Summary of the NHLBI Working Group on Research on Hypertension During Pregnancy

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Abstract—A Working Group on Research in Hypertension in Pregnancy was recently convened by the National Heart, Lung, and Blood Institute to determine the state of knowledge in this area and suggest appropriate directions for research. Hypertensive disorders in pregnancy, especially preeclampsia, are a leading cause of maternal death worldwide and even in developed countries increase perinatal mortality rates 5-fold. Much has been learned about preeclampsia, but gaps in the knowledge necessary to direct therapeutic strategies remain. Oxidative stress is a biologically plausible contributor to the disorder that may be amenable to intervention. Hypertension that antedates pregnancy (chronic hypertension) bears many similarities to hypertension in nonpregnant women, but the special setting of pregnancy demands information to guide evidence-based therapy. The recommendations of the Working Group are to attempt a clinical trial of antioxidant therapy to prevent preeclampsia that is be complemented by mechanistic research to increase understanding of the genetics and pathogenesis of the disorder. For chronic hypertension, clinical trials are recommended to direct choice of drugs, evaluate degree of control, and assess implications to the mother and fetus. Recommendations to increase participation in this research are also presented. (Hypertension. 2003;41:437-445.)

Key Words: hypertension, pregnancy □ preeclampsia □ pregnancy □ research □ oxidative stress □ mortality

The hypertensive disorders of pregnancy affect up to 8% of all gestations and remain major causes of maternal and neonatal mortality and morbidity in the United States and worldwide. Most adverse events are attributable directly to the preeclampsia syndrome, characterized by new-onset hypertension with proteinuria during pregnancy. Women with chronic hypertension also manifest increased maternal and neonatal morbidity and mortality. In this setting, these adverse outcomes usually are largely attributable to preeclampsia because preeclampsia is both more common and more devastating in women with chronic hypertension.

In developed countries, where maternal mortality attributable to preeclampsia has been reduced, the condition primarily affects fetal well-being through intrauterine growth retardation, preterm birth, low birth weight, and perinatal death. The increased infant morbidity and mortality rates are especially disheartening because at least part of it is attributable to preterm delivery undertaken to prevent further deterioration in the fetus and mother.1 In fact, 15% of all preterm births are indicated early deliveries for preeclampsia. Preterm birth is associated with increased mortality rates and long-range neurological disability. Preeclampsia also increases the risk of intrauterine growth restriction (IUGR). These low-birthweight babies have not only acute problems but more alarmingly, IUGR may confer a long-term burden in the form of future cardiovascular risk.2,3

From another public health perspective, it is alarming that the rate of preeclampsia has increased by 40% between 1990 and 1999,4 probably the result of a rise in the number of older mothers and multiple births, scenarios that predispose to preeclampsia. Older maternal age during pregnancy may contribute to preeclampsia because of an increased frequency of chronic hypertension.

Because of the clear public health concerns engendered by hypertensive disorders of pregnancy and the urgency of providing new directions in research, the National Heart, Lung, and Blood Institute (NHLBI), with participation from the National Institute of Child Health and Human Development (NICHD), convened a Working Group on Research on Hypertension During Pregnancy. The Working Group was charged with evaluating the current state-of-the-science and making recommendations for a focused agenda of basic, clinical, and translational research addressing key issues in pregnancy-related hypertension. This effort was designed to complement and be guided by the prior efforts of the NHLBI to improve treatment of these disorders through recommendations from the National High Blood Pressure Education Program (NHBPEP).5 The review that follows is based on...
material presented by Working Group members at the meeting (see Appendix for roster).

**Classification of Hypertensive Disorders of Pregnancy**

Hypertension during pregnancy is categorized as follows: preeclampsia/eclampsia, gestational hypertension, the continued presence of chronic hypertension, and the superimposition of preeclampsia on chronic hypertension. These categories identify disorders with different epidemiological characteristics, pathophysiology, and risks for mother and baby. These categories are summarized below and detailed further in the NHBPEP report.5

