Long-term Plan for Research and Translation in Hypertension for Enhancing Public Health

Cutler J, Czajkowski S, Einhorn P, Kaufmann P, Loria C, Obarzanek E, Sorlie P, Thom T, Division of Epidemiology and Clinical Applications; **Dunn R, Ershow A, Lin M, Pearson G, Rabadan-Diehl C, Srinivas P, Velletri P,** Division of Heart and Vascular Disease; **Hunt C, Twery M,** National Center on Sleep Disorders Research; **Fulwood R, Roccella E,** Office of Prevention, Education, and Control

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Introduction

Hypertension affects over 50 million US adults, and above-optimal but non-hypertensive levels of blood pressure (BP)–now termed "pre-hypertension"-- are found in another tens of millions. The risk of developing hypertension during the remaining years of life for non-hypertensive adults aged 55 years has been estimated as approximately 60-90%, depending on diagnostic criteria. In addition, at least two million children and adolescents have hypertension, according to current definitions. Hypertension and pre-hypertension are among the most important risk factors for coronary heart disease (CHD), stroke, heart failure, and chronic kidney disease leading to renal failure. On a worldwide basis, a World Health Organization report has estimated that about two-thirds of the burden of cerebrovascular disease and about one-half of the CHD burden are attributable to above optimal BP.

While we have learned a great deal about the etiology, prevention, and treatment of hypertension and there have been parallel public health gains since the National High Blood Pressure Education Program was launched by the National Heart, Lung, and Blood Institute (NHLBI) in 1972, we are clearly in need of both more knowledge and better means to apply what we know. In the U.S., after decreasing for several decades, hypertension prevalence may now be increasing in concert with epidemic obesity. Recently published trend analyses for children and adolescents show rising mean systolic and diastolic BP from 1988-94 through 1999-2000 as well, in part attributable to overweight that is rapidly increasing in the young.. In adults, awareness, treatment, and control rates continue to improve, but control remains at only about 34%, far below national goals.

Several significant NHLBI-sponsored/supported research and translation efforts are underway; the ability to judge their contributions is still several years away. The purpose of this report is to recommend a course for the NHLBI regarding activities to be initiated over the next 5 years that may be expected to result in public health benefits within 10 years. The report consists of assessments of the current state-of-the-science and of ongoing activities in 17 topic areas, accompanied by recommendations for research initiatives and translation projects. These concepts have been developed and reviewed by NHLBI staff, then further reviewed by senior non-Federal scientists. When finalized, the report will be provided to the Board of Extramural Advisors and the National Heart, Lung, and Blood Advisory Council.

Executive Summary

The purpose of this report is to recommend a course for the National Heart, Lung, and Blood Institute (NHLBI) regarding hypertension-related activities to be initiated or continued over the next 5 years that may be expected to result in public health benefits within 10 years. The report consists of assessments of the current state-of-the-science and of ongoing activities in 17 topic areas, accompanied by recommendations for research initiatives, pre-initiative planning activities, and translation projects. Its preparation was begun at the request of the former NHLBI Director, Dr. Claude Lenfant, and its completion encouraged by the Acting Director, Dr. Barbara Alving. The report represents collaborative efforts of four units of the Institute: the Divisions of Epidemiology and Clinical Applications, and of Heart and Vascular Diseases; the Office of Prevention, Education, and Control; and the National Center on Sleep Disorders Research.

The proposals for each area are listed in the Table (pages 6-9). Suggested priorities have been developed based on voting by 16 of the report's authors, who were requested to indicate their top five choices. Five of the listed proposals were not included in the voting: the continuation of surveillance of prevalence, awareness, treatment, and control (via (NHANES) as well as mortality, hospitalization, and drug use through existing NCHS data systems, because these were deemed essential to continue; and the first four proposals listed under dissemination and implementation programs, as these are proceeding in any case. One other activity was also viewed as already in place, namely addressing issues of design, sample storage, and consent for pharmacogenetic studies right from the onset of planning large hypertension treatment trials.

The three top choices for new activities were: 1) initiate a multi-center sodium reduction trial in infants, with long-term follow-up to investigate an "early programming" effect; 2) convene a working group to address research on chronic stress and its blood pressure effects; and 3) convene a working group to evaluate the feasibility of a trial of multi-component lifestyle and behavioral intervention, which includes stress management and cognitive approaches, to reduce the need for antihypertensive drugs. The next tier of preferences included four proposals: 1) initiate validation studies of manual and automated sphymomanometers, including determination of usefulness in populations with specific morbidities affecting measurement; 2) encourage further studies of mechanisms relating blood pressure to body mass, fat distribution, and patterns of physical activity, including race/ethnic variation; 3) develop an RFA for primary-care-based or community-based trials of simple behavioral interventions to change diet and physical activity for blood pressure reduction; and 4) institute a multi-center clinical trial to evaluate effects of lower systolic blood pressure treatment goals and compare various classes of second-step drugs for effects on CVD events. Finally, the next five choices were: 1) encourage longitudinal analysis of ongoing children's cohort studies with very long follow-up to allow risk stratification

of children with high blood pressure; 2) initiate a clinical trial of individually tailored approaches to intervention on adherence to determine efficacy and applicability; 3) develop an RFA for mechanistic studies of hypertension in the young; 4) define a core of sleep-related information for collection in various NHLBI studies to test for associations with blood pressure and other factors; and 5) conduct a pilot program of educating and disseminating to health professionals patient adherence enhancing strategies for hypertension treatment and prevention.

The authors of this report have not attempted to lay out phasing of the various proposals or to estimate budgets, although there are clearly a number of low-cost activities and at least one very large one (the hypertension treatment trial). Should the Institute decide to implement the Plan, these tasks would fall to the involved Divisions/Office/Center, with whatever continuing cross-Institute oversight or coordinating mechanism judged to be appropriate. Proposals would be developed guided by the convening of Workshops/Working Groups or directly as Requests For Applications (grants or cooperative agreements), Requests For Proposals (contracts), or Program Announcements. Concept review of fully developed initiatives is customarily conducted by the Board of Extramural Advisors and the National Heart, Lung, and Blood Advisory Council. With dissemination of this Plan through the NHLBI web site, some topics may be left wholly to the interest and initiative of investigators.

Long-term Hypertension Plan

Table of Proposals

Topic	New or continuing activity
Descriptive epidemiology and surveillance	–Continue surveillance of prevalence, awareness, treatment, control (via NHANES), plus hypertension- related mortality, hospitalization, and drug use.
	–Propose additional over-sampling by race-ethnicity in NHANES.
	–Consider cohort and surveillance studies of trends and disparities in hypertension incidence, plus related morbidity and treatment.
Pathogenesis	–Convene an expert panel on pathogenesis of hypertension: research needs for next 5-10 years. (*Implemented, 5/04)*
Obesity and physical activity as etiologic factors	–Encourage further studies of mechanisms relating BP to body mass, fat distribution, and patterns of physical activity, including race/ethnic variation.
	–Encourage further studies of BP effects of intensity, frequency, duration, and type (aerobic/resistance) of physical activity, including interactions with degree of adiposity.
	–Encourage studies to improve measurement of physical activity, including validation in race-ethnicity sub-groups.
Diet composition as etiologic factor	–Initiate a multi-center outpatient feeding study to identify causal components of DASH diet.
Psychosocial stress as etiologic factor	–Convene a working group on chronic stress and its BP effects. (*Partially addressed by Working Group on CV Consequences of Chronic Stress, 6/04)*
Sleep-disordered breathing as etiologic factor	–Evaluate screening tools for sleep-disordered breathing against polysomnography in observational studies.

Long-term Hypertension Plan

Table of Proposals, continued

Sleep-disordered breathing, continued	–Define core of sleep-related information for collection in various NHLBI studies to test for associations with BP and other factors.
	–Encourage or initiate trials lasting 1 year or longer of treatment for sleep-disordered breathing for improving hypertension control.
BP measurement: technical issues	–Initiate validation studies of manual and automated sphygmomanometers, including determination of usefulness in populations with specific morbidities affecting measurement.
	–Coordinate one or more meetings of voluntary, professional, regulatory, and technical organizations to develop procedures for certification of sphygmomanometers, and for training and certification of BP observers.
BP measurement: behavioral issues	–Convene working group on ambulatory- and self-measurement of BP in diagnosis, monitoring, and treatment of hypertension.
Prevention/lifestyle treatment in children	–Encourage randomized trials of weight control and BP.
	–Initiate collaborative feeding studies of dietary patterns and reduction of dietary salt and BP.
	–Initiate a multi-center sodium reduction trial in infants, with long-term follow-up to investigate “early programming” effect.
	–Develop RFA on mechanistic studies of hypertension in the young.
Prevention/lifestyle treatment in adults	–Develop an RFA for primary-care-based or community-based trials of simple behavioral interventions to change diet and physical activity for BP reduction.
	–Evaluate feasibility of conducting a trial of a multi-component lifestyle and behavioral intervention, which includes stress management and cognitive approaches, to reduce need for drugs.

Long-term Hypertension Plan

Table of Proposals, continued

Prevention/lifestyle in adults, contin.	–Develop an RFA to evaluate environmental interventions to modify physical activity opportunities and/or sales and consumption of foods and nutrients that affect BP.
Drug treatment in adults	–Initiate a multi-center clinical trial to evaluate effects of lower systolic BP treatment goals and compare various classes of second-step drugs for effects on CVD clinical events.
Pharmacogenetics	–From the onset of planning large hypertension treatment trials, address issues of design, sample storage, and consent for pharmacogenetic studies.
Chronic hypertension in pregnancy	-- Consider initiating a randomized trial of antihypertensive drug treatment with assessment of BP control, fetal safety, and genetic variation in response.
Drug treatment in children	–Consider initiating long-term safety and efficacy studies.
	–Encourage longitudinal analysis of children's cohort studies with very long follow-up to allow risk stratification of children with high blood pressure.
Patient adherence	–Initiate a clinical trial of individually-tailored approaches to adherence intervention to determine efficacy and applicability.
	–Develop an RFA or PA to encourage development and testing of practical strategies and simple tools to measure adherence in research, patient care, and community settings.
	–Develop an RFA or PA to further understanding of effects on adherence of various antihypertensive medication formulations, particularly advantages/disadvantages of combination pills.
	–If successful adherence methods are found in studies funded under the RFA "Overcoming Barriers to Treatment Adherence in Minorities and Persons Living in Poverty", design a follow-up RFA to test approaches for disseminating/integrating these methods into various health care settings.

Long-term Hypertension Plan

Table of Proposals, continued

Clinical practice	–Develop an RFA to support randomized trials to evaluate cost-effective strategies for changing clinical practice toward better BP control and better selection of treatment modalities.
Dissemination and implementation programs	–Convene a working group to revise previous guidelines on high blood pressure in children and adolescents (*completed 5/04*).
	–Develop new web site materials for HBP Education Month, 2004, addressing population-based approaches for primary prevention of hypertension, reinforcement for treated patients to stay on therapy, and other objectives.
	–Form a small working committee with the National Committee on Quality Assurance to review the HEDIS hypertension measure, and determine if it can be lowered.
	–Work with the American Heart Association Working Group on Blood Pressure Measurement on updating recommendations. *(completed, 1/05)*
	–Consider a pilot program of educating and disseminating to health professionals patient adherence enhancing strategies for hypertension treatment and prevention.

Long-term Hypertension Plan
Topic Sections

1.0 Descriptive Epidemiology and Surveillance

A. Definition of the Problem

Over 50 million Americans have hypertension, one of the major risk factors for stroke, coronary heart disease (CHD), heart failure, and other cardiovascular-renal diseases. The effectiveness of the detection, treatment, and control of hypertension plays a major role in the primary and secondary prevention of these diseases. This seems to be especially true for stroke, possibly because the relationship between blood pressure and risk of stroke is even stronger than the relationship between blood pressure and CHD. The marked acceleration of the downward trend in age-adjusted stroke mortality in the United States after 1972 coincided with the major national health education effort to detect, treat, and control hypertension. For planning and evaluation of hypertension research and education activities it is critical that these trends and population disparities in blood pressure and disease be monitored in the future, using standard methodology, sampling designs, and data collection procedures.

B. Current state of the science

National health examination surveys show that among persons 18 to 74 years of age, average systolic and diastolic blood pressures declined between 1971-74 and 1988-94 but did not change further in 1999-2000, which is consistent with offsetting trends in prevalence and treatment/control (as described below). Declines through 1988-94 were observed in men and women and in the white and black populations. Declines were greater among older than among younger age groups. Both mean systolic and diastolic pressures were significantly higher in the black than in the white population, and mean blood pressures were higher in men than women overall. Men had higher mean blood pressures than women at younger ages, but later in life the reverse is true.

The prevalence of hypertension is defined as blood pressure $\geq$140 mm Hg systolic or $\geq$90 mm Hg diastolic or taking antihypertensive medication. For persons 20 to 74 years of age, prevalence was substantially lower in the 1988-94 survey than in 1976-80, but the 1999-2000 survey showed an apparent increase in prevalence in men and women over the 1988-94 period. In 1976-80, 51% of persons with hypertension were aware of it, 31% on treatment, and 10% had it under control. By 1999-2000, 70% were aware of it, 59% were on treatment, and 34% had it under control. These improving trends have occurred in all population groups, but treatment is still being underutilized and control has not reached goals for the year 2000. The 1999-2000 survey shows little progress in

awareness, treatment, and control in women since 1988-94.
Between 1970 and 2000, the age-adjusted death rate for CHD and stroke, the two major cardiovascular diseases, declined 58 percent and 62 percent respectively. However, for congestive heart failure, the end-stage of heart disease for which hypertension plays a key role, the death rate more than doubled, but the trend in recent years has been essentially flat. Since 1970, the rate of hospitalizations was essentially flat for CHD and stroke but for congestive heart failure it tripled.

C. Ongoing activity

Data from the 1960–1962 National Health Examination Survey, from the NHANES studies of 1971–1974 (NHANES I), 1976–1980 (NHANES II), 1988–1994 (NHANES III), and 1999-2000 (NHANES Continuous) are the primary sources of information on trends in blood pressure, hypertension, and the proportion aware, treated and controlled. Blood pressure is measured using standard and well established protocols. In the health interviews, respondents are asked whether a physician has ever told them that they have hypertension or whether they are taking antihypertensive medication. On the basis of the two interview questions plus actual blood pressure measurements, the hypertensive person's awareness of his or her condition and treatment and control status can be ascertained. Other interview questions ascertain the extent of non-pharmacologic means to control blood pressure. With regard to behavioral factors related causally to BP, which are important to track, NHANES collects dietary information primarily using the 24-hour recall method, includes questions of physical activity, and measures weight and height, allowing calculation of body mass index (an indirect index of adiposity). There are well-recognized limitations of physical activity questionaires and 24-hour recall data, especially for measuring sodium chloride intake.

Demographic disparities and time trends in national mortality statistics reported from tabulations of death certificates are continually tracked for the hypertensive-related causes of death. Annual rates of inpatient hospitalizations and emergency and outpatient visits are tracked by age, sex, and diagnosis from several national surveys. They have important deficiencies, including concerns about the validity of data by race and ethncity, so they are no substitute for the lack of adequate measures of incidence and morbidity from the hypertensive-related diseases.

Trends in the annual number of drug mentions in physician visits by class of antihypertensive drugs has been tracked in the National Ambulatory Medical Care Survey of the NCHS and from the National Disease and Therapeutic Index of a private company, IMS Health, the latter having data extending back more than 20 years.

