and even a sprained ankle -- are more serious or more threatening than high blood pressure.

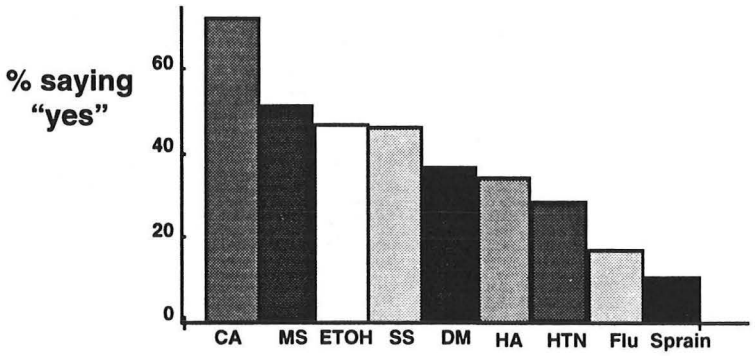

Figure 35. Responses of 104 African-American residents of a housing project to the question, "Do you believe another illness is more threatening than high blood pressure?" CA, cancer; MS, multiple sclerosis; ETOH, alcoholism; SS, sickle cell anemia; DM, diabetes mellitus; HA, headache; HTN, hypertension; Flu, influenza. From R Wilson, *Stanford University Press* 1986.

Of note, 22% of the respondents said *hypertension is more serious than high blood pressure*, which is a vivid demonstration that the community members believed hypertension and high blood pressure to be separate illnesses.

Because this study was conducted 15 Y ago in California, we recently conducted a pilot survey to determine if such misbeliefs are still prevalent in Dallas. My colleagues asked 60 African-American men and women on the street in Oak Cliff "What does high blood pressure mean?"

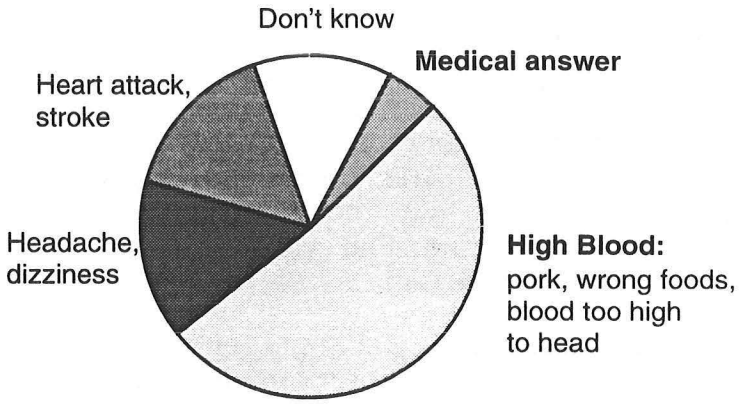

Figure 36. Meaning of "high blood pressure" to 60 African-American residents of Oak Cliff in 1998.

Only 5% of the people surveyed knew the medical definition of high blood pressure. Over 50% of the sample used the term "high blood" to mean literally that eating too much pork or other wrong food causes the blood to be too thick and to suddenly shoot up to the head. Despite the phonetic similarity with the medical term, "high blood" is not at all what we mean by high blood pressure.

There is a suprisingly large anthropology literature on this topic, indicating very similar folk beliefs about high blood pressure not only in African-Americans but also in other (mainly low-income) ethnic groups including American- and Canadian Indians, Mexican Americans, and Caucasians.[101-107] The common denominator is the misconception that "high blood" is episodic and symptomatic rather than chronic and assymptomatic.

The ***key questions*** are whether: **(1)** certain specific folk beliefs influence a person's behavior to such an extent that they impede the awareness, treatment, and control of blood pressure, and **(2)** community education programs about high blood pressure need to deal directly with these beliefs if they are going to substantially improve the control of blood pressure in the high risk African-American community.

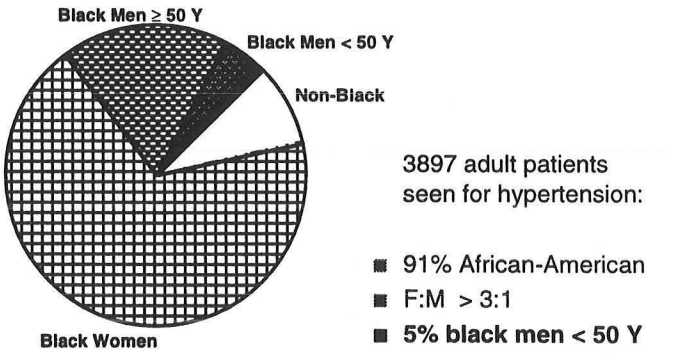

Figure 37. Demographics of Bluitt-Flowers Clinic: June 1997 - May 1998

Lets begin with the demographics of the Bluitt-Flowers Clinic. During the past year, a total of 3897 adult patients were seen for hypertension, of whom 91% were African-American. The key observations are: (1) female hypertensives outnumber male hypertensives by 3 to 1; and (2) only 5% of all these hypertensive clinic patients are African-American men under the age of 50 Y. This percentage is much lower than the