**Preeclampsia**, a pregnancy-specific syndrome that occurs after midgestation, is defined by the de novo appearance of hypertension (systolic blood pressure of \( \geq 140 \text{ mm Hg} \) or diastolic blood pressure of \( \geq 90 \text{ mm Hg} \)), accompanied by new-onset proteinuria, defined as \( \geq 300 \text{ mg per 24 hours} \). Previous definitions included edema, but this sign is nonspecific and is observed in many normotensive pregnant women. Thus, edema is no longer considered part of the diagnostic criteria for preeclampsia. Likewise, previous criteria in which a rise of \( 30 \text{ mm Hg} \) in systolic pressure and/or \( 15 \text{ mm Hg} \) in diastolic pressure were considered diagnostic have been eliminated as too nonspecific, identifying up to 25% of pregnant women.6 In addition, probably because of this lack of specificity, it is very difficult to demonstrate an excess of morbidity in these women.6 As proteinuria may be a late manifestation of preeclampsia, the NHBPEP advises clinicians to be suspicious when de novo high blood pressure is accompanied by headache, abdominal pain, or abnormal laboratory tests, specifically low platelet count and abnormal liver enzymes, and that it is prudent to treat such patients as if they have preeclampsia.

**Eclampsia** occurs when preeclampsia progresses to a life-threatening convulsive phase. Such convulsions usually occur after mid-pregnancy or during delivery, but as many as one third of eclamptic convulsions occur during the first 48 hours of the immediate postpartum period.

**Gestational hypertension** is defined as de novo hypertension arising after mid-pregnancy and is distinguished from preeclampsia by the absence of proteinuria. This category is broad and includes women who later satisfy diagnostic criteria for preeclampsia and other women with increased blood pressure before pregnancy but whose true diagnosis is masked by the tendency of blood pressure to decrease in early pregnancy. However, in many cases proteinuria never occurs, the course is relatively benign, and blood pressure normalizes after delivery, at which time the diagnosis of gestational hypertension is changed to transient hypertension of pregnancy.

**Chronic hypertension** refers to an elevated blood pressure in the mother that predated the pregnancy. It can be assumed when elevated blood pressure is detected before mid-pregnancy and can also be diagnosed in retrospect, when hypertension fails to normalize 12 weeks after delivery. Chronic hypertension may not have been recognized before the pregnancy. At present, there is little consensus on how to treat pregnant women with preexisting hypertension. The absence of data to direct medical treatment strategies is particularly disconcerting because women with chronic hypertension are at increased risk of superimposed preeclampsia (25% risk), preterm delivery, fetal growth restriction or demise, abruptio placentae, congestive heart failure, and acute renal failure. The outcome for mother and infant with preeclampsia superimposed on existing hypertension is worse than with de novo preeclampsia. It is uncertain if treatment of chronic hypertension affects the high risk of this group to develop preeclampsia and its complications.

**Preeclampsia and Chronic Hypertension: Distinct Disorders**

A major discrimination emphasized in the taxonomy of hypertensive disorders of pregnancy is between preeclampsia and chronic hypertension. Both disorders are characterized by increased blood pressure in pregnancy. In preeclampsia, increased blood pressure is not only of new onset but, in addition, is an important indicator of an underlying multisystem syndrome. Relatively few of the adverse effects of preeclampsia are due to increased blood pressure. It is not surprising that pathological and pathophysiological changes are different in the two disorders.7 The consequences of preeclampsia and chronic hypertension also are quite different. Preeclampsia presents acute risks to mother and baby. Chronic hypertension increases the risk of growth-restricted infants but its major acute effect on morbidity is secondary to the increased risk of superimposed preeclampsia. Chronic hypertension is a well-established cause of cardiovascular morbidity and mortality, but it is still unclear whether preeclampsia alone is a cause of later-life cardiovascular disease.

The pathology and pathophysiology of chronic hypertension is better understood than that of preeclampsia. For instance, much of what has been learned from studying the disorder in nonpregnant populations is relevant to chronic hypertension in pregnancy. What is lacking for treating pregnant patients with chronic hypertension is evidence-based therapy directed by such knowledge. On the other hand, although the past 10 years have witnessed a dramatic increase in the understanding of preeclampsia as a complex multisystemic disease, many important facts necessary to guide therapy remain unknown. Thus the focus of the Working Group discussion was largely on the need to increase understanding of preeclampsia to guide future therapy, whereas chronic hypertension was considered from the perspective of the gaps in evidence necessary to adequately treat the disorder.