D. Proposals

The NHLBI has supported the determination of blood pressure in the national surveys with current funding of NHANES examinations conducted in 1999-2004. The National Center for Health Statistics will be continuing the NHANES surveys every year. Because of the critical value of the national estimates of blood pressure and hypertension, and awareness, treatment and control, the NHLBI should continue funding the blood pressure and weight components of NHANES.

Consideration should be given to funding an expansion of the survey samples to collect these data in additional race-ethnicity population groups. The tracking of national mortality, hospital discharge, and drug mention statistics should be continued. Surveillance and cohort studies should be encouraged to fill gaps in knowledge about trends and disparities in incidence, morbidity, and treatment relating to hypertension.

2.1 Pathogenesis

A. Definition of the Problem

Hypertension, a major health concern affecting more than 50 million people in the United States, continues to be the major risk factor for congestive heart failure, myocardial infarction, renal disease and stroke. However, the biological mechanisms underlying the causes of high blood pressure remain unclear.

B. Current State of the Science

Hypertension is a multi-factorial disorder. From its outset, hypertension research has been saddled with the exceptionally difficult task of identifying and integrating the numerous underlying biological mechanisms responsible for elevated blood pressure. Basic research on its pathogenesis has led to the identification of many contributing factors, both biological and environmental. For more than ten years, a major focus of hypertension research has been molecular genetics. Early on in the study of the genetics of hypertension, it became clear that each gene by itself only contributes to the elevation of blood pressure to a small degree, with the only notable exceptions being several rare forms of monogenic hypertension, where a single mutation can fully account for high blood pressure. For example, a mutation of a protein kinase gene was recently identified as the cause of the elevated blood pressure in pseudohypoaldosteronism type II. Interestingly, a variant of this kinase gene has now been shown to associate with salt-sensitive hypertension in whites, but not in blacks. This finding illustrates how the study of a rare form of hypertension may help us to understand genetic factors contributing to common types of high blood pressure.

In addition to the study of rare forms of hypertension, many regions of the chromosome, referred to as quantitative trait loci, have been shown to associate statistically with high blood pressure in animal models and in the human population. Many potential candidate genes have been suggested. With the completion of the human genome project, additional candidate genes can now be deciphered from the quantitative trait loci shown to associate with hypertension. Furthermore, cross-species genetic homology from mice to rats and to humans has been demonstrated. The chromosomal regions shown to be linked to hypertension in animal models can now be extrapolated into homologous regions in humans. These candidate genes can be used to predict phenotypes that contribute to the pathogenesis of hypertension.

The identification of phenotypes that contribute to blood pressure regulation allows for the dissection of the pathogenesis responsible for high blood pressure, which is a complex index of many factors. Many contributing phenotypes preceding the elevation of blood pressure have been identified. In many cases, the contributing phenotypes are other components of the metabolic

syndrome. In fact, these physiologic abnormalities can be considered as risk factors for hypertension. It is not surprising that many QTLs associated with hypertension are shared by components of the metabolic syndrome, such as insulin resistance and obesity. Hypertensive patients can be stratified based on many contributing phenotypes, including components of the metabolic syndrome, and their linkage to specific genetic variants can then be further verified.

It is increasing appreciated that the complexity of hypertension is in part due to its co-existence and interaction with other disorders, such as dyslipidemia, atherosclerosis, and the metabolic syndrome. Therefore, an integrative approach to the study of these interacting disorders is essential to the understanding of the origin of high blood pressure.

C. Ongoing Activities

Currently, there are more than 500 active grants of various activities, including R01, R13, R15, R37, R43, R44, P01 and P50, in the hypertension field. The majority of these grants are investigator-initiated. The major hypertension-related areas are covered, such as salt-sensitivity, neuronal control, vasoactive factors, vasculature, ion transport and other complicating vascular diseases. In addition, there are two major ongoing programs addressing the pathogenesis of hypertension, namely the SCOR Program on Molecular Genetics of Hypertension and the Family Blood Pressure Program (FBPP). The current Hypertension SCOR program consists of five centers and is in its eighth year of funding. The main objective of the program has been the identification of quantitative trait loci and the specific genes within these regions that regulate blood pressure and contribute to hypertension through mechanistic studies of unique human population and animal models. The FBPP is a multi-center genetics study of high blood pressure and related conditions in multi-racial groups. The program consists of four networks which were originally established separately since 1995. Due to their similarities and the need to coordinate and collaborate closely, a Steering Committee was formed. This program has enrolled more than 12,000 study participants to date.

In addition, during the last fifteen years, there have been six workshops or working groups and nearly 20 RFAs focusing on basic high blood pressure research. However, a cohesive collaborative effort among major programs would facilitate the dissemination of the knowledge accumulated thus far and help to understand the fundamentals of blood pressure regulation.

D. Proposal

In order to determine the future direction in the study of hypertension pathogenesis, an expert panel was recommended and convened in May 2004 to help assess the research priorities for the next 5 to 10 years. The scientific areas included:

1. Genotypic characterizations of hypertension.

With the recent completion of the human genome project, it is time to assess the best possible application of the molecular genetics of hypertension accumulated through the study of humans and animal models. Furthermore, with emerging new technologies, such as proteomics and gene expression profiling, and newly developed resources, such as the Programs for Genomic Applications, new tools are now available.

2. Mechanistic studies of contributing factors towards high blood pressure.

Natural and transgenic animal models have been used for dissecting the mechanisms leading to elevated blood pressure. As we identify additional contributing factors, both genetic and environmental, their involvement needs to be studied and understood.

3. Interrelationship between hypertension and other cardiovascular risk factors

Many cardiovascular disorders are known to co-exist with high blood pressure. The clustering of genes with linkage to hypertension, diabetes, obesity, insulin resistance and inflammation has been shown. Also, components of the metabolic syndrome can be considered as risk factors for hypertension. Therefore, it is essential to understand their relationship and interaction.

4. Long-term control of blood pressure

Little is known about the long-term control of blood pressure in humans and animal models over extended periods of time (months to years). The kidney and the central nervous system are involved in a complex interaction that is key to the overall homeostasis of blood pressure, but the specific biological pathways have yet to be deciphered. The knowledge of the involvement of ion homeostasis and neuronal control of blood pressure regulation is essential to the understanding of hypertension.

5. Novel computational modeling for hypertension

While we continue to identify contributing factors of high blood pressure, there is an urgent need to take an integrative approach to characterize and understand this disorder. Integration of genetic, environmental and behavior variables should be taken into account through development of computational modeling in the analysis of all contributing factors towards pathogenesis of hypertension.

2.2 Obesity and Physical Activity

A. Definition of the Problem

Excess adipose tissue leads to overweight and obesity and has a deleterious effect on blood pressure (BP). Exercise raises blood pressure in the short term but sustained physical activity and better aerobic fitness are associated with lower resting blood pressure.

B. Current state of the science

Obesity

The relation between BP and body mass index (BMI), overweight, and obesity has been well-established in both cross-sectional and longitudinal studies. Obesity and weight gain are associated with an increased risk of developing hypertension. Findings from several studies suggest that obesity or weight gain may contribute to race-ethnic disparities in hypertension. For example, data from young adults in the Coronary Artery Risk Development in Young Adults Study (CARDIA) showed that obesity and lifestyle factors explained 40 percent of the racial difference in blood pressure over 7 years. Some studies have suggested that abdominal obesity is a better predictor of hypertension than overall fat mass in adults, although this is not well-established. Obese children have a 3-fold higher risk for hypertension than non-obese children with risk increasing across the entire range of BMI . Clinical trials have demonstrated BP reductions with moderate or greater weight loss even without attaining desirable body weight. In a study summarizing results from 11 weight loss trials, average systolic and diastolic BP were reduced by 1.6/1.1 mm Hg per kilogram of weight loss.

However, the specific mechanisms by which blood pressure is reduced through reduced adiposity are not well understood. For many years a simplistic mechanical relationship was thought to explain the relationship between adiposity and blood pressure, but a new understanding has recently evolved to explain how excess adipose tissue may generate undesirable health effects. Adipose tissue is now viewed as a type of diffuse endocrine organ, capable of elaborating cytokines and other biologically active compounds and peptides, which enter into the circulation and reach their end organs with deleterious results. Among these compounds are angiotensinogen and angiotensin II, which are known to play a role in the development of hypertension through activation of the renin-aldosterone axis. In addition, sympathetic nervous system activation leading to hypertension has been observed in the presence of obesity. The basis for this is not known but may include the downstream effects of obstructive sleep apnea (common in obese individuals), as well as physical compression (by fat) of the renal capsule leading to diminished glomerular function and excess renal retention of sodium. The mechanisms of interaction between the autonomic nervous system and systems of energy balance regulation are in need of clarification.

Physical activity

Low levels of physical activity or fitness have also been associated with increased risk of hypertension independent of BMI in epidemiologic studies. Clinical trials have confirmed that increases in physical activity can lower BP, independent of changes in weight. Aerobic exercise has been shown to reduce systolic (-3.8 mm Hg) and diastolic (-2.6 mm Hg) blood pressure in both hypertensive and normotensive persons based on a meta-analysis of 27 randomized trials. The same study showed that blood pressure was reduced in both hypertensive and normotensive participants and in overweight and normal weight participants. However, most studies have investigated the effects of aerobic exercise, whereas few studies have examined the effects on BP of resistance exercise (i.e., weight training).

C. Ongoing activity

Approximately 3 dozen grants supported by DHVD in FY03 are investigating mechanisms of blood pressure regulation in relation to obesity or physical activity. Most of these investigations use animal models (rats, mice, rabbits, dogs, cats), with a smaller number carried out in humans. Exercise (physical activity) is studied with regard to its effects on central regulation of blood pressure and on peripheral vessel dilation and constriction. Genetic and dietary models of obesity are used to examine how increased fatty acid flux and various adipose tissue secretory products (such as angiotensin) have the capacity to activate central and peripheral neurohumoral pathways that can lead hypertension. Grants recently funded under the aegis of RFA HL-02-016, Pathophysiologic Mechanisms of Obesity-Associated Cardiovascular Disease, are addressing the interaction between obesity and blood pressure; two human studies are examining how body fat mass affects diurnal variation in blood pressure, and one study in rats is evaluating how angiotensin secreted by adipose tissue interacts with blood pressure regulatory mechanisms. DECA has about 30 grants relating blood pressure to body mass/overweight or physical activity. Most of the portfolio funds prevention trials where increased physical activity is part of several lifestyle changes and blood pressure is a main or secondary outcome. Several trials focus on weight loss, short- or long-term, and the effects on blood pressure. One trial is examining the effects on BP of various doses of physical activity. DECA is funding a validation study for instruments measuring physical activity and energy expenditure. The portfolio also includes several grants and 8-10 contracts that examine associations of blood pressure with physical activity and/or BMI within observational studies. Many of these cohort studies are exploring race-ethnic and gender differences in risk of developing hypertension, including CARDIA, ARIC, and the Jackson Heart Study.

D. Proposals

One gap in knowledge regarding obesity and BP is the role of body mass vs. body fat distribution, particularly visceral fat. In addition, it is unclear if body mass and body fat distribution relate similarly to BP in different race-ethnic groups. Further research is also needed into proposed mechanisms that are unique to obesity-associated hypertension, including intrarenal physical forces

associated with obesity-induced changes in the renal medulla, genetic and metabolic factors, and metabolic effects of abdominal visceral fat.

Research challenges regarding physical activity and BP lie in delineating specific mechanisms whereby exercise improves blood pressure control. Further research is needed to determine optimal intensity, frequency, and duration of exercise for improved blood pressure, and the relative benefits of aerobic vs resistance exercise. Investigation of the beneficial effects of exercise under conditions of obesity, even in the absence of weight loss, is also warranted. Furthermore, the effects of physical activity on body fat composition and distribution, and their effects on BP, needs better delineation.

The lack of precise, valid techniques for measuring physical activity in humans poses a serious barrier to progress in the field. Improved devices and technology for research and lay application may add precision to measurements and resolve some of the apparent contradictions in the research literature. *(Note: A proposed FY05 RFA on Bioengineering Approaches for Prevention and Treatment of Overweight and Obesity might provide a means of addressing this gap*). In addition, lack of valid physical activity questionnaires for women and minority groups inhibits our ability to determine if gender and ethnic differences in the association between blood pressure and physical activity are real.

2.3 Diet Composition

A. Definition of the Problem

Twenty-five percent of the U.S. adult population (or about 50 million people) has high blood pressure (BP), and this percentage increases substantially with age, such that at age 60 or older, half the population has high BP. Because the risk of cardiovasuclar disease and mortality increases with increasing BP throughout the entire range of BP, a large segment of the population has BP levels that are not considered high, but would benefit from having lower levels (<120/80 mm Hg). Reliance on treatment alone is impractical and inefficient given the high prevalence of the condition. Thus, knowledge of which aspects of diet could help prevent high BP would guide intervention studies and public health recommendations to deal with the public health problem of high BP and its health sequelae.

B. Current State of the Science

A large body of evidence from ecological, cross-sectional, and longitudinal observational studies as well as intervention studies has accumulated to show that dietary factors are related to BP, and that altering specific nutrients can reduce BP in people with and without hypertension. Nutrients and dietary factors for which strong evidence exists as having a favorable influence on BP include weight loss, sodium reduction, limiting alcohol intake, and increasing potassium intake. Strong evidence also exists for the salutary effect on BP of a dietary pattern that is rich in fruits, vegetables, and low-fat dairy projects with a reduced content of saturated and total fat. The JNC 7 (2003) reported the approximate BP reductions that could be expected from adopting each of these diet-related recommendations, ranging from 2 to 20 mm Hg systolic BP.

Less clear regarding BP effects are nutrients and dietary factors that have been shown in observational studies to be related to BP, but results from trials have been inconclusive. These include calcium, magnesium, protein (total or vegetable-derived), polyunsaturated fatty acids, including omega-3 fatty acids (or fish oil), and fiber, which are thought to favorably influence BP, while total fat, saturated fat, and cholesterol are thought to unfavorably influence BP. These aspects of diets have recently been reviewed in a volume on Lifestyle Modification for the Prevention and treatment of Hypertension (2003). General conclusions from these reviews are that BP effects from mineral, fiber, and fish oil supplements were not sufficiently substantial or documented to warrant recommendation of supplements. The most promising are results from recent observational studies, including INTERMAP, a large cross-sectional study, that dietary protein, mainly vegetable protein, is associated with lower BP.

C. Ongoing Activity

Several studies are currently underway seeking to identify whether macronutrient composition of the diet can influence BP levels. The INTERMAP study is testing associations between dietary

macronutrients and BP in 4680 adults age 40-59 in 17 population samples from four countries, using multiple measures of urine, diet and BP. This epidemiologic study will examine associations between BP and protein, including type of protein (animal or vegetable) and individual amino acids.

Two intervention studies of macronutrients and BP are under way. Examining the vegetable vs. animal protein hypothesis, the Protein and Blood Pressure Study is testing the effects on BP of 8 weeks of vegetable (soy) protein compared with animal (milk) protein supplements in 280 adults with prehypertension or Stage 1 hypertension. Another trial, Optimal Macronutrient Intake to Reduce Heart Disease (Omni-Heart), is testing two dietary patterns with different macronutrient compositions of 6 weeks duration in an outpatient feeding study in 260 adults with prehypertension or Stage 1 hypertension. The control diet is a diet similar to DASH, rich in fruits, vegetables, and dairy products, reduced in saturated fat and total fat, and increased in carbohydrate. Two dietary patterns to be tested are reduced in carbohydrate content (48% kcal): one rich in unsaturated fatty acids (31% kcal), particularly monounsaturated fat, and another rich in protein (25% kcal) with an emphasis on vegetable protein. The results of this trial will show whether substituting unsaturated fat or protein for carbohydrate will result in better lipoprotein profile (with regard to HDLc and triglycerides) than was obtained with the DASH diet while still lowering BP.