actual overall prevalence of hypertension for African-American men: 21% in the 30-39 year old group and 38% in the 40-49 year old group.[17] In these age groups, the overall prevalence of hypertension in African-American women is a bit less: 14% in the 30-39 Y group and 32% in the 40-49 Y group. Simply put, young African-American men generally do not go to clinic, and we will need to go outside the clinic to find hypertensive young African-American men. They are the high risk individuals that go untreated until they are admitted to Parkland Hospital with hypertensive crises and advanced target organ disease.

Our **working hypotheses** are: (1) In African American women, folk beliefs about the causes and consequences of hypertension constitute a major barrier to controlling high blood pressure; whereas (2) in African-American men, folk beliefs about medication-induced sexual dysfunction constitute a more important barrier. To test these hypotheses, we soon will develop and employ a random household survey of 500 households in the catchment are of Bluitt-Flowers. Based on the results of the survey, we will design and test the efficacy of a community-wide educational program to improve the awareness, treatment, and control of hypertension in this target minority community.

As an aside, this public health study provides a new opportunity to develop a large data base for genetic epidemiology. We are planning to draw blood for DNA on as many family members as possible.

Male sexual dysfunction has been shown to be a major factor causing withdrawal from antihypertensive drug trials (i.e., noncompliance),[108] although African American men were under-represented in these trials. However, recent evidence suggests that **the true impact of antihypertensive drugs on male sexual dysfunction is far less than previously assumed,** with much of the dysfunction being caused not by the drugs but rather by underlying vasculopathy (impaired endothelial dependent vasodilation) related to uncontrolled hypertension, hyperlipidemia, atherosclerosis, insulin-resistance, alcohol and tobacco abuse, advancing age, and other comorbidity.[108,109] For example, in the Treatment of Mild Hypertension Study (TOMHS) of predominately Caucasian previously untreated mild hypertensives 45-69 years of age, there was a significant degree of sexual dysfunction before the patients had ever received any antihypertensive medications. The reported prevalence of male sexual dysfunction increased both with increasing age and blood pressure.[109]

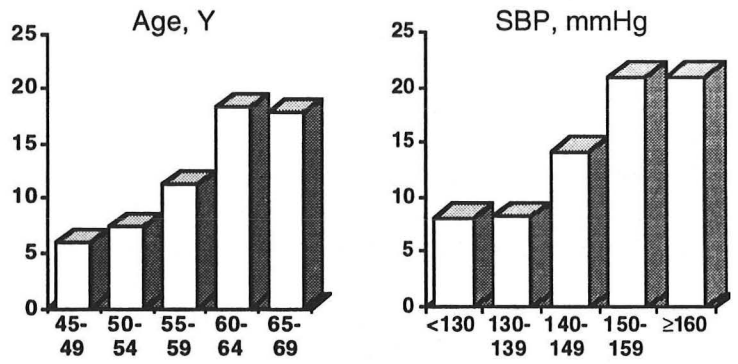

Figure 38. Prevalence of sexual dysfunction in 902 untreated hypertensive men in TOHMS. From RH Grimm et al. *Hypertension* 1997.

Patients were then randomized to testament for two years with placebo or monotherapy with one of 4 classes of medications.

During the first year of study, the incidence of sexual dysfunction was 17% for those receiving the thiazide diuretic chlorthalidone compared with 8% for those receiving placebo; for those receiving monotherapy with 1 of 4 other classes of medications (including a beta-blocker), the incidence of male sexual dysfunction suprisingly was indistinguishable from a placebo. During the second year, the incidence of sexual dysfunction in all 4 treatment groups were indistinguishable from placebo.

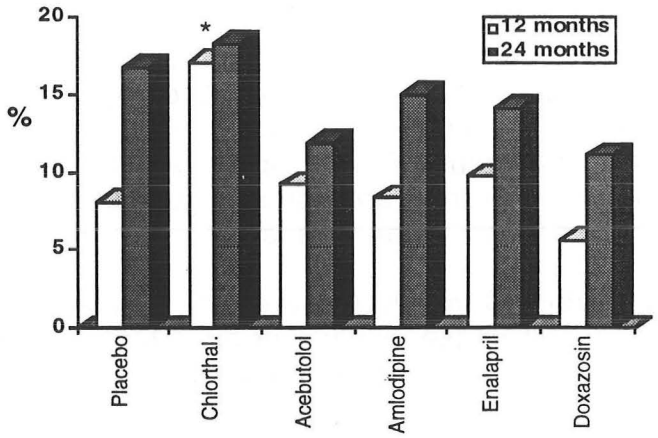

Figure 39. Incidence of sexual dysfunction with antihypertensive medications in TOMHS. * p<.05 vs. placebo From RH Grimm et al. *Hypertension* 1997.