**Preeclampsia: Current Concepts**

**History**

Historic perspective is helpful to understand the concepts that have guided studies of preeclampsia. Eclampsia was described by Celsus in 100 AD as seizures during pregnancy that abated with delivery,8 and for the ensuing 2000 years, eclampsia was considered to be a pregnancy-specific seizure disorder. It was not until the mid-1800s that the similarity of the edematous eclamptic woman and the dropsic patient with Bright’s disease (acute glomerulonephritis) stimulated clini-
Epidemiology
Preeclampsia is a disease primarily of first pregnancies and extremes of maternal age. Of interest is the observation that nulliparas pregnant by a new partner have a risk of preeclampsia intermediate between that associated with first pregnancies and subsequent pregnancies with the same partner. Because new paternity is also associated with a longer interpregnancy interval, this finding suggests an immunologic basis for preeclampsia where the risk is increased by delayed exposure and/or new paternal antigen. This concept is also supported by the observations that the risk is reduced when there is a longer period of intercourse with the father before conception and that barrier contraceptives that prevent exposure to semen increase the risk of preeclampsia.

Genetics
The epidemiological factors of preeclampsia suggest a genetic basis for the disorder. Preeclampsia is more common in daughters of preeclamptic women and in pregnancies fathered by sons of preeclamptic women, suggesting the involvement of both maternal and fetal genes in the syndrome. Studies of the epidemiological genetics of the disorder are hampered by the fact that the overt disease only occurs in women at the time of reproduction. Furthermore, information from older records frequently is inadequate to establish family history definitively. Genome-wide searches have begun but as yet have not yielded consistent results. Function-perturbing polymorphisms have been identified for several candidate genes, but the findings again are inconsistent in different populations. In addition, genetic differences have not been exploited to explain differences in response to therapy in treatment trials. Genetic markers of the disease would be useful not only in identifying relevant molecules but also would facilitate longitudinal studies of pathogenesis.

Pathology and Pathophysiology
The pathophysiology of preeclampsia is appropriately divided into two stages: alterations in placental perfusion (stage 1) and the maternal syndrome (stage 2).

Stage 1
There are considerable data to support the theory that the placenta is the key component of pregnancy that leads to preeclampsia. Preeclampsia can occur without uterine distention and without a fetus. The pregnancy disorder hydatidiform mole, an abnormality in which there is very little fetal tissue with the products of conception being almost exclusively trophoblastic, is associated with an increased risk of preeclampsia. It also appears that the feature of the placenta that leads to preeclampsia is reduced perfusion. The reduced placental perfusion is primarily due to abnormalities in implantation and vascular remodeling. In normal pregnancy, the spiral arteries that perfuse the placenta undergo remarkable remodeling, from small muscular arteries in the nonpregnant state to significantly distended vessels that have lost both their smooth muscle and inner elastic lamina layers. This extensive modification does not occur in preeclampsia. There may be some superficial remodeling, but it never extends beyond the decidual lining, whereas in normal pregnancy, the modified vessels extend into the inner third of the myometrium. Thus, many vessels in preeclamptic women undergo no remodeling, and this results in reduced placental perfusion. There have been enormous increases in the understanding of human trophoblast invasion, its relation to vascular remodeling, and aberrations that occur in preeclampsia. It is now evident that these interactions include precisely regulated expression of molecules involved in attachment and invasion in response to environmental and maternal signals and that this process is disordered in preeclampsia. Several medical conditions associated with microvascular disease, such as hypertension, diabetes, and collagen vascular disease, also increase the risk of preeclampsia, fueling speculation that impaired placental perfusion may be the common denominator. Likewise, obstetric conditions associated with large placentas (hydatidiform mole, hydropic placentas, and placentas with multiple gestations) all increase the risk of preeclampsia. It is proposed that in these large placentas there is a relative reduction in placental perfusion. Another alteration of the spiral arteries in preeclampsia, atherosis, results in occlusion of the decidual vessels reminiscent of the vascular findings of allograft rejection. This finding further supports an immunologic component of preeclampsia.