D. Proposal

Much research has already been conducted on single nutrients, with reviews and/or meta-analyses suggesting little BP benefit from supplements of calcium, magnesium, and fiber. Although previously understudied, several studies are now focusing on macronutrients, including protein. The successful Dietary Approaches to Stop Hypertension (DASH) feeding studies have generated much interest and conjecture as to what aspect of this dietary pattern accounts for its BP lowering effect. Studies on how the DASH diet works to lower BP is of interest because diets can then be more focused and tailored to individual preferences once the effective components of the diet are understood. A multi-center outpatient feeding study could design a series of short-term feeding protocols that could serially isolate each component of the DASH diet to determine the effective BP-lowering component. Ancillary studies could also be included to examine potential mechanisms. A 4-year study with 4 centers to recruit about 400 participants to assure adequate power for BP and lipid outcomes is proposed.

2.4 Stress-induced hypertension

A. Definition of the Problem

The hypothesis that mental or psychological stress is involved in the etiology of hypertension has a long history of investigation in animal models and in humans. Numerous questions remain concerning the relationship between systems mediating the stress response and the etiology of hypertension, their impact on the evolution of hypertension over time, and (in spite of a considerable number of published clinical trials) their implications for prevention and clinical interventions.

B. Current state of the science

Two primary systems mediate the stress response: the hypothalamic-pituitary-adrenocortical axis and the sympatho-adrenomedullary system. Both of these influence cardiovascular function acutely, with good evidence that they respond differentially in individuals with confirmed cardiovascular disease or its risk factors. Moreover cross sectional, and to a lesser extent longitudinal epidemiological data show that chronic job stress and cardiovascular reactivity in response to stress are associated with hypertension, coronary heart disease and stroke. The underlying physiological mechanisms remain poorly understood.

Animal studies have shown that adrenocorticotrophic hormone (ACTH)- glucocorticoid-induced hypertension is not prevented by drugs that block the classical glucocorticoid or mineralocorticoid receptors, suggesting alternative mechanisms and/or abnormalities in glucocorticoid metabolism . Recently ACTH receptors have been identified in aortic endothelial cells suggesting a role of ACTH on the action of glucocorticoid on the vasculature. Stress also affects the renin-angiotensin system. In rabbits, angiotensin receptors in the rostral ventrolateral medulla have been shown to mediate the pressor effects of emotional stress. Also, a recent report showed that, in the brain, central alpha-adrenergic receptor and CRH mediate hemodynamic responses to stress and are suggested to be implicated in the development of hypertension in rats. Furthermore, dopamine has been observed to protect against BP increases under acute stress conditions. Alterations of the dopaminergic system might contribute to the onset of hypertension. Therefore recent findings point to new and innovative areas of research in the understanding of stress-induced hypertension.

Research in humans is more difficult and while results have been more variable they are consistent with those from animal models. Evidence from longitudinal studies of cumulative exposure to job strain provides support for the hypothesized association between stress and blood pressure. Studies from research on cardiovascular reactivity may also be relevant. Cardiovascular reactivity to stress in childhood predicts rising systolic and diastolic blood pressure. Studies in cohorts with pre-existing coronary disease or essential hypertension consistently show a positive relationship between stress reactivity and subsequent clinical outcomes. In a cohort with initially high normal blood pressure, longitudinal data show an association between high cardiovascular reactivity to

stress and incident stroke after 11 years. Nonetheless, links between chronic stress and hypertension have not been established conclusively. In part this is due to the fact that estimating the exposure to chronic stress over an extended time is difficult. Therefore the acute cardiovascular response to stress, which is thought to serve as a marker of susceptibility to chronic stress, has been used as a surrogate for chronic stress in many studies. Measuring chronic stress exposure in longitudinal observational studies remains an important objective in this area. Studies of genetic polymorphisms, including polymorphisms of dopamine receptors, are in early stages. Results from these and other studies may account for some of the variance in human studies of hypertension.

C. Ongoing activity

Research funded by DHVD and by DECA is under way to examine sympathetic nervous system responses to stress; plasticity of the autonomic nervous system and baroreflexes in response to environmental demands; genetic and familial factors which influence susceptibility to psychosocial stress; psychological and individual traits which predispose to hypertension; minority status factors which influence risk of hypertension; and observational studies of environmental influences, including occupational stress, on hypertension. Although the individual projects address a broad range of questions, a comprehensive understanding of the role of stress in hypertension has not emerged. Furthermore, although efforts to evaluate non-pharmacologic, stress-management approaches continue on an occasional basis, exceedingly few well-designed clinical trials have been conducted to evaluate the potential of stress management for reducing blood pressure or to cope with the effects of chronic stress. Well-conducted stress management trials for hypertension in stress -positive patients would inform not only the potential for clinical interventions, but shed light on the hypothesized relationship between stress (e.g., cardiovascular reactivity) and hypertension.

D. Proposal

More information and integration is needed concerning the mechanisms through which chronic stress influences blood pressure. In addition, clinical and epidemiological experience should be brought to bear, so that basic and clinical research inform each other. A working group consisting of experts in the fields of physiology, neuroendocrinology, stress, heart and vascular biology, genetics, epidemiology and clinical trials could provide a valuable assessment of the state of knowledge and identify the most promising research directions in this area. (*This is being partially addressed by a Working Group on CV Consequences of Chronic Stress, convened in June 2004.)*

2.5 Sleep Problems, especially Sleep-Disordered Breathing

A. Definition of the Problem

Sleep disordered breathing (SDB) is an independent risk factor for the development of hypertension and cardiovascular disease. Cardiovascular risk factors such as diabetes, central obesity, dyslipidemia, and insulin resistance (without clinical diabetes), have each been reported to be present in as many as 30-90% of SDB cases. Despite these observations, however, the mechanisms underlying this increased risk for hypertension are not well understood. Additionally, it is not known to what extent treatment of SDB will mitigate this risk. Other major gaps include (1) to what extent important antecedents of hypertension-related consequences of SDB are present in children, (2) the extent of risk for hypertension associated with sleep deprivation and sleep disorders other than SDB, and (3) the extent to which current drug therapies for hypertension may adversely affect sleep quality/duration and hence interfere with successful treatment for hypertension.

B. Current State of the Science

There have been consistent data suggesting that individuals with SDB have higher blood pressure. Adjusted odds ratios for this association for an apnea▲hypopnea index (AHI) > 30 events/hour range from 1.37 in the Sleep Heart Health Study to 3.1 in the Wisconsin Sleep Cohort. The most compelling data thus far have come from the Wisconsin Sleep Cohort Study which demonstrated that in patients with untreated SDB, those with an AHI > 15 per hour had a three▲fold increased risk of the development of hypertension over a period of 4 years, independent of other known risk factors.

Obesity/overweight is a risk factor for SDB and for the hypertension associated with SDB. When controlling for overweight/obesity, however, as well as gender and race, SDB is an independent risk factor for hypertension. No published studies to date have apparently also controlled for physical activity and diet composition. SDB also occurs in normal weight persons and the epidemiological data indicate that SDB in young adults of normal weight is associated with a greater risk of hypertension and CVD than in older adults with SDB.

In general, hypertensive patients whose blood pressures do not fall appropriately at night (non-dippers) appear to be at increased risk for cardiovascular damage. Patients with SDB frequently have repetitive episodes of blood pressure elevation in conjunction with their apneic episodes. Individuals with SDB may be particularly likely to manifest a non-dipper pattern on 24-hour blood pressure monitoring. Moreover, some individuals with SDB also can demonstrate resistant hypertension (hypertension not appropriately controlled by three or more pharmacologic agents). Recent data suggest that treating SDB lowers not only nighttime but also daytime blood pressure.

There are a number of possible mechanisms by which nighttime SDB events could raise blood pressure even during the daytime. Among these are increased sympathetic activation, endothelial dysfunction, and the pressor effect of endothelin (ET-1) release. Experimental and clinical studies demonstrate that sympathetic overactivity occurs with SDB. The repetitive episodes of airway occlusion with hypoxia, hypercapnia and the dramatic changes in intrathoracic pressures result in diverse autonomic, humoral, neurohumoral and hemodynamic responses. These may affect cardiovascular function even when breathing is normal during the day. Urinary catecholamines are elevated in untreated SDB subjects and return to control levels following effective treatment. In both children and adults, sympathetic overactivity is associated with SDB. Sympathetic stimulation can contribute to insulin resistance and can modulate leptin expression, which may facilitate the development of a vicious cycle of worsening obesity, hypertension, and SDB. A major physiologic result of repetitive nocturnal SDB events is intermittent, often profound hypoxemia. Intermittent hypoxia (IH) is known to activate the sympathetic nervous system both acutely and chronically.

There is increasing evidence that endothelial dysfunction may be involved in linking SDB to the vascular pathophysiology of hypertension. In patients with SDB, the nocturnal hypoxemia results in a significant elevation in plasma ET-1, accompanied by increases in blood pressure. The hypertensive effects of ET-1 may persist for hours leading to sustained daytime blood pressure elevations as a consequence of its release during sleep. Effective treatment of the SDB by continuous positive airway pressure (CPAP) lowers ET-1 levels over three to four hours. The endothelial cell production of NO may also be diminished in patients with SDB, thus further contributing to impaired vasodilation.

Inflammation may be an important contributor to endothelial dysfunction in SDB. Hypoxemia and sleep deprivation may each induce production of pro-inflammatory cytokines. Indeed, patients with SDB have higher levels of C-reactive protein compared to closely matched control subjects. Activation of inflammatory mechanisms may directly impair endothelial function in patients with sleep apnea, resulting in impaired vasodilation and higher blood pressure.

Recent evidence indicates that sleep deprivation (insufficient time in bed) also contributes to metabolic and endocrine abnormalities. Insufficient sleep is associated with decreased glucose tolerance, elevated sympatho▲vagal balance, increased concentrations of evening cortisol, abnormal profiles of nocturnal growth hormone secretion, and markedly decreased leptin levels. In addition, when chronically short sleepers (sleep duration < 6.5hrs) are compared to normal sleepers (sleep duration >7.5hrs and <8.5 hrs), insulin sensitivity was reduced by nearly 40% in the short sleepers. These observations suggest sleep loss attributable to modifiable behaviors and not related directly to sleep disorders can also adversely impact components of the metabolic syndrome and may represent a risk factor for obesity and cardiovascular disease.

Obesity is a major risk factor for SDB, and patients with SDB may be at increased risk for weight gain. Resistance to appetite suppressant effects of leptin may be involved since SDB patients have higher leptin levels than similarly obese subjects without SDB. Increased leptin levels also appear

to be associated with SDB with levels declining after treatment with CPAP.

C. Ongoing Activities

NHLBI supports a program of investigator-initiated grants related to SDB pathophysiology, intermittent hypoxia, and treatment. Two multi-site clinical trials are now underway to determine whether the treatment of SDB using CPAP improves symptoms of daytime sleepiness and neurocognitive dysfunction. Population studies are investigating the epidemiology and genetics of sleep disordered breathing. In response to a recent initiative, 12 grants have recently been funded to study the relationship between sleep restriction, sleep disorders such as SDB, and aspects of the metabolic syndrome.

D. Proposals

The following are substantial gaps in our knowledge and represent opportunities for future research related to sleep problems and sleep disorders:

- Pathophysiologic link among sympathetic dysfunction, target organ change, and structural damage in blood vessels.

  Additional studies, which might be best performed in animal models, will need to consider the impact of differential effects because all blood vessels are not alike, e.g. receptors for inflammatory mediators may be dissimilar according to the type and/or size of blood vessel.

- Relationships among inflammatory biomarkers, vascular disease, and the initiation or propagation of endothelial injury associated with hypertension and SDB.

- Interactions among obesity, sleep deprivation and sleep fragmentation as contributing factors in the pathophysiology of hypertension.

- Identifying genes common to SDB and hypertension.

- Extent to which SDB▲related stressors may exacerbate hypertension, and degree to which effects may differ in individuals with different underlying genetic susceptibility to hypertension.

- Follow-up studies of children with SDB are in order to determine to what extent SDB in young children predicts the development of hypertension, metabolic syndrome, and endothelial dysfunction in adults.

In order to address many of the epidemiologic issues, new screening tools are needed and will be crucial to identification of the presence of SDB in large populations. Full polysomnography is relatively burdensome and expensive for epidemiologic research and clinical trial purposes. A number of less intrusive diagnostic techniques are available, but additional studies are needed to

compare their validity against polysomnography in larger numbers of subjects. One cost-effective approach to address some of the epidemiological issues may be to determine the extent to which SDB is a modifiable risk factor in NHLBI-funded hypertension/CVD clinical studies. There are several ways to get this information using surrogates for SDB and therefore not necessarily requiring overnight sleep recordings (polysomnograms). A related approach may be to define a core of sleep related information that would be obtained in all subjects enrolled in clinical studies, whether related to etiology and mechanisms, monitoring for risk factors/clinical evaluation, prevention/lifestyle treatment, treatment studies, or dissemination and implementation initiatives. Much could be learned in this way without having discrete stand-alone sleep-related studies. Equally important will be studies to determine the extent to which treatment for impaired sleep quality and excessive daytime sleep associated with other common sleep disorders (e.g. insomnia) can reduce risk for hypertension and improve treatment outcomes for established hypertension.

As part of a comprehensive clinical research effort, clinical trials of longer duration will be necessary to determine the extent to which successful treatment of SDB can reduce risk for hypertension and can improve treatment outcomes for patients with established hypertension. Before undertaking such trials, however, there is a need to develop simpler screening tools to identify individuals with SDB, and to gain a better understanding of the underlying pathophysiological mechanisms and the potential benefits of therapy. Clinical trials can probably be designed using intermediate endpoints in the causal pathway rather than relying on hard endpoints such as death or morbid events.

3.1 Blood Pressure Measurements: Technical Issues

A. Definition of the Problem

The mercury sphygmomanometer operated by a well-trained human is regarded as the most accurate and reliable noninvasive blood pressure (BP) measurement method . However, modern clinics and physicians' offices typically use anaeroid manometers or electronic oscillometric manometers, manual or automated. Additionally, it is becoming increasingly common for the lay person to monitor his BP in the home with manual or automated manometers sold in drug stores and over the internet.

Each type device—mercury, aneroid, or oscillometric—involves problems of variability in measuring BP. Common reasons are: biological variability of the subject due to the time of day, physical exertion or excitability (the white coat effect), and inaccuracies related to suboptimal technique of the operator. The oscillometric or automated manometer is particularly vulnerable to error in certain clinical circumstances, such as in elderly patients with stiff arteries due to atherosclerosis. However, both manual auscultatory measurements using the aneroid device as well as oscillometric devices have been shown to be highly variable in patients with arrhythmias. Errors due to operators taking BP measurements are well-described, including inaccurate cuff selection and application, cuff positioning, observer bias and lack of repeated measurements (1). Use of automated devices eliminates some of these problems, but introduces others,usually due to the idiosyncrasies of proprietary algorithms.

The question becomes one of validity of the BP measurements from any one device, and comparability of measurement values from different devices of the same type and different types of devices, particularly for epidemiologic-based recommendations of BP levels for diagnosis and treatment of hypertension (1,2).