We postulate that among young men of all ethnic groups an exaggerated fear of medication-induced sexual dysfunction constitutes an important deterrent to seeking and complying with medical treatment for hypertension.

C. Choosing the Right Antihypertensive Regimen

1. Diet. In overweight hypertensive individuals, a moderately low calorie/ low sodium/ high potassium diet can produce a moderate reduction in blood pressure.[13] There are few data on the effects of weight loss on blood pressure in African-Americans. The Dietary Intervention Study in Hypertension indicated that weight loss of even 10 lbs. alone without antihypertensive medications was sufficient to normalize blood pressure at one year in over 50% of overweight African-Americans with mild hypertension (n= 212).[110] African-Americans tend to consume lequivalent amounts of sodium but less dietary potassium than other ethnic groups.[4,5]

2. Medications. Much has been made about ethnic differences in the efficacy of various classes of antihypertensive medications.[4,5,8-12,111,112] Consonant with the view that the elevated blood pressure in African-Americans constitutes a volume-dependent, low renin form of hypertension, most authorities conclude that thiazide diuretics and calcium channel blockers are particularly effective in treating African-American hypertensives, while ACE inhibitors and beta-blockers are less effective in African-Americans compared with Caucasians. The question is how much. This is an important question because, independent of blood pressure lowering, ACE inhibitors are of particular benefit in reducing

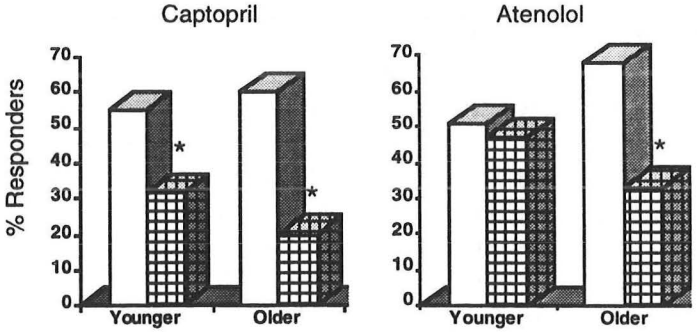

Figure 40. Percentage of hypertensive men (654 Caucasian and 621 African-American)responding to12 months of captopril or atenolol monotherapy in the VA Cooperative Study. Response, DBP<90 mmHg. * p<.05 vs. Caucasians From BJ Materson et al *NEJM* 1993.

mortality from progression of renal insufficiency and left ventricular dysfunction (and possibly LVH) while beta-blockers are of major benefit in reducing mortality after acute myocardial infarction.[10,13] The best data are those from the VA Cooperative Study Group on Antihypertensive Agents.[112] A total of 654 white and 621 black men were randomized to monotherapy with one of six different drugs (HCTZ, captopril, atenolol, prazocin, clonidine, diltiazem) or placebo and followed prospectively for one year. Dosages were titrated to maximum or until DBP was < 90 mmHg. A key conclusion of the study was that captopril and atenolol were the only two drugs that were less effective in African-American vs. Caucasian men. The other classes of drugs were equally effective. I want to point out that the largest ethnic differences were in men over the age of 60Y. Of the younger men, atenolol was equally effective in both ethnic groups and captopril alone lowered diastolic BP to < 90 mmHg in 32% of the blacks compared with 55% of the whites. Furthermore, the **absolute magnitude** of the ethnic differences in blood pressure lowering were rather small.