Stage 2
In women with preeclampsia, blood flow to organs other than the placenta is reduced, and hemorrhage and necrosis can occur. In the liver, for example, evidence can be found of reduced perfusion with secondary necrosis and hemorrhage. In the heart, subendocardial necrosis can occur similar to that

Researchers to determine whether women with eclampsia, like individuals with Bright’s disease, had protein in their urine. Protein was indeed present in the urine of eclamptic women. Furthermore, it was recognized that the proteinuria antedated the seizures. In another 50 years, it was possible to measure blood pressure noninvasively. Again, an association of increased blood pressure and eclampsia was recognized, as was the fact that the hypertension also antedated the seizures. It was soon evident that hypertension and proteinuria during pregnancy, even without seizures, identified a woman with the potential for a rapidly progressive life-threatening disorder and a fetus at increased risk for stillbirth. These two findings of renal dysfunction and hypertension guided research for more than 80 years. It was not until about 10 years ago that investigators began focusing on the pathophysiology and multiple systemic manifestations of preeclampsia.
seen in with hypovolemic shock. The explanation for systematically reduced perfusion includes vasoconstriction, microthrombi, and reduced plasma volume secondary to loss of fluid from the vascular compartment. The vasoconstriction is not attributable to increased endogenous pressors but rather to an increased sensitivity to virtually all circulating pressor agents.22

Preeclampsia also is characterized by activation of the coagulation cascade. Although consumption of procoagulants sufficient to be detected by standard testing occurs in only about 10% of preeclamptic women, sensitive tests of activation of the cascade can be detected in most preeclamptic women. Thus, platelet size is larger in preeclampsia, indicating increased platelet turnover.23 Other indicators of platelet activation are also apparent.

Perfusion in preeclampsia is further limited by reduced plasma volume. Women with preeclampsia have accelerated loss of protein from the vascular compartment, as indicated by an increased rate of disappearance of the protein-bound dye, Evans blue.24

The sequence of events, and thus cause and effect, are difficult to discern in the overtly ill preeclamptic woman. Most useful information comes from longitudinal studies in which women destined to have preeclampsia are examined before clinically evident disease. These studies reveal that abnormal activation of coagulation and reduced plasma volume antedate clinically evident preeclampsia.23 Similarly, some but not all authors have found increased sensitivity to exogenous pressors weeks before the manifestations of clinically evident preeclampsia.25-26

One pathological change provides particular insight. Renal biopsy specimens from women with preeclampsia reveal a change seen in no other form of hypertension. Termed glomeruloendotheliosis, the lesion consists primarily of enlargement of the glomerulus caused by hypertrophy of endothelial cells.27 This finding was one of the bases for the hypothesis put forward a decade ago that the diverse pathological changes of preeclampsia could be accounted for by a common target, the endothelial cell.28 Since that time, this hypothesis has been extensively tested and largely supported. Numerous markers of endothelial activation are present in the circulation of preeclamptic women weeks to months before clinically evident disease.29 Therefore, hypertension does not appear to be causing the endothelial injury. Vessels from women with preeclampsia manifest reduced endothelial-mediated relaxation, and plasma or serum from preeclamptic women can adversely alter endothelial function in vitro either with cells in culture or intact vessels.29

Maternal-Fetal Interactions in Preeclampsia

A principal unanswered question is how reduced perfusion of the placenta can result in the maternal syndrome. One thing that is quite clear is that the reduced perfusion alone is not sufficient to explain this linkage. Intrauterine growth restriction is the result of reduced placental perfusion. Yet many women with growth-restricted infants do not have preeclampsia, and a small percentage of preeclamptic women have large fetuses. In addition, the implantation defect and failure to remodel blood vessels that supply the placenta that are characteristic of preeclampsia also are present in pregnancies with growth restriction30 and in one-third of pregnancies ending in spontaneous preterm birth.31 This has led some to the postulate that the reduced perfusion must interact with maternal factors to result in the maternal syndrome. These factors are posited to be genetic, behavioral, or environmental. As this list is assembled, it is interesting that there these factors and those predisposing to cardiovascular disease in later life are quite similar (Table 1).