Certification of medical devices in the United States is the responsibility of the Food and Drug Administration (FDA). The FDA delegated regulation of sphygmomanometers to the American Association for Medical Instrumentation (AAMI), generally accepting manufacturers' certification that their equipment meets AAMI standards (3).

An ancillary problem involves the cuffs used by all devices. BP variability due to cuffs is well-known. Although AAMI standards have been published for cuffs, these are mostly ignored (1). Regarding performance of BP observers, there are recommendations from the American Heart Association, but no organization overseeing such training or monitoring performance. The goal is validation and regular recalibration of devices, standardization of cuffs, and standardizing procedures and training for all users of devices.

B. Current state of the science

Sphygmomanometers continue to proliferate. Compliance with AAMI standards for validation and standardization of cuff sizes are voluntary. There is no enforcement of the AAMI standards; and devices are marketed which have not complied. Checks for calibration are not always included, and for some devices like the wrist unit, not possible. Standards are being proposed for neonatal and pediatric populations, but may be necessary for other subgroups by age and disease.

For automated oscillometric devices, AAMI validation standards prescribe a procedure whereby automated measurements are compared with same-limb measurements made simultaneously with cuff-bladder manual auscultation. Since aneroid and oscillometric devices depend upon different biomechanical phenomena to determine BP, the question remains as to comparability of measurements between the two modalities. Engineers have stated that it is not possible for an oscillometric device to correspond one-to-one with an aneroid device (3). However, there is general agreement that "on the average" the two methods give comparable numbers. There has been no rigorous demonstration of this assumption. Definitive studies are needed on comparability, at the population level as well as for individuals.

C. Ongoing Activity

AAMI continues to work on refining the validation standard for sphygmomanometers and is considering recommendations for subpopulations such as hypertensive and obese. Development of such recommendations is hampered by lack of data for these groups.

Because the British Standards Institution (BSI) and the European Union have standards different from AAMI's, it has been proposed that a joint committee of the International Standards Organization (ISO/IEC) group be convened to write a world-wide global standard on sphygmomanometers. AAMI continues to support the concept of identifying an organization that could review medical devices and give a "seal of approval" to those devices that meet the standards. AAMI is not charged with this task and does not have the authority. FDA has declined to take the lead.

D. Proposals

NHLBI should sponsor a study to determine the accuracy and comparability of manual, electronic and automated manometers, as well as a comparison to the gold-standard mercury manometer.

NHLBI should sponsor studies of variability in subpopulations such as those with arrhythmias, elderly patients with peripheral artery disease, and the obese to determine if current validation statistical procedures are adequate.

As can be seen from its role in the Lipid Standardization Program, NHLBI has a history of

assuming a leadership role in standardization of diagnostic measurements. NHLBI should sponsor a meeting at which all concerned parties (FDA, AAMI, American Heart Association, American Society of Hypertension, etc.) reach agreement upon a certification procedure for validation of devices, calibration procedures and standardization of cuffs. This certification process should ensure that manufacturers provide package insert material for consumers noting limitations and proper use of the instrument in conformance with the standards. Additionally, this committee should recommend training procedures to be followed by professional and non-professional users, as well as the means by which this should be accomplished. The committee should identify the organization or organizations responsible for providing the "seal of approval" for devices, and certification for observers.

Blood Pressure Measurements: Behavioral Aspects

A. Definition of the Problem

The clinical management of hypertension relies on the use of conventional sphygmomanometry for measuring blood pressure, a method that has both advantages (low cost, simplicity) and disadvantages ("white-coat hypertension," observer bias, normal variability in blood pressure). Newer techniques, such as ambulatory blood pressure measurement (ABPM)and self-blood pressure measurement (SBPM), provide alternatives that reduce or eliminate some of the problems associated with conventional sphygmomanometry. However, there is a need to determine whether these newer blood pressure measurement methods represent reliable, valid and cost-effective approaches for ascertaining blood pressure as part of the clinical management of hypertensive patients, and whether and under what circumstances they may be preferable to use of sphygmomanometry in the diagnosis, monitoring and treatment of hypertension. A related question is whether "white coat hypertension," also called isolated clinic hypertension, is a benign phenomenon, a precursor to hypertension, or itself a prognostic indicator of adverse outcomes.

B. Current state of the science (*This topic was covered in detail by an Evidence Report/Technology Assessment entitled "Utility of Blood Pressure Monitoring Outside the Clinic Setting", released by the Agency for Healthcare Research and Quality in November 2002.*)

Clinic blood pressure measurement using conventional sphygmomanometry has the advantage of simplicity and low cost, and, because it has been the measurement method used in all clinical trials which have established the benefits of antihypertensive therapies, is considered by many to be the only valid measurement for use in treatment decisions. However, use of sphygmomanometry in the clinical setting can result in imprecise or inaccurate blood pressure readings because of both instrument error and behavioral factors. The former is discussed in detail elsewhere (see section 3.1); the latter include errors or imprecision attributable to the observer (nurse, physician or other health professional who measures the blood pressure) and those based on behavioral and psychosocial aspects of the patient. Examples of observer error include terminal digit preference (observer rounds actual blood pressure up or down) and observer bias (observer adjusts the blood pressure based on preconceived expectations). With regard to patient behavior, the so-called "white-coat effect" (more recently labeled "isolated clinic hypertension"), in which blood pressure rises in response to its measurement by a health professional, can result in overestimation of blood pressure and thus an inaccurate diagnosis of hypertension, leading to potentially costly and unnecessary treatment. Blood pressure is highly variable, responding to behavior and psychological state and exhibiting large diurnal variation, thus single measurements or even multiple measurements taken at the same time of the day will result in less precise or even inaccurate measurements of a patients' blood pressure.

Recent studies of ambulatory blood pressure measurement (ABPM) and self-blood pressure measurement (SBPM) show these methods to have some advantages over conventional clinic measurement using sphygmomanometry. ABPM is thought to be a better measure of usual blood pressure than conventional office blood pressure because it provides many measurements over a longer period of time (typically over a 24-hour period) in the patients' natural environment (eliminating the "white coat effect"). There is also evidence that ABPM is a better predictor of cardiovascular endpoints, especially for individuals with treatment-resistant or untreated hypertension who have high clinic blood pressure. ABPM also allows for assessment of physiologic and environmental determinants of blood pressure variability that may be useful in assessing individual risk, for example, circadian blood pressure rhythm, mental stress (including work stress), and sleeping disorders. It is currently unclear whether the ability to account for these determinants of ABPM variability add to its prognostic value and would therefore be of use in managing the hypertensive patient.

Self-recorded home blood pressure measurement (SBPM) also has been found to improve adherence to antihypertensive therapy and to reduce the number of clinic visits needed. However, unlike ABPM there are no accepted guidelines for initiation and maintenance of antihypertensive therapy using SBPM values. In order for SBPM to be of optimal use in the management of hypertension, studies are needed to establish thresholds at which treatment should be initiated and adjusted. Finally, a separate but related issue is the unknown prognostic significance of "white coat" hypertension. While some studies show individuals who demonstrate this effect to be at lower cardiovascular risk than those with sustained hypertension, others have found the "white coat" effect to be predictive of target organ damage. Further investigation of the possible predictive value of this effect is needed.

C. Ongoing activity

Several reports and conferences (8th International Consensus Conference on Blood Pressure Monitoring in Sendai, Japan; October 28-31, 2001 – Task Force reports appear in Blood Pressure Monitoring, 2001 Dec;6(6):313-341) have examined the state of the science in blood pressure measurement and made recommendations regarding blood pressure measurement methods in clinical practice settings and needs for future research in this area. These reports identify the need for further evaluation of the phenomenon of "white coat" hypertension as well as studies to evaluate the value and cost-effectiveness of integrating ABPM and SBPM into the routine care of hypertensive patients.

D. Proposal

The development of ABPM and SBPM as alternatives to clinic-based blood pressure monitoring and their potential use in promoting better management of hypertension is a rapidly developing area that may profit from review from a working group of experts who could sort through the literature, determine gaps in knowledge and highlight the areas most in need of research and/or translation activities. There is a large and rapidly changing literature in this area, and a working

group charged with making recommendations for future needs may be useful in structuring the many questions that have arisen with the advent of home and ambulatory BP devices.

There are several avenues that such a group might focus on, and that may lead to initiatives or other activities. First, there is a need to determine the optimal role of ABPM and SBPM in the diagnosis, monitoring and treatment of hypertension; to identify the extent to which they represent reliable, valid and cost-effective alternatives to clinic-measured blood pressure; and to determine whether they provide additional prognostic value as part of the clinical management of hypertensive patients. Studies are needed to establish thresholds using SBPM that can guide diagnosis and treatment of hypertension. Studies should also assess whether hypertensive treatment protocols involving use of ABPM and SBPM would result in better blood pressure control, cardiovascular outcomes and be more cost-effective than those based on conventional clinic-measured sphygmomanometry. Such studies might be designed as ancillary or substudies within larger trials of antihypertensive treatments.

There is also a need to investigate whether various physiologic and environmental determinants of blood pressure variability (for example, circadian blood pressure rhythm, mental stress, and impaired sleep duration and sleep quality) are useful both in the diagnosis and treatment of hypertension, and as prognostic indicators of adverse outcomes. This would include the "white coat" effect – is isolated clinic hypertension of prognostic significance, and is it useful in hypertension diagnosis and treatment? Again, such studies might be included as ancillary studies to larger epidemiologic studies or trials of antihypertensive treatments. Alternatively perhaps an RFA could be designed that encourages studies of BP variability and the possible value of including BP variability measures in hypertension management protocols.

4.1 Prevention/Lifestyle Treatment in Children

A. Definition of the Problem

The 1996 NHLBI Task Force Report on High Blood Pressure in Children and Adolescents defined high-normal blood pressure as systolic or diastolic blood pressure greater than or equal to the 90th percentile but less than the 95th percentile (redesignated as "prehypertension" in the 2004 Report), and hypertension as greater than or equal to the 95th percentile for age and sex based on normative data from 10 pediatric populations. The etiology of hypertension is different in children when compared to adults. In very young children it is often secondary to a vascular or renal cause, and treatment has been directed towards the specific etiology. As children age and become teenagers, the etiology shifts from secondary causes to primary or essential hypertension, and there has been little focus on the prevention and management of essential hypertension in children. Children at the upper percentiles of the blood pressure distribution, although not defined as having hypertension, may nevertheless be at future risk of hypertension and cardiovascular disease when they become adults. Blood pressure in childhood often correlates with blood pressure in early adulthood, such that children at the upper percentiles of blood pressure maintain this upper ranking as they approach adulthood. In addition to higher levels of blood pressure, other risk factors tend to cluster in children, including obesity, dyslipidemia, and impaired glucose tolerance.

B. Current State of the Science

Major factors known to be associated with higher blood pressure in children are age, family history of high blood pressure, height, and obesity. Sexual maturation is also related to higher blood pressure in children, but this association is generally explained by the accompanying increase in body mass index. The strong relationship between obesity and blood pressure has been demonstrated in both observational and intervention studies in children. Although weight loss lowers blood pressure in adolescents, we do not know what factors modify (interact with) obesity regarding the predisposition to develop hypertension in children, as there are many obese children who are not hypertensive. Sodium intake is likely one of these factors. Obesity has been shown to increase insulin insensitivity, even in children. Insulin insensitivity triggers a cascade of counterregulatory hormones such as norepinephrine and aldosterone that increase vasomotor tone and increase sodium and fluid retention, which increases the risk of hypertension.

In adults, lifestyles that include achieving a healthy weight, engaging in regular physical activity, and following diets that are rich in fruits and vegetables, reduced in sodium and alcohol, and increased in potassium, have been found to be associated with lower BP, and randomized trials

and/or meta-analyses have confirmed these associations. However, very little information exists on the association between healthy lifestyle and BP in children, and the urgency of acquiring such information is underscored by a recent report of adverse temporal trends in childhood BP, not fully explained by increasing overweight. Only one randomized controlled trial in adolescents demonstrated that weight loss reduced BP. It is not clear whether regular physical activity is associated with lower BP or whether increasing regular physical activity will decrease BP in children, as has been demonstrated in adults. Likewise, observational studies examining nutrients and diets that have been shown to be related to lower BP in adults have been inconclusive when studied in children. Few well-designed randomized trials with adequate sample size have been conducted to determine the effects of diet on BP in children. The most extensively studied nutrient is sodium, and results from the methodologically stronger observational studies, and trends in the randomized controlled trials, suggest but do not conclusively show that higher sodium intake is related to higher BP in children. A reason for inconclusive results for physical activity and diet in children is the low magnitude of the associations in observational studies and the large variability in the measurement of physical activity, diet, and BP. In addition, small BP effect sizes have been found in intervention studies. Thus, many studies have reported nonsignificant findings. Little is also known about the optimal way to lower BP in children that might include multiple components such as physical activity and weight control in addition to a healthy diet.

Essential hypertension in children is multifactorial in etiology. Expression of familial tendencies to hypertension usually begins in adolescence. In rare cases, families have severe hypertension caused by mutations in single genes that regulate renal salt-handling, but this represents a tiny fraction of hypertensive cases. For most children and adolescents, multiple genetic and environmental factors influence the incidence of essential hypertension. The development of hypertension in those who are genetically predisposed toward hypertension can be accelerated when the child is overweight or obese. Since blood pressure is likely higher in children with acute and chronic sleep deprivation or with a sleep disorder and hence poor sleep quality, normative blood pressure studies should include basic information about acute and chronic sleep deprivation, chronic snoring (especially loud and frequent), hyperactivity, and excessive daytime sleepiness..

There is increasing evidence that intrauterine environment and fetal growth patterns play an important role in the development of childhood hypertension. Better understanding is required of how the intrauterine milieu predisposes to development of hypertension and learn how to optimally manage a pregnancy to prevent the development of hypertension in later life. Studies in infants have shown that reduced sodium for just 6 months in newborns can lower BP. It was later reported that when 35% of those infants were followed 15 years later, those who were originally assigned to the lower sodium intervention still had lower BP than those who were in the control group without further intervention during the intervening years.

Classification of hypertension and high-normal BP in children is currently limited, as it is based on population norms and not on health outcomes. It also is unclear whether and at what BP in children target organ damage occurs.

C. Ongoing Activity

Several studies are under way examining the pathophysiology of hypertension in children: Blood Pressure Control in Juveniles is a longitudinal investigation of the role of sodium retention and its regulation by angiotensin II and the amiloride-sensitive sodium channel; Divergence of Blood Pressure by Race in Adolescent Girls examines hemodynamic changes, including cardiac output, total peripheral resistance, and left ventricular mass, to determine if racial differences account for higher BPs observed in older adolescent African American girls; End-Organ Injury in Hypertensive Children examines the association between BP and hypertensive end-organ injury in children with hypertension; and Cardiac Disease in Children with Chronic Renal Failure identifies risk factors for left ventricular hypertrophy and vascular abnormalities which lead to cardiovascular disease in children with renal disease. Two other observational studies that focus on obesity in children also measure BP. One study, The Epidemiology of BMI Rebound, follows children from age 3 to 7 to determine the vulnerable point in time when obesity risk may increase sharply, and will also examine the relationship between BMI trajectory and BP. Another study, Visceral Adiposity and CVD Risk in Women, examines the relationship between visceral fat and CVD risk factors, including BP, in the NHLBI Growth and Health Study (NGHS) cohort of girls who had been studied since age 9 and 10 years.