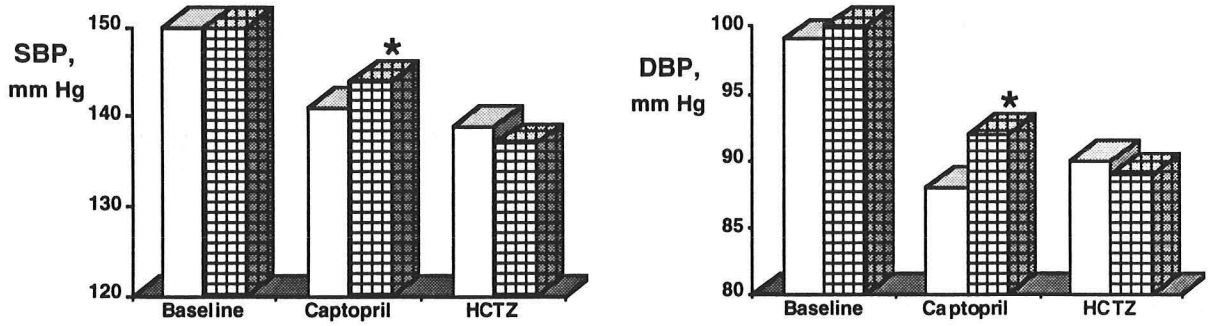

Figure 41. Systolic and diastolic blood pressures in Caucasians (white bars) and African-Americans (black bars) at baseline and after 8-weeks of captopril or HCTZ. Combined data for younger and older patients in theVA Cooperative Study. *p<0.05 vs. Caucasians. From BJ Materson et al. *NEJM* 1993.

The main limitation of this study was the emphasis on monotherapy, because most hypertensive patients today are treated with multiple medications to enhance efficacy while reducing side-effects caused by larger doses required with monotherapy.[13] An earlier study also by the VA Cooperative Study Group, but published in a rather obscure journal, provided vivid evidence that the addition of HCTZ (50 mg) greatly augmented the antihypertensive efficacy of captopril in black and white men and abolished an ethnic differences.[111]

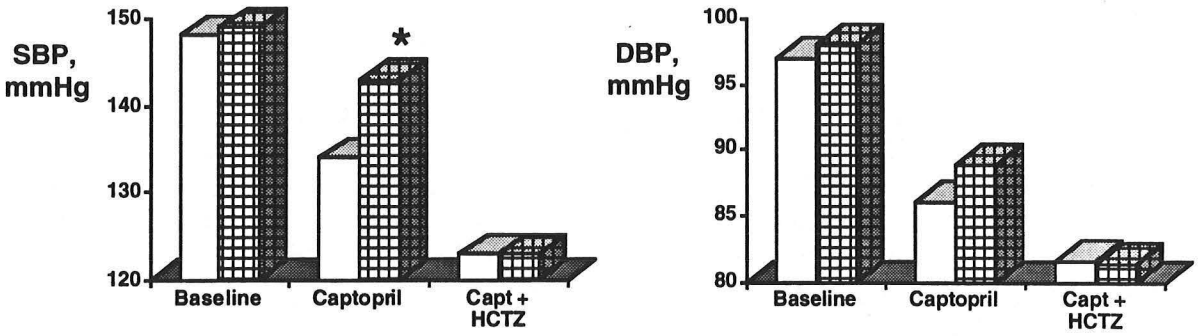

Figure 42. Systolic and diastolic blood pressures in 170 Caucasian and 151 African-American men at baseline and after 8 weeks of treatment with either captopril alone or captopril plus HCTZ. *p<0.05 vs. Caucasians. From the VA Cooperative Study Group *Br J Clin Pharmacol* 1982.

Preliminary data suggest that angiotensin receptor blockers, when combined with low dose HCTZ, may constitute a very effective strategy for controlling blood pressure in African-Americans.[113] If confirmed, this would be an important finding because ACE intolerance due to cough seems to be more common in African-American than Caucasian hypertensives: 10 vs. 3%.[114]

From all these data, I believe that ethnic differences in the efficacy of different classes of antihypertensive drugs have been over stated.

V. Conclusions

In closing, I have tried to accomplish two aims. First, I have tried to distinguish what is known about hypertension in African-Americans from what is not known. I believe that fundamental ethnic differences in the causes and consequences of hypertension often have been over stated in the clinical literature, and the issues are not black and white. Given the current body of scientific knowledge, I believe that ethnicity should not be a major consideration in the clinical approach to the hypertensive patient.

Second, I have outlined of our efforts and plans to fill in some of the large knowledge gaps on this important problem as part of our academic mission. While the problems are complicated, this is an important challenge for the 21st. century and an opportunity to make a difference.

ACKNOWLEDGMENTS

I want to acknowledge the following individuals who contributed to the original research presented here: Yasser Mansour, Nicola Abate, Ali Kizilbash, Ron Peshock, Nina Radford, Geoffery Clarke, Bahman Chavoshan, Temple Howell-Stampley, Kasi Pollock, Willie Faye Young, Debbie Arbique, Sybil Wallace, Bob Dobbins, Dennis McGarry, Scott Grundy, Peter Snell, Abhimanyu Garg, Anne Freeman, Mike Kazda, Ruth Wilson, Robert Haley, Leonard Berry, Shannon Harris, Rick Weisberg, Amber Dunn, and Nina McIntosh. This research is supported by funding to Dr. Victor from the National Institutes of Health and the American Heart Association.

I want to thank Drs. Norman Kaplan, Helen Hobbs, and Donald W. Seldin for their insightful comments, and Ms. Sybil Wallace for superb administrative assistance.

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