Several intervention studies for general cardiovascular disease risk reduction are also measuring BP as secondary outcomes. These include CVD Reduction in Minority Pre-school Children, which tests the effectiveness of nutrition education and change in food service on children's diet, blood cholesterol, weight, and BP; and four intervention studies focusing on increasing physical activity in adolescents to improve cardiovascular fitness and reduce obesity that also measure BP (Interventions to Increase Physical Activity; Adiposity Prevention by Exercise in Black Girls, APEX; Lifestyle, Adiposity, and CV Health in Youths; Families Implementing Good Health Traditions for Life). Two intervention studies, Girls health Enrichment Multi-site Studies (GEMS) are testing 2-year interventions to decrease excessive weight gain and prevent obesity in a total of 560 African American girls age 8-10. Effects on BP will also be measured.

In addition, a meta-analysis is currently being conducted examining the effects on BP of physical activity interventions in children. Finally, NHLBI, under the auspices of the National High Blood Pressure Education Program, has sponsored the 2004 Working Group on High Blood Pressure in Children and Adolescents which has considered several topics in pediatric hypertension, including lifestyle and prevention.

D. Proposal

Remarkably few randomized controlled studies have tested the effects of weight loss on BP in children even in the short-term, let alone long term. Given the Department's current emphasis on obesity, initiatives for weight loss and obesity prevention in children are likely to be developed. These studies should also measure BP as an outcome to improve the evidence base on the efficacy of weight loss for BP reduction in children, and particularly for obesity prevention studies, to

determine whether obesity prevention will also prevent elevated BP in children.

Because little is known about the efficacy of dietary factors on BP levels in children, a randomized intervention trial with adequate sample size should be undertaken where as much of the food is provided as possible to study the effects of diet on BP. The dietary intervention should not focus on nutrients but rather dietary patterns, such as the DASH diet, as dietary patterns have been successfully studied in adults, and results are more easily translatable into public health recommendations than interventions involving single nutrients. The independent effect on BP of dietary sodium should also be evaluated. It would be important to know the extent to which lower sodium reduces BP in children. The current food supply is high in sodium, and life-long exposure from young ages to high-sodium diet may create the environment that causes BP to increase with age. A multi-center trial, or a series of diet protocols, should be undertaken to provide adequate sample size to answer the research question on the effects of diet on BP in children.

To further evaluate the role of early "programming" on BP in the young, a multi-center sodium intervention trial in infants, with plans for long-term follow-up, should be undertaken to provide adequate sample size and diverse population for greater generalizability. Results from this study will help inform public health recommendations regarding infant diets. (This trial was a recommendation of a 1998 Working Group on Research Directions for Cardiovascular Prevention in Children and Adolescents.)

Finally, an RFA for single-center research project grants should be released to study fundamental mechanistic studies of the pathophysiology of hypertension in children, including studies examining the disease process and studies investigating why obesity leads to hypertension in children. Mechanistic studies may help identify therapeutic interventions that may interrupt the disease process before the establishment of irreversible disease.

4.2 Prevention/Lifestyle Treatment in Adults

A. Definition of the Problem

In the face of high prevalence rates of hypertension, a lifetime incidence rate estimated at 90%, and BP control rates of only 34%, lifestyle modification is an important strategy for the treatment and prevention of hypertension. However, people generally do not follow lifestyle recommendations for hypertension prevention and BP control, and adherence to lifestyle recommendations in people who have attempted to make behavioral changes to control their BP has been an elusive goal especially over the long term. New efforts are needed to develop more effective methods of fostering lifestyle change, especially among individuals in the "pre-hypertensive" stage who thereby might delay a reliance on drugs.

B. Current State of the Science

After 3 decades of intervention research, much of it supported by the NHLBI, a great deal is known about the efficacy of lifestyle interventions, both single- and multiple-factor, for controlling BP. These interventions are well-summarized in the two NHBPEP publications on primary prevention of hypertension, and in a recently published book, "Lifestyle Modification for the Prevention and Treatment of Hypertension." Among lifestyle modifications, weight loss and dietary change, including sodium reduction, have been shown to reduce blood pressure significantly among individuals with hypertension, with good results in normotensive individuals whose blood pressure approaches the border of hypertension. Results from randomized clinical trials of exercise for reduction of blood pressure have been less consistent and accompanied by high drop-out rates and insufficient attention to measurement of potentially confounding lifestyle variables. An ongoing related issue in research is the ability to assess with greater precision in a clinical setting assessment measures of the risk factors for hypertension, i.e., diet and physical activity.

In addition to these lifestyle risk factors, psychosocial risk factors, particularly stress, depression and cardiovascular reactivity, have been associated with hypertension. Results from clinical trials of interventions that reduce these psychosocial risk factors have been inconclusive in part because clinical trials have been small and of inconsistent methodological quality. For single psychosocial interventions such as biofeedback, relaxation therapy and stress management, results typically are not significantly different from placebo or sham interventions, although evidence exists that more intensive interventions involving combinations of cognitive therapies may lower blood pressure significantly.

A critical need is to increase our knowledge about how to assist people to adopt healthy lifestyles. To address this need involves translational research to identify how primary health care systems can better implement clinical guidelines and promote healthy lifestyles, as well as community interventions to facilitate and motivate people to the same ends. A potential and novel strategy is

to use psychosocial approaches to improve the effectiveness on adherence to lifestyle interventions. There is strong evidence that depression, for example, influences adherence to healthy lifestyles as well as to medical regimens. Combining lifestyle and psychosocial approaches, particularly by using psychosocial support through stress management and cognitive behavioral strategies to improve adherence, may improve effectiveness and maintenance of lifestyle programs involving diet, weight loss and physical activity. Finally, since adherence is a continuing problem for all types of interventions, including pharmacotherapy, a strategy of using psychosocial interventions, particularly cognitive methods targeting stress and depression, may result in improved blood pressure control.

C. Ongoing Activity

Several ongoing intervention studies are focused on efficacy and biological effects on BP of interventions rather than effectiveness and translation. These include: three studies investigating the role of genotype in the BP response to various interventions, including diet (Dr. He, Genetic Epidemiology of Blood Pressure Intervention; Dr. Lefevre, Diet, Genetics, and CVD Risk Factors in Blacks; and Dr. Shuldiner, Genome-wide Search for CVD Gene-Environment Interactions) and a study investigating the effect on BP of differing exercise intensities in adults with hypertension (Dr. Posner, Treatment of Hypertension with Two Exercise Intensities).

There are two ongoing multicenter trials with interventions that could be used in health care practices and work sites, making them highly translatable. The PREMIER study, a trial of multicomponent interventions for BP control, tests the effects on BP and hypertension prevalence of two behavioral lifestyle interventions versus an advice only group. This trial showed that diverse, community-dwelling adults can be counseled to successfully make multiple lifestyle changes for six months. The Weight Loss Maintenance trial will test the effect on long-term maintenance of weight loss of two forms of intervention delivery over a period of 2½ years compared to a usual care intervention. Despite the recommendations of two NHLBI Workshops several years ago, this study is the only ongoing trial specifically aimed at a comparative assessment of lifestyle change maintenance. One small trial evaluates the use of cognitive therapy as an adjunct for a diet/weight loss program for treating hypertension.

A PAR has been released by the National Cancer Institute (PAR 03-009) requesting applications on Improving Diet and Physical Activity Assessment. Some of these applications may address methodological issues for clinical and translation research.

D. Proposals

A critical need is to develop methods so that more of the population follows healthy lifestyles to prevent hypertension. If we can reduce the age-related risk in BP, the incidence of hypertension will substantially diminish. Experience from recent trials (Activity Counseling Trial, PREMIER) suggest that primary care providers and community health organizations may be effective in causing behavioral change, as behavioral change was noted in the usual care group which received

brief sessions with health care providers or health counselors providing advice for healthy lifestyle. An RFA calling for trials of primary-care-based intervention and/or community-based programs to give advice or simple behavioral interventions for healthy lifestyles versus no advice would be an important step toward determining whether simple interventions provided by health care professionals are sufficient for adults to adopt health behaviors. Developmental work on methods of assessing diet and activity in these settings would be encouraged.

Feasibility should be assessed of a clinical trial which combines the most promising features of weight loss, diet, physical activity, stress management, with cognitive interventions for depression and stress to reduce reliance on drugs for individuals identified as "pre-hypertensive," i.e., having blood pressure above-optimal but not yet hypertensive. Feasibility of such a trial and its design should be evaluated by a working group consisting of experts in pharmacological and non-pharmacological interventions for hypertension, clinical trials and psychosocial factors as related to hypertension and to adherence. The working group would make its recommendations to NHLBI for further consideration through the customary initiative development process.

Most interventions for behavioral change shift the entire burden to adopt healthy behaviors on individuals, while the environmental context under which the individuals must operate promotes unhealthy lifestyle behaviors. Thus, individuals have to constantly work against environmental pressures in order to eat healthful diets, achieve healthy weight, and be regularly active. Going beyond the Worksite RFA for prevention and control of overweight/obesity, an RFA for interventions to test environmental interventions that promote healthy lifestyles would be a major step forward. One area to concentrate is environmental interventions to reduce sodium in the food supply, restaurants and supermarkets. Simple assessment tools for diet would be particularly important to develop for this type of intervention.

5.1 Drug Treatment for Adults

A. Definition of the Problem

Of the estimated 58 million U.S. adults with hypertension, only 59% report receiving drug treatment and only 34% have their blood pressure (BP) controlled to <140/90 mm Hg. The gap between treatment and control may relate to the clinical trials evidence available to clinicians who treat hypertension. Although clinical guidelines have classified BP < 120/80 mm Hg as "optimal" based on epidemiologic evidence, national data suggest that many physicians who treat hypertension are satisfied with systolic BP in the 140-159 mm Hg range, with diastolic pressure below 90 mm Hg. This may be because no completed clinical CVD end-point trial has been designed to test the effect of treating to goal systolic pressures below 140 mm Hg. Further, available data suggest that most patients will need 2 or more drugs to achieve control. While previous major antihypertensive treatment trials have allowed for multi-drug regimens, usually in a stepped-care approach, the focus of trials that have compared regimens has been on the initial drug given. Thus it is not known if any drug combination will better prevent major cardiovascular (CV) events than any other. Finally, while the choice of first-step and additional drugs have been broadly guided by clinical end-point trials, tailoring of choices based on biological characteristics remains a poorly studied area of therapeutics.

B. Current state of the science

In NHANES III data, 77% of patients with treated but uncontrolled hypertension had isolated systolic elevations, with a mean systolic BP of 155 mm Hg. In a national survey of primary care physicians, 43% of physicians said they would not initiate drug therapy for patients with systolic pressures of 140-159 mm Hg and 1/3 reported they would not intensify treatment in a patient with a systolic pressure of 158 mm Hg. The majority of these respondents were familiar with JNC guidelines that call for initiating treatment at systolic BP of 140 mm Hg or greater, and treating to below this level. It is unknown to what degree this common failure to pursue or achieve consensus targets results from gaps in the evidence from large-scale trials. Placebo-controlled clinical endpoint trials that have selected patients based on systolic pressure have used >160 mm Hg, and targeted pressures in the 140-159 range. However, it is not widely recognized that major trials which found mortality/morbidity benefits from BP reduction achieved mean systolic levels of as low as 131 mm Hg (the HDFP) and 138 mm Hg (the hypertensive stratum of the PROGRESS trial). In terms of what levels of BP should call for initiation of drug treatment, in the "non-hypertensive" stratum (mean systolic BP in the 130's) in PROGRESS (stroke survivors) and in HOPE (patients with chronic CHD and/or diabetes), treatment with BP-lowering regimens significantly reduced CV events. These results are extended by epidemiologic data in broader populations showing that"pre-hypertension" (formerly "high normal BP") confers substantially increased risk, particularly in older persons. The JNC7 guidelines do not recommend drug treatment for pre-hypertension, but only use of BP-lowering drugs for any "compelling indication" present in such patients.

The 5 classes of drugs most commonly prescribed for treating hypertension are thiazide-type diuretics (thiazides), beta-adrenergic blockers (BBs), calcium channel blockers (CCBs), angiotensin-converting-enzyme (ACE) inhibitors, and angiotensin-receptor blockers (ARBs). All have been shown in large randomized trials to reduce the risk of major CV events compared with placebo or alternate treatments. Three of these 5 classes were evaluated in the hypertension component of the Antihypertensive and Lipid Lowering Treatments to Prevent Heart Attack Trial (ALLHAT), and the low-moderate-dose thiazide-based treatment was found to be superior for preventing one or more CV outcomes compared to CCB-based or ACE-inhibitor-based treatment. Another ALLHAT arm using an alpha-adrenergic blocker was terminated earlier because of significantly higher risk of CV events than with thiazide-based treatment. A recently published "network" meta-analysis combining results from 42 trials (including ALLHAT) involving 192,478 patients supports these conclusions, and also found evidence of superiority of thiazides compared to BBs and ARBs.

In ALLHAT, only 30% of patients had their BP controlled to <140/90 mm Hg on a single-antihypertensive drug. Compared to typical patients, ALLHAT participants had characteristics that may have made their BP easier to control–the eligibility requirement that pre-randomization BP be <160/100 mm Hg on no more than 2 drugs–, or harder to control–older age (mean of 67 years), high proportion of diabetics (1/3 of patients). The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) concluded that "the majority [of patients] will require 2 or more antihypertensive drugs." The most common combination in the diuretic arm of ALLHAT was thiazide plus BB (atenolol). There are abundant data in the literature that all of the main classes of antihypertensive drugs combine effectively with thiazides in terms of BP lowering, and there are theoretical reasons for advantages of each combination for one or more outcomes.

Considerable data support the idea that BP responds somewhat better, on average, to some classes of drugs than others; demographic factors, especially race and age, appear to predict response as well or better than physiologic characteristics. Regarding clinical events, in ALLHAT stroke and combined CVD outcomes differed between the diuretic and the ACE inhibitor more for Black than non-Black patients; much of this could be attributed to a greater BP difference in Blacks. There is also much activity regarding genetic variants and BP response to drugs (see "Pharmacogenetics"). It has also been suggested that type and stage of subclinical target organ damage (LVH, athereosclerotic markers, renal damage) may identify patients in whom different classes of antihypertensives have differential effect. A few trials (in LVH, diabetic nephropathy, and non-diabetic renal disease) have found that ACE-inhibitors or ARBs have advantages over BBs and CCBs for selected outcomes.

C. Ongoing activity

The only major trials comparing effects on CV outcomes from treating to different systolic BP goals are in Type 2 diabetics (especially the NHLBI-NIDDK ACCORD trial). There are no NHLBI-funded clinical trials comparing different drug combinations with the same BP goals in

each group. In ALLHAT, on-treatment analyses (which no longer have the protection against bias afforded by randomization) are being conducted, but because of the design there are relatively few patients on a diuretic plus a drug from another major class besides a BB. There is a large clinical end-point trial underway in Europe, the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), which is comparing an arm based on "traditional drugs" (thiazides +/- BB) with a CCB +/- ACE inhibitor. ASCOT is scheduled to report results in 2004. Only the ongoing GenHAT (ancillary study to ALLHAT) is addressing candidate genes as predictors of treatment-related differences in CV events.

An NHLBI Workshop on Future Directions for Hypertension Treatment Trials was held in September 2003, with participation of about 35 non-Institute (mostly non-Federal) scientific experts in hypertension treatment and/or CVD clinical trials. The main objective was to consider the need for further hypertension treatment trials with clinical event outcomes. Three themes for trials will were explored :

- determining how low blood pressure (initially or at goal) should be targeted for treatment;
- determining optimal treatment regimens for a broadly representative patient population;
- assessing the role of treatment guided by non-BP patient characteristics at initial evaluation or in response to treatment.

Variations on these concepts were discussed in terms of importance, especially potential impact on medical practice, feasibility, and priority compared to other trials and compared to research explicitly targeted at practice changes to achieve better BP control.

Preliminary recommendations on the three themes are as follows:

- A trial was recommended to test the effect on CV events of lowering systolic BP from untreated levels of 130-149 mm Hg, or partially treated levels >140 mm Hg. The design might involve treatment to stated goals using a wide variety of antihypertensive (AHT) drugs open label (like ACCORD), or use limited titration using a masked design (like SHEP), or use allocation to a fixed 2-3 drug combination versus placebo.
- A trial was recommended to compare up to 4 classes of drugs as second-step therapy for effects on major CV events. Classes suggested for consideration were: an ACE inhibitor, an ARB, a CCB, an aldosterone antagonist, and perhaps a beta-blocker.
  (N.B. - Designs addressing both questions in a factorial design were considered, but not extensively.)
- It would be premature to pursue a large trial specifically testing gene-directed therapy at this time, but genetic considerations (with regard to design, stored samples, and consent) should be addressed in any large trial from the outset. The concept of a trial based on a particular effect on subclinical CV disease beyond that mediated by BP-lowering met with skepticism that such treatment regimens could be identified, and that the screening needed to apply the results would be cost-effective (except possibly for urinary albumin excretion).

Also, consideration was given to pursuing a clinical endpoints trial by establishing a Hypertension Clinical Research Network, which could serve as well as for studying translation issues, both bench-to-clinic and clinic-to-practice (see section 6.2).

D. Proposal

An updated proposal awaits final recommendations from the September Workshop. The following is an example of one trial that would address both BP targets and drug selection:

Building on ALLHAT results, a large simple trial could be conducted to compare the effect on major CV events of adding to a thiazide a second drug from 3-4 of the other main classes, including an ACE inhibitor and/or an ARB, a CCB or a BB, and possibly an aldosterone antagonist. The study population would be similar to ALLHAT's–older hypertensives with one or more other risk factor, but enriched with patients with chronic kidney (CK) disease and increased risk of stroke. They would need to be tolerant of a thiazide, and have BP levels not optimally controlled on a single drug. In addition, patients could either be assigned to a target systolic BP of around 140-145 or around 120-125 mm Hg in a factorial design, or a placebo arm could be included in a simple multi-armed design. The primary outcome would be major CV-renal events, defined as death attributed to CV or CK disease, or non-fatal myocardial infarction, non-fatal stroke, non-fatal heart failure, or kidney failure. Depending on the number of arms, the probable sample size requirement would be 30,00 to 40,000. Approximately half the study population would be African American, and half would be women. Genetic and economic sub-studies would be included. The total trial duration is estimated as 9 years: 1 year for planning, 3 years for recruitment, 4 years of additional follow-up, and 1 year for analysis and reporting.

5.2 Pharmacogenetics of Antihypertensive Drugs

A. Definition of Problem

. According to the 7th Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, the overall adequacy of blood pressure control in clinical practice is approximately 34 percent, well below the goal set for Healthy People 2010. Although poor adherence to prescribed drug regimens is a major contributor to inadequate blood pressure control, the heterogeneous nature of the condition, in part due to its polygenic origins, is a major impediment to effective treatment as well.

At present, antihypertensive medications are usually prescribed on an empirical basis, based on the personal clinical experience of the prescriber and on clinical guidelines. Under optimal circumstances, such guidelines and drug prescribing is based on evidence from randomized clinical trials when it is available. Traditional management of hypertension involves an initial prescription, followed by reassessment and initiation of additional dosage or different drugs if required. Choosing an optimal drug and dosing regimen is not infrequently complicated by perceived side effects or occasional adverse reactions, and it is presently difficult to predict which patients are more likely to develop problems.

An ongoing effort exists to identify genetic determinants of essential hypertension both in people and in animal models of the disease. The goal of this genetic research is to understand the etiology and underlying biological mechanisms of high blood pressure in order to improve preventive strategies and treatment. It is not known at this time whether stratifying the hypertensive population into subgroups by genotype or intermediate phenotype is practical. Furthermore, it is not clear whether genetically guided preventive strategies or gene-directed therapy will provide clinical advantages over standard care. Particularly important in this regard is whether gene-directed therapy can reduce adverse responses to medications and the trial-and-error period that often accompanies selection of the most efficacious and best tolerated drug regimen.

B. Current State of the Science

Individual variability in both drug efficacy and adverse reactions results from multiple and complex biological processes that can be assessed through well-established pharmacokinetic and pharmacodynamic techniques. Genes controlling the physiological disposition of a drug, quantified through pharmacokinetic assessment, determine the presentation of a drug at its target, including such processes as absorption, metabolism, and renal excretion, while genes responsible for pharmacodynamics determine the drug's effect after it reaches its target. The biological variability to drug response is therefore influenced by a variety of genetic polymorphisms that operate in concert. These genes might code for drug-metabolizing enzymes, drug receptors, ion

transporters, intracellular enzymes, orproteins involved in signal transduction pathways. Other genes that are associated with the pathophysiology of hypertension could also be determinants of a drug's effectiveness.

Over the past several years, there have been a series of relatively small studies in which the presence of specific genetic mutations have been linked to antihypertensive medication responsiveness. Variations in both postulated disease genes, drug target genes, and drug metabolizing genes have been studied. Specifically, a series of studies-----some of which have been supported by the National Heart, Lung, and Blood Institute-----have been reported in the literature monitoring drug responsiveness as a function of variance in genes coding for: hepatic drug-metabolizing enzymes, such as cytochrome P4502C9 (CYP2C9); signal transduction molecules, such as G proteins; α-adducin, a protein contributing to renal sodium retention; the β1-receptor, which modulates cardiac chronotropy and inotropy; endothelial nitric oxide synthase (NOS), which catalyzes the formation of the vasodilator nitric oxide; and two components of the renin-angiotensin-aldosterone system, i.e., angiotensin I-converting enzyme (ACE) and the angiotensin II type1 receptor.

All studies published to date have in common: the relatively small number of people studied (all under 800 subjects), lingering questions about the generalizability of the findings, varying justifications for the genes and drugs selected, the absence of data for many widely used antihypertensive drugs, the need to have results independently confirmed, and the lack of consideration of how useful are the genes studied to date for future examination in a large-scale clinical trial. A critical void that is in need of immediate attention is the absence of infrastructure and tools for data warehousing. In short, there have been no effective coordinated efforts to develop a sufficiently strong fundamental knowledge base to proceed to the next important step of translating basic findings in human subjects to population-based research.

Interestingly, there has been a renewed interest within the pharmaceutical industry to develop pharmacogenomic approaches due to the recent FDA guidance that encourages genetic testing during drug development. Industry has already invested resources towards generating the appropriate databases and the supporting statistical framework. The academic community can certainly benefit from the existing infrastructure within the private sector in addressing numerous issues related to trial design, biostatistics, and diagnostic criteria to help understand the genetic variability of drug action. A strong public-private partnership would be critical in helping move the field forward and bringing any pharmacogenetic based test to the forefront and for clinical use.

C. Ongoing Activities

The NHLBI is currently supporting three pharmacogenetic initiatives. The *first* program is the NIH-wide "Pharmacogenetics Research Network and Knowledge Base" that is coordinated by the National Institute of General Medical Sciences. Its stated objective is to link academic institutions conducting human pharmacogenetic research on cancer, cardiovascular, and pulmonary disease. The *second* program is the "Ancillary Pharmacogenetics Studies in Heart, Lung, Blood, and Sleep

Disorders" that has recently undergone its first competition and that supports studies on the genetic determinants of drug action and biological disposition using patients, reagents, and other resources from currently active and established clinical studies. The *third* program is GenHAT, which is an ancillary study utilizing patients and the infrastructure of ALLHAT. Its objective is to determine whether a group of preselected candidate genes can contribute to the antihypertensive response, as well as effects on cardiovascular disease end-points, of a diuretic, a beta-blocker, an ACE inhibitor, and an alpha-blocker.

It is anticipated that these three programs will yield important observations on the role of genetic variability on drug action. However, none of them has been designed in a concerted fashion with the specific objective of identifying the most likely candidate genes to study in a clinical trial setting in which gene-directed therapy is compared with standard and usual care. The three programs mentioned above use different populations, different genes or polymorphisms of the same genes, different drugs and dosing regimens, different methods, and different phenotypic measurements. It will not be an easy matter to make final decisions from these three different programs about which genetic polymorphisms will be the most important to study in a randomized, controlled clinical trial. Exactly what kind of genetic information is required and how it should be obtained prior to initiation of a clinical trial needs to be discussed by trialists, clinical pharmacologists, geneticists, and cardiovascular researchers prior to the design of any large complex study of the sort being contemplated. Equally important is the need to discuss whether the field is ready to conduct a clinical trial assessing gene-directed therapy.

D. Proposal

The assessment of genotype might prove to be an effective strategy in designing optimum therapy, yet that principle has yet to be established in a gold-standard randomized clinical trial of optimal statistical power. To conduct such a trial, it is essential that the most potentially important genetic polymorphisms be identified for study, as there are clear design and financial limitations to the number of genes that can be studied. Hence, if investigators were to embark on such a large and complex trial, it would seem essential to establish beforehand the candidate genes that are worthy of further investigation prior to initiation of larger studies.

Because there have been no coordinated efforts to develop a sufficiently strong fundamental knowledge base to proceed to the important next step of translating basic findings in human subjects to population-based research, additional studies may be needed to explore the relationship of gene variance and pharmacological responsiveness to different antihypertensive agents. Particular emphasis should be placed on the generalizability of findings and the prioritization of genes worthy of more extensive study. The next step would then be a clinical trial to determine whether tailoring therapeutic choices based on genotype confers clinical advantage over current clinical practice.

These concepts were explored in depth by leaders in the field as part of a workshop organized by the National Heart, Lung, and Blood Institute in Bethesda MD on September 17, 2003. This

meeting, titled the " Workshop on Future Directions for Hypertension Treatment Trials," focused on three primary issues: the determination of optimal blood pressure target levels for adequate treatment of hypertension; the optimal treatment regimens for the general population to prevent cardiovascular and renal events; and the utility of subclinical markers and gene-directed therapy in treating essential hypertension. The rationale for pursuing pharmacogenetics of hypertension was discussed, including the objectives and design of GenHAT (described above). It was agreed that improvement of treatment should be possible with a gene-directed approach. Nevertheless, it would be premature to pursue a large trial of gene-guided therapy at this time. Two major recommendations regarding pharmacogenetics were made by Workshop participants:

- In planning hypertension treatment trials, appropriate design factors should be addressed so that data and samples can be suitably used to inform future pharmacogenetic trials.
- Hypertension trials should include the appropriate informed consent for genetic analyses (for storage and possible data and sample sharing, at least).

5.3 Chronic Hypertension in Pregnancy

A. Definition of the Problem

Hypertension is the most common medical disorder during pregnancy. The hypertensive disorders of pregnancy are usually divided into chronic hypertension, preeclampsia/eclampsia, preeclampsia superimposed on chronic hypertension, and gestational hypertension. Chronic hypertension is defined as the presence of sustained hypertension before 20 weeks gestation. Most pregnant women with hypertension have preeclampsia, but chronic hypertension may affect up to 1/3 of pregnant women with hypertension, or about 120,000 pregnancies a year in the US. Women with chronic hypertension have a significantly increased risk of developing superimposed preeclampsia, and a risk of maternal and fetal morbidity and mortality. There is no systematic evidence supporting a treatment approach to these women.

B. Current State of the Science

NHLBI's 2000 Working Group Report on High Blood Pressure in Pregnancy defined chronic hypertension as a systolic blood pressure of at least 140 mmHg, or a diastolic blood pressure of at least 90 mmHg on more than one occasion. Most women with chronic hypertension in pregnancy have mild to moderate hypertension, and are at low risk for adverse cardiovascular or perinatal events. There is no evidence that pharmacological treatment results in improved outcomes in this situation, and the normal decreased systemic vascular resistance during pregnancy may normalize their blood pressures. Much of the increased risk associated with chronic hypertension occurs in the 25% of such pregnancies in which superimposed preeclampsia develops. This combination significantly increases both maternal and fetal risks, which are further exacerbated if renal disease is also present. In the extreme situation of pregnancy after renal transplantation, fetal prematurity occurs in more than half of all pregnancies. Maternal complications include placental abruption, stroke, pulmonary edema, hypertensive encephalopathy, retinopathy, acute renal failure, and death; fetal complications include, in addition to prematurity, low birth weight and perinatal death.

Treatment of chronic hypertension in pregnancy requires balancing risks and benefits to both mother and fetus. For women with mild hypertension and no other risk factors, the preponderance of scientific evidence suggests that drug treatment during pregnancy confers little benefit and is not likely to be necessary. There has been at least one small study that identified an increase in fetal complications (low birth weight) in women treated with an antihypertensive agent. For women with severe hypertension, placebo-controlled trials have not been performed due to ethical considerations, but there also are not good studies comparing therapeutic agents in different classes in this population. Neither have there been studies of treatment of hypertension in pregnant women with other risk factors, such as pre-existing renal disease, diabetes mellitus, cardiac disease, or sleep-disordered breathing. Information about safety of antihypertensive drugs for the fetus in humans is limited, except for a specific proscription against the use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in the second or third trimester

due to known renal anomalies that develop in the fetus.

C. Ongoing Activity

The Institute currently supports no studies of chronic hypertension in pregnancy.

D. Proposal

One of the priority recommendations of the Working Group on Research on Hypertension During Pregnancy in 2001 was for a randomized clinical trial of antihypertensive medications in pregnancy to evaluate blood pressure control, fetal growth and safety, and genetic variation in response to therapy. This recommendation has not been implemented, and should be strongly considered.

5.4 Drug Therapy for Hypertension in Children

A. Definition of the Problem

Based on current definitions, at least two million children between 10 and 19 have hypertension, most of which is primary or "essential".. It is not clear how to treat hypertensive children once they have been identified. Most practitioners are comfortable recommending lifestyle interventions (see Section 4.1), but when it comes to deciding which children to treat pharmacologically and with what drug, there is a great deal of uncertainty. Most clinical sequelae of hypertension, including atherosclerosis, heart failure, and stroke, do not occur until well into adulthood, although autopsy studies have provided convincing evidence that pathological vascular changes are present in childhood. There are more than 60 antihypertensive medications marketed in the United States, but few have been tested and labeled for use in children. Even if we knew whom to treat and what toprescribe , drug therapy in children presents challenges not present in treating adults. Many children will not be able to swallow pills so extemporaneous compounding of medications is required. This increases the likelihood of subtle pharmacological variations, as well as the price and inconvenience to families because such drugs often have short shelf lives, and are not widely available. Drug pharmacokinetics and pharmacodynamics may vary with age and growth rate, making it difficult to ensure constant bioavailability. Drug side effects may be different in children than in adults, and there is widespread concern about many drugs adversely affecting growth and development. Finally, although all antihypertensives lower blood pressure, there are no validated measures of target organ damage that could be used to monitor therapeutic effect.

B. Current State of the Science

Hypertension in the young has many etiologies. The conventional wisdom that most hypertension in children is secondary to other causes, primarily renal disease, is changing. This probably is still true in children under 10, but pediatricians treating hypertension are now more typically treating an obese adolescent with a family history of hypertension or an ethnic predisposition to hypertensive disease. Nevertheless, common causes of secondary hypertension must be ruled out before treatment of essential pediatric hypertension is considered. The Task Force Report on High Blood Pressure in Children and Adolescents, and its updates, developed by the NHBPEP, is widely considered to represent expert consensus on blood pressure management in children. The Task Force's stated goal for antihypertensive therapy is to reduce blood pressure to less than the 95th percentile for age, gender, and height. If non-pharmacological therapy fails to achieve this goal, the next steps are governed by general recommendations and recognition of the need to individualize therapy. There simply are not sufficient data to support more specific recommendations or a specific treatment algorithm. Before progressing to drug therapy, it is important to have a sufficient period of observation. In one of the studies cited below, 17% of

children with hypertension by Task Force guidelines experienced normalization of their blood pressure during the 2-week placebo period.

In recognition of the lack of information on drugs used in children, Congress included the Pediatric Exclusivity Provision in the 1997 Food and Drug Administration Modernization Act. This provision gave drug manufacturers a 6-month extension of current patents if they conducted dose-ranging, safety, and pharmacokinetic studies in children. More than 50 antihypertensive medications were eligible for exclusivity if studied in children. To date at least 6 of these drugs have been studied, and their manufacturers granted patent extensions. Three of these, enalapril, fosinopril, and lisinopril, have been granted new pediatric labels. All drugs studied lower blood pressure, but target control blood pressures may not be reached. As expected, pharmacokinetics varied by age group. In one case (fosinopril), expected dose-response relationships were not demonstrated. The studies also are demonstrating that the magnitude of reduction in blood pressure is not as great as in adult studies. This is in part due to the fact that children can be considered hypertensive with considerably lower blood pressures than adults. Some authors are recommending that percentage change in blood pressure, rather than absolute decrease, may be more relevant in children. In addition, as in adults, a sizeable placebo effect has been noted in at least one study. Many other trials are ongoing, and 2002 legislation, the Best Pharmaceuticals for Children Act, added provisions for testing drugs for which the patents have expired. None of the completed studies, however, addresses long-term safety, or the effects of the drugs on long-term outcomes, such as left ventricular hypertrophy or carotid intimal-medial thickness. In addition, there still are no data on the relative benefits of beginning antihypertensive drug therapy in childhood compared to early adulthood.

C. Ongoing Activity

NHLBI convened a Working Group on High Blood Pressure in Children and Adolescents, which submitted its report in May 2004. This group considered current data and made recommendations on a wide range of issues concerning hypertension in children, including timing of drug therapy, and development of intermediate outcome measures for use in evaluating drug efficacy. This activity was conducted under the auspices of the Coordinating Committee for the NHBPEP. There are no studies currently underway in DHVD or DECA of antihypertensive drug therapy for children. NHLBI staff are serving as consultants to the NICHD and FDA in the implementation of the Best Pharmaceuticals for Children Act, which may result in one or more studies of antihypertensive medications.

D. Future Directions

- Previous versions of the Task Force Report recommended beginning treatment with diuretics, but this advice was dropped in the 1996 Update. Findings from ALLHAT, however, may suggest the need to revisit the merits of diuretics as initial therapy for hypertensive children.

- Large pediatric population studies of hypertensive children are needed to determine long-term safety and efficacy of pharmacological and lifestyle interventions. This may be a potential role for the Pediatric Heart Network, although additional centers might have to be added to this purpose under subcontract.

- Studies that result in risk stratification are required. For example, it will be important to know the long-term risk for clinical CVD for an adolescent with a positive family history and an ethnic predisposition to hypertension, or one with manifest hypertension, type 2 diabetes, elevated triglycerides, or sleep-disordered breathing. Such information would help determine which populations of children are likely to receive a substantial benefit from drug therapy. Some of this information could come from very long-term follow-up using old cohort studies of children, such as Bogalusa and Muscatine.

6.1 Patient Adherence

A. Definition of the Problem

Nonadherence to antihypertensive treatment is a significant problem, with up to 50% of patients who begin antihypertensive therapy discontinuing treatment within one year. Of those who remain in treatment, about one-half take less than 80% of their medication, and in some populations, those rates fall to less than 50% (e.g., Lee et al. showed 47% adherence rates in an African American hypertensive population). Since blood pressure control has been found to be significantly better in patients taking at least 80% of their medication compared with those taking less than 50%, the low adherence rates reported for antihypertensive regimens have important implications for the management of hypertension and associated cardiovascular complications. With respect to behavioral interventions, studies show better initial success with interventions that promote behaviors used to prevent and treat hypertension, such as physical activity, healthy diets and weight loss, than with maintenance of these behaviors over time. Although lifestyle adherence does not have standard definitions, it has been estimated that in dietary studies of blood pressure reduction, about 50% adhere to the regimen for six months, and 20% adhere for three years.

B. Current state of the science

Adherence is a complex phenomenon involving many different behaviors, ranging from appointment-making and keeping to obtaining prescription refills and taking the medication consistently and correctly. Medication adherence can be reduced by one or more "behavioral errors" occurring in varying patterns over time. Types of behavioral errors include failure to adopt the regimen, early stoppage of treatment, reduction in levels of treatment, over-treatment, variability in the conduct of treatment, dosage interval errors, and other performance errors. Research has documented many reasons why patients may not take their medications as prescribed, including perceptions of drug side effects, costs (both financial and behavioral) of treatment, forgetting, schedule disruptions, inadequacy of instructions, and beliefs about the disease or treatment regimen. Adherence is also highly variable, changing over time in sometimes dramatic fashion. In addition, adherence can be measured in multiple ways, via self-report, pill counts, or electronic monitoring, with assessments focusing on the percent of doses taken, percent of days compliant, duration of medication taking, and/or percent of doses within a therapeutic window. The highly complex and variable nature of adherence may explain why, despite almost 30 years of research on the topic, the problem of non-adherence remains a pervasive and persistent one.

With regard to hypertension, studies suggest that simplifying the regimen and combining several behavioral strategies (e.g., tailoring the regimen to patients' routines, use of self-monitoring, cues and reward systems) are the most effective ways to increase adherence to medication. Some practical strategies shown to be useful include simplifying the regimen, where possible, and tailoring it to the patient's lifestyle; asking the patient about adherence at every visit; involving the

patient as a partner in the treatment process; providing clear written and oral instructions; and using behavioral strategies, such as reminder systems, cues, self-monitoring, feedback and reinforcement. Unfortunately, these and other known methods for improving adherence are not routinely used in health care practice.

Research also shows that patients' perceptions of adverse effects of antihypertensive medications are an important cause of treatment non-adherence. Since patients with psychological disorders (depression, anxiety or panic disorders) are more likely to show intolerance to multiple antihypertensive drugs, particularly nonspecific drug intolerance , and to have poor rates of adherence to antihypertensive medications, psychological and pharmacologic treatments for the underlying psychological condition may be useful in promoting adherence in this group of patients.

Studies of adherence to behaviors that affect blood pressure, such as weight loss regimens, exercise and dietary practices, indicate that the maintenance of healthy behaviors over time is the most challenging aspect of lifestyle change. While some studies have examined the motivations underlying individuals' maintenance of healthy lifestyles, more research is needed to better understand how to motivate people to maintain healthy behaviors over the long term.

Problems also exist with current methods of measuring adherence, leading to inaccurate assessment in research studies and in patient care settings. Self-report measures of adherence are most often used, but they greatly inflate adherence rates. Dunbar-Jacob et al. found that rates of adherence to antihypertensive medications differed based on whether self-reported adherence was used (75%) or whether adherence was assessed with pill counts (52%). Estimates from electronic monitoring are even lower, in the range of 50% and below. However, pill counts, whether electronic or manual, are more difficult to incorporate into research studies and practice settings than simply asking patients about their adherence. The lack of a "gold standard" measure that is simple, inexpensive and practical results in use of less accurate self-report measures. One way in which inaccurate measurement of adherence can affect outcomes is when non-adherence is misinterpreted by the healthcare provider as therapeutic ineffectiveness. There is evidence that about half the patients who fail to respond to their present antihypertensive treatment, and are about to be escalated to stronger treatment, are in fact clinically unrecognized non-compliers. If self-report is used to measure adherence, the extent to which non-adherence is the true problem may go undetected, and such misinterpretations may lead to intensification of treatment regimens with substantially higher costs but without additional benefit for the non-adherent patient.

C. Ongoing activity

In recent years, the NHLBI has sponsored several conferences, workshops and working groups on adherence, including a conference on "Maintenance of Behavior Change in Cardiorespiratory Risk Reduction" in 1998; a 1999 Working Group on "Adherence to Medical and Lifestyle Interventions;" and a 2003 Workshop on "Effects of Sleep Disorders and Sleep Restriction on Adherence to Cardiovascular & Other Disease Treatment Regimens: Research Needs". There have also been several RFA's, among them an RFA on "Adherence in Clinical Trials," one on

"Improving Hypertensive Care for Inner City Minorities;" and a recently funded RFA on "Overcoming Barriers to Treatment Adherence in Minorities and Persons Living in Poverty." The latter includes 8 clinical trials aimed at improving adherence to treatment in hypertensive minority and low income patients. These studies are testing a variety of strategies, ranging from counseling approaches to computer-based strategies and methods for improving physician-patient communication. These trials should result in identification of adherence-enhancing strategies that can improve medication and lifestyle adherence in hypertensive patients; following their completion, it would be important to encourage dissemination and implementation of findings from the successful projects in this program, perhaps through a follow-up RFA.

Other projects, both Institute and non-Institute funded, focusing on adherence in hypertension treatment, include several non-Institute sponsored panels and working groups, such as the AHA Expert Panel on Compliance and the Canadian Coalition for High Blood Pressure Prevention and Control's panel of health care providers, and an ancillary study on "Hypertension Control: Knowledge, Attitudes and Practices," conducted in conjunction with the ALLHAT clinical trial, which assessed physician practice and behaviors related to patient adherence to hypertension treatment. In addition, an RFA initiated by the Office of Behavioral and Social Sciences Research (OBSSR) on "Testing Interventions to Improve Adherence to Pharmacologic Treatment Regimens" includes a project evaluating a telephone-delivered adherence intervention in patients being treated with oral medications for Type 2 diabetes comorbid with either hypertension, hyperlipidemia, or both (Jacqueline Dunbar-Jacob, PI). Two additional RFA's initiated by the OBSSR on health behavior change – one involving adoption of healthy behaviors (Behavioral Change Consortium), and a more recent RFA on Maintenance of Behavior Change – while not directly addressing adherence to treatment for hypertension, include projects designed to test interventions that promote adoption and maintenance of behaviors, such as healthy diets, physical activity, and weight loss, that are related to blood pressure control.

D. Proposals

The following are research recommendations based on review of findings/recommendations from the various working groups, panels and workshops and the results of studies in the area of adherence to hypertensive treatment:

(1) Intervention studies in the area of adherence – including the studies being conducted as part of the RFAs outlined above – have generally used either theoretically-driven strategies applied to patients regardless of specific patient characteristics, or tailored approaches based on broad demographic (gender, ethnicity, SES), cultural, and disease/treatment-related features of the patient. While these strategies represent important and potentially useful approaches, another approach that has not been tested involves tailoring adherence-enhancing strategies to address the specific pattern and type of non-adherence being shown by an individual. For example, does the individual miss doses at a particular time of the day, or do they take medications at inappropriate intervals? Is the reason for low adherence forgetting to take the medication, perception of side effects, cost of medications or negative beliefs about medication-taking that inhibit following a medication

regimen? No studies to date have tested whether tailored approaches that are based on an individual's unique patterns of adherence and reasons for not adhering are more useful than theoretically-based or other, less individually-oriented tailored approaches. Using electronic medication monitors, an in-depth assessment of a person's "adherence profile" (their specific pattern of day-to-day medication-taking, revealing when and under what conditions they are failing to adhere) could be obtained and used as the basis for exploring the patient's reasons for non-adherence, the specific environmental barriers or situational constraints that might be affecting their adherence, as well as the cultural, attitudinal, and personality factors that may be involved – their beliefs, needs, psychological conditions, psychiatric co-morbidity, as well as patient preferences for treatment. Based on this information, individualized, stepped-care plans for enhancing adherence could be prescribed and monitored over time by teams of heath care personnel, including physicians, nurses and psychologists. A clinical trial should be conducted comparing this kind of individually-tailored approach to other types of adherence interventions to determine whether such finely-grained tailoring approaches improve adherence and are feasible within existing health care settings.

(2) An RFA or PA could be developed to encourage development and testing of valid and practical strategies and simple tools to measure adherence in patient care and community settings, as well as in research settings, with minimal patient and staff burden. This might involve, for example, developing self-report adherence measures that are less reactive to situational demands and more accurately represent adherence rates, or electronic measures that are simple, easy to use and inexpensive. Incorporating adherence measurement studies as ancillary or substudies within future clinical trials of antihypertensive treatments is a fruitful avenue to consider.

(3) Recent advances in the development of combination pills (e.g., medications that combine drugs to treat multiple risk factors, such as hypertension, diabetes, hyperlipidemia, that often occur together) suggest this may be an area for future research. If multiple drugs are often needed to control hypertension, is it better to combine those most often used together into one pill? Would that promote adherence? Although studies suggest simpler medical regimens promote better adherence (e.g, we know that adherence is better with once-daily dosing than multiple daily dosing regimens), very little research has been done on exactly what elements of treatment regimens carry the most weight in determining adherence – e.g., is adherence really substantially better with once than twice-daily dosing regimens? What about multiple pills taken once per day? What issues may arise with respect to multiple side effects from the various medications contained in a single pill? What about other dosing requirements and regimen features, e.g., intervals between medications, dietary/water and other restrictions or requirements? An RFA or PA might be developed to further our understanding of the benefits of various features of medical regimens for adherence to hypertensive medications, and the advantages/disadvantages of combination pills versus multiple medications.

(4) a follow-up RFA to the "Overcoming Barriers to Treatment Adherence in Minorities and Persons Living in Poverty" RFA should be designed to test methods for disseminating/integrating the successful adherence methods found in these studies to various health care settings.

6.2 Clinical Practice

A. Definition of the Problem

Application of efficacious preventive and therapeutic strategies to clinical practice is the ultimate goal of medical research. Efficacious strategies exist for both life style and pharmacologic treatment of hypertension, and their use in clinical practice should lead to blood pressure (BP) control to below recommended levels in large majority of hypertensive patients, and prevent or delay onset of Stage I hypertension in a large proportion of individuals. The problem is that these strategies are not being applied effectively in medical practice, which comprises part of what has been termed a "quality chasm" by the Institute of Medicine (IOM). The IOM identified hypertension as one of the priority areas for national action to improve health care quality.

B. Current State of the Science

Traditional approaches to improving translation of research findings into medical practice have focused on disseminating information to clinicians. However, most clinicians can barely keep pace with the rapid advances in health-care knowledge, even if it is presented in a practical format of systematic reviews and guidelines. In addition, changing medical practice in response to new evidence is a multilevel process that only begins with acceptance of new information. Substantial evidence suggests that change in patient care is possible, but generally requires multi-level approaches (clinician, team practice, patient, organization, wider environment), tailored to specific settings and target groups. Demonstration of quality of care becomes increasingly important but standardized measures of performance and measurement systems are yet to be developed. More than a decade ago, the IOM developed a definition of quality of care that is now widely accepted: "Quality of care is the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current medical knowledge." This definition encompasses the complexity of clinical decisions to improve quality of patient care, which starts with good knowledge of the disease (medical evidence), but at the same time must take into account patient-specific aspects of medical care (contextual evidence)

Hypertension is a common disorder affecting over 50 million adults in the United States. Since it is not manifested by symptoms, its diagnosis is made in a medical setting or during community screening, and a majority of hypertensive patients are cared for in a primary care setting. The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a recently published practice-based trial conducted in a diverse North American setting, showed that BP control to below 140/90 mm Hg was possible to achieve in over 60% of high-risk hypertensive men and women (white, black and Hispanic) age 55 and older. This level of control was achieved using a system-level intervention of reminders, feedback, access to consultants, one-on-one and group education, and free study drugs. While the study investigators believe that even better control rates can be achieved and free drugs may not be necessary, the study experience brought out a

realization that many physicians are comfortable with systolic BP levels between 140 and 150 mm Hg, perhaps because no clinical trial has been conducted to show better CVD outcomes with systolic BP control to below 140 relative to about 150 mm Hg.

ALLHAT concluded that inexpensive thiazide-type diuretics should be used as a first-step treatment of hypertension and be a part of any multi-drug regimen due to their superiority in preventing one or more complications of hypertension, including heart failure. Heart failure is a costly and deadly complication of hypertension. Framingham data have shown that hypertension antedates heart failure in 91% of cases. ALLHAT showed that thiazide-type diuretics are superior to the other drugs tested in preventing transition from hypertension to overt heart failure. In addition, two recently published metaanalyses of trials using antihypertensive drugs point to potential differences among antihypertensive drugs in their ability to prevent the onset of overt heart failure, an effect that seems to depend less on the BP differential than for other complications of hypertension.

The past three decades have witnessed a steep (near 60%) decline in the age adjusted CVD mortality rates, a combined effect of prevention efforts and improved treatment outcomes. Yet, the gap in premature CVD mortality between African Americans and Caucasians persists (two-fold higher CVD mortality rates for ages 35-64) and for men has even increased since 1960. A recent publication in the NEJM points to hypertension as the single initiating cause of death independent of economic status that contributed the most to the racial disparity between African Americans and whites in potential years of life lost. In addition, race, gender, and age-specific analyses of NHANES 1999-2000 not only confirm the long-recognized high prevalence and early onset of hypertension among African Americans but also identify BP control among treated African American patients as a specific action point for interventions to improve BP control among African Americans (given relatively high awareness and treatment rates). The same analyses also identified the elderly as a group with poor BP control to below 140/90 mm Hg, despite high awareness and treatment rates. In Mexican Americans, the most important issue appears to be access to or drop-out from care (low treatment rates among those aware of hypertension).

C. Ongoing Activities

Dissemination and implementation programs, including the National High Blood Pressure Education Program, are described in 7.0. These regional and national activities play a vital role in prevention, detection, treatment and control of hypertension through development and implementation of treatment guidelines and effective partnership with community and professional organizations. Dissemination and implementation research complements and informs these activities and is necessary to evaluate promising interventions in the areas relatively resistant to the education and dissemination efforts.

An ongoing research program resulting from the RFA "Overcoming barriers to Treatment Adherence in Minorities and Persons Living in Poverty" is described in 6.1.

An RFA entitled "Trials Assessing Innovative Strategies to Improve Clinical Practice through

Guidelines in Heart, Lung, and Blood Diseases" was issued in 2001 and 8 grant applications were funded in 2002 (5 in the area of CVD and stroke). None of these originally funded grant applications was directed at improving BP control; one focuses on improving the use anti-thrombotic drugs in stroke prevention, two on adherence to ATP III guidelines, one on adherence to guidelines for complex MI patients with co-morbidities, and one on adherence to multiple cardio-respiratory guidelines where hypertension represents a chronic disease, asthma a cyclic disease, diabetes a chronic disease with co-morbidities, smoking simple screening, and cholesterol complicated screening. Subsequently, three applications were re-submitted after revisions and funded in FY 2003. One of these applications focuses on improving BP control through strategies based on physician/pharmacist collaborative teams. Of the other two, one aims to change aggregate coronary heart disease (CHD) risk in a high-risk, low-SES population using patient case-management in a context of locally developed national guideline-based program; the other focuses on adherence to CHD secondary prevention guidelines in hospitalized patients with CHD or CHD risk equivalent.

In addition to these RFA-related grants, the Institute portfolio includes four research projects aiming to improve BP control while not limited to direct targeting of patient adherence. One focuses on a role of a pharmacist/physician team, another one (Hypertension Improvement Project) is a multi-level clinic-based behavioral intervention targeting both the physician and the patient (medical treatment includes life-style intervention). A small grant aims to describe/analyze factors determining failure to achieve BP control in the elderly: physician practice (behavior), antihypertensive medication efficacy, and adherence to prescribed medications (patients factors). The SBIR phase I grant currently in progress was designed to develop and formatively test a working prototype of an interactive web site based on the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC6) guidelines, which aims to educate patients and provide feedback to both patients and clinicians.

In September 2003, NHLBI released an RFA, “Interventions to Improve Hypertension Control Rates in African Americans”, which aims to evaluate clinically feasible interventions to effect changes in medical care delivery leading to an increase proportion of treated hypertensive African American patients whose BP is controlled to levels specified by the JNC 7 guidelines. Application receipt date is January 20, 2003 and grant applications are expected to be funded in FY 2004.

Falling in the domain between research and programs is the JNC7/ALLHAT joint project, “Improving Blood Pressure Treatment in the Community”, which is an educational practice change project implemented largely through the former ALLHAT clinical sites, and includes an evaluation component.

D. Proposal

Given the magnitude of the problem and the relatively small number of studies underway, an RFA

is warranted. The RFA would support randomized concurrently controlled studies to evaluate cost-effective strategies to bring about changes in clinical practice leading to improved BP control in treated hypertensive patients and to better use of treatment modalities, through implementation (with adaptation as needed) of the JNC7 guidelines. The JNC7 guidelines embody both lifestyle and pharmacological interventions to prevent and control hypertension. Lifestyle approaches to prevention and treatment of hypertension are discussed in 4.2. In medical practice, lifestyle changes can be used to prevent hypertension (especially in patients with pre-hypertension) or to supplement pharmacological treatment. Thus, the proposal described in 4.2 calling for trials of primary care-based intervention to give advice or simple behavioral interventions for life-style changes can be conducted both in conjunction with and independently of translation studies involving drug treatment.

Studies would target populations of treated hypertensive patients with BP control rates of less than 50%, with BP control defined by JNC7 goals. Study populations would be defined by geographic location, race, ethnicity, gender, age, practice setting, co-morbidity, etc. Special emphasis would be placed on patients with co-morbidities requiring application of two or more treatment guidelines (e.g., elderly). Interventions would target the clinician's behavior [e.g., academic detailing (individual or small groups), continuous quality improvement, decision support systems] and/or the practice environment [e.g., peers/standards of practice (including opinion leaders), reimbursement, formularies, organizational constraints, patient expectations]. Changing medical practice would be the primary focus of interventions. Patient-level interventions, especially directed at self-care, would be allowed as supplemental measures. Improvement in BP control would be the primary endpoint. Studies would consist of 3 phases, 1) a formative assessment to evaluate feasibility and acceptability of the intervention, 2) the actual intervention, and 3) an institutionalization and dissemination phase. Consequently, 5 years of support would be required.

7.0 Dissemination and Implementation Programs

A. Definition of the Problem

In general, high blood pressure control continues to be a major issue, particularly in high-risk communities. It remains a major risk factor for CHD, stroke, heart failure, and chronic kidney disease . About 50 million adult Americans have high blood pressure. Its prevalence is nearly 40 percent greater in African Americans than in whites (an estimated 6.4 million African Americans have hypertension), and its effects are more frequent and severe. Hypertension is also very common in older people.

Even though high blood pressure control rates have increased steadily (NHANES II to NHANES IV), many challenges to increasing those rates remain. The increasing weight gain of the U.S. population can be an obstacle to the blood pressure lowering and protective effects of antihypertensive medications, which can create additional challenges to increasing high blood pressure control rates in the future.

B. Ongoing Activities

The NHLBI's Office of Prevention, Education and Control's National High Blood Pressure Education Program develops and implements guidelines on the latest strategies for prevention, detection, treatment, and control of high blood pressure. The NHBPEP has effective partnerships in place to encourage community-based screening and referral programs that build on existing community resources and enables community members to maintain interventions over the long term. For example, faith-based high blood pressure activities are being implemented by a number of groups including: National Black Nurses Association, International Society of Hypertension in Blacks, and Association of Black Cardiologists. Educational materials and tools are available to support these efforts. In addition, print, radio, and TV public service announcements have been used to encourage young adults to get their blood pressure checked and to take their medicines as their doctor prescribes. Furthermore, recent research in lifestyle approaches are being implemented by promoting the application of dietary approaches to controlling systolic hypertension (DASH) findings and promoting physical activity. In addition, new guidelines to help public health practitioners better implement the high blood pressure guidelines are now released in line with a new website and information to emphasize that the "mission is possible" to prevent and control high blood pressure.

The main activities of the NHBPEP Coordinating Committee during the past year have been the "Program Repositioning" and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7 Express). The goals of the Repositioning effort are to raise the importance of high blood pressure on the national public agenda, revitalize the image of NHBPEP as the U.S. leader in high blood pressure prevention and control, and mobilize the American public to take action--in short, to make high blood pressure

prevention and control America's Business. A major focus is to bring in new nontraditional partners with whom there can be aggressive co-marketing, advertising, promotional marketing, and event tie-ins. The NHBPEP Coordinating Committee organizations will be encouraged to take a more active role in implementing high blood pressure prevention and control activities. The centerpiece for partnership development will be "Mission Possible", an intensive cause-related marketing effort to convince all Americans, including corporate entities, to become involved in high blood pressure prevention and control activities. To implement Mission Possible, three sets of materials and a special Web site have been developed. They emphasize the call to action and provide tools to help partner and potential partner organizations participate in Mission Possible. These include educational and promotional materials that they can adapt for distribution to their employees, customers, and/or other local organizations.

The JNC 7 Express was published in the May 21, 2003 issue of JAMA. On May 14, the NHLBI conducted a press conference regarding the release of this new clinical guide. Four additional printed products accompanied the JNC 7 report: a revised booklet on the DASH eating plan; a new brochure for patients; a JNC 7 slide show for professionals, and a clinician reference card. The Report has been presented at several major scientific meetings, and presentations on JNC 7 are scheduled to be given at other NHBPEP member organizations' scientific sessions this coming year. The development, writing, achieving consensus and publication of this work including graphic design and printing the three education documents, two Web sites, PowerPoint slides plus the government printing office version was completed in five months. A longer version to support the JNC 7 Express recommendations is under construction and will be submitted for publication by the end of this calendar year.

In addition, the NHLBI has established Enhanced Dissemination and Utilization Centers (EDUCs), community-based programs, that personify thinking globally but acting locally to apply the fruits of research. These partners are using science-based information to inform their communities of the public health burden of CVD and to develop and implement focused educational strategies to reduce this burden through changes in health care provider practice behavior, patient behavior, and general public behavior related to the prevention and control of CVD. These are intended as prototypes for a new way of delivering the benefits of health research--particularly outcomes related to better control of hypertension--directly to the people. They provide personal stories filled with the promise that learning and new opportunities bring, as Americans of all ages understand (some for the first time) the health risks they face, the costs of those risks, and the actions needed to reduce those risks. The first six NHLBI CVD EDUCs were awarded in April 2001. Their results will be reported in FY 04. Six additional CVD EDUCs were awarded in September 2002, and their results will be reported in early FY 06.

Other activities that address among their objectives better hypertension prevention, treatment, and control include the following: a number of minority outreach projects, such as Salud para su Corazon and projects directed at Asian-Americans and Native Americans to address health disparities and high blood pressure; the Obesity Education Initiative; and the Heart Truth Campaign, on the cardiovascular health of women.

C. Proposals

The NHLBI will create new activities to continue the implementation of new research results. New activities will be added periodically. The following are major proposed activities based on information currently in hand:

The NHBPEP Working Group Report on High Blood Pressure in Children and Adolescents. The 1997 NHBPEP working group report on HBP in children and adolescents is rapidly becoming dated. New scientific information is available which would help redefine BP classification in children. In addition, there is a need to provide consensus regarding BP treatment algorithms using lifestyle changes and antihypertensive medications. Clinicians are faced with difficult treatment decisions because there is scare clinical trial data on BP lowering in children. Further, there is developing information regarding sleep apnea in children and the relationship to rising blood pressure. A Working Group was convened to update the 1997 NHBPEP working group report and has developed a new set of guidelines on high blood pressure in children and adolescents.

National High Blood Pressure Education Month Many communities and civic organizations download materials from the NHBPEP web site to develop their High Blood Pressure Month activities. These materials stimulate several different types of high blood pressure prevention, screening, and control activities at church sites, sporting events and community screening programs. It is proposed that new web site materials be developed which incorporates the recommendations for primary prevention of hypertension through population based approaches, provide reinforcement for hypertensive patients to stay on therapy, and include materials from the new NHBPEP repositioning program designed to develop programs with new partners. In addition, the Month will provide links to Health Beat Radio and will also provide sample news articles, press releases, and suggestions for innovative community-based activities.

The National Committee on Quality Assurance (NCQA) has partnered with the NHBPEP in developing their HEDIS hypertension measure. This measure has stimulated blood pressure control programs at managed-care organizations. During this past fiscal year, NCQA reported that participating managed-care organizations have achieved a 50% control rate among their non-complicated hypertensive enrollees. It is proposed to develop a small working committee to re-examine the HEDIS Hypertension measure and to determine if the criteria for hypertension control can be lowered, that is to less than 140/90 mm Hg. In addition, this working group would be asked to consider a HEDIS measure to address the issue of pre hypertension and diabetic hypertensive patients.

American Heart Association Working Group on recommendations on blood pressure measuremen: The AHA has periodically published recommendations on blood pressure measurement. These recommendations have become dated as new scientific information has appeared regarding automated BP equipment, oscillometric and auscultatory devices. Recently, the AHA and NHLBI conducted a scientific workshop to address these scientific issues. The

proceedings of this workshop were published in the Journal *Hypertension.* Based on these proceedings the AHA is updating its recommendations. The NHBPEP Coordinator serves as the liaison from NHLBI to this working group.

Adherence Education and Dissemination activities should be considered, in order to highlight the problem with lack of adherence to preventive measures and treatments for cardiovascular, lung and blood diseases and disorders; to educate the public, health care providers and health care systems about the importance of adherence to medication/lifestyle change in the prevention and treatment of these diseases/disorders; and to promote the dissemination of proven methods for improving adherence to patients, providers and health care systems. These activities could involve ongoing meetings and review of literature on adherence to medication/lifestyle treatment programs by panels of experts in adherence, in order to identify methods shown to be effective and that should be part of standard practice in clinical and community health settings. In addition, greater emphasis could be placed on implementation of these proven intervention strategies within OPEC's ongoing outreach and education activities including the Enhanced Dissemination and Utilization Centers, Minority Health activities, as well as national education program activities. Given that hypertension control is an area of special interest to the Institute, a pilot program focusing on education and dissemination of adherence-promoting strategies in the area of hypertension prevention and treatment could be one of the first such activities undertaken. Such an activity could be developed to complement and build on the efforts of the National High Blood Pressure Education Program.

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