Relation of Preeclampsia to Cardiovascular Disease

In addition to the shared risk factors, a relation between preeclampsia and the atherosclerotic and hypertensive cardiovascular diseases has been noted for some time. Early studies suggesting that preeclampsia caused cardiovascular disease were compromised by poor diagnostic criteria and inappropriate controls. In the early 1930s, Chesley32 began a masterful follow-up study of women with eclampsia. He chose women with eclampsia to increase diagnostic specificity. He followed these women for 47 years and concluded that eclampsia (and by extension, preeclampsia) did not cause later cardiovascular disease. This conclusion was based on findings from women with eclampsia in their first pregnancy. At long-term follow-up, these women had no excess of hypertension or cardiovascular disease compared with a control group matched for age, race, and socioeconomic status but with unknown pregnancy history. However, women who had eclampsia in pregnancies other than the first had a striking increase in hypertension in later life. He concluded that preeclampsia did not cause later cardiovascular disease but that preeclampsia in later pregnancies was caused by preexisting (subclinical) cardiovascular disease. Sibai et al33 followed women with severe preeclampsia rather than eclampsia with similar findings. Women with severe preeclampsia in only their first pregnancy did not have an increased risk of later life hypertension, whereas women with preeclampsia in later pregnancies had increased risk. Fisher and Lindheimer34 expanded these findings in a follow-up study of women with renal biopsy diagnosis of preeclampsia. In their study, women with preeclampsia were compared with women who had been pregnant and did not have preeclampsia. There was no excess of hypertension or other cardiovascular diseases in women with renal biopsy evidence of preeclampsia when compared with the general female population. However, women who had pregnancy without preeclampsia had a lower incidence of cardiovascular disease than the general population. In other studies, women who

<table>
<thead>
<tr>
<th>TABLE 1. Risk Factors for Preeclampsia</th>
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<tbody>
<tr>
<td>Hypertension</td>
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<tr>
<td>Collagen vascular disease</td>
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<tr>
<td>Obesity</td>
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<tr>
<td>Black race</td>
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<tr>
<td>Insulin resistance</td>
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<tr>
<td>Diabetes</td>
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<tr>
<td>Increased circulating testosterone</td>
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<tr>
<td>Thrombophilia</td>
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have had preeclampsia years previously manifest many risk factors for cardiovascular disease including dyslipidemia, insulin resistance, and blunted endothelial relaxation.\textsuperscript{35-37} The data would tend to support the concept that the same factors that predispose to preeclampsia also predispose to cardiovascular disease in later life.

There are other similar findings in preeclampsia and atherosclerotic cardiovascular disease. Preeclampsia is characterized by a dyslipidemia identical to that predisposing to cardiovascular disease. Increased triglycerides, increased LDL and reduced HDL cholesterol, and an increased prevalence of small dense LDL all are present in women with preeclampsia.\textsuperscript{38} Furthermore, there is an exaggerated activation of the inflammatory response in preeclampsia compared with normal pregnancy.\textsuperscript{39} Markers of inflammation antedate clinically evident preeclampsia,\textsuperscript{40} and the endothelium appears to be an important pathogenetic target in preeclampsia, as it is in atherosclerosis.\textsuperscript{29}

These similarities have suggested that the disorders may share a common pathophysiology. The oxidation hypothesis of atherosclerosis proposes that inflammatory activation of endothelium and circulating blood cells generate free radicals. The impact of these reactive oxygen species is increased by the dyslipidemia of atherosclerosis. Small dense LDL particles have preferential access to the subendothelial space, where they are sequestered from circulating antioxidants. In addition, these lipoprotein variants are inherently more easily oxidized. The oxidized LDL generated acts on endothelium-altering function and upregulating VCAM, leading to recruitment of monocytes. These cells take up the oxidized LDL with the eventual formation of the fatty streak and atheromatous plaque.\textsuperscript{41}

**Oxidative Stress in Preeclampsia**

Oxidative stress has been proposed as the linkage between the two stages of preeclampsia.\textsuperscript{42} The oxidative stress hypothesis proposes that hypoxia at the fetal-maternal interface results in the generation of free radicals that may lead to oxidative stress dependent on the maternal constitution. Abundant evidence of oxidative stress in blood and tissues of women with preeclampsia support the hypothesis (Table 2).\textsuperscript{38} Further support comes from a small study in which antioxidants were administered from early gestation to women at high risk of preeclampsia. The goal of the study was to determine if prophylactic antioxidants could prevent evidence of endothelial activation, as measured by soluble PAI-1, a marker of endothelial activation. The ratio of PAI-1 (made by endothelium) to PAI-2 (made by placenta) was reduced in the women receiving antioxidants. In addition, and even more important from a clinical standpoint, the frequency of preeclampsia was reduced in the treated women.\textsuperscript{43} This study, although encouraging, was quite small, and thus the efficacy and safety of antioxidant treatment for the infant require confirmation in larger studies.

**Implications of Current Scientific Knowledge**

The current knowledge about preeclampsia has important implications. The interaction of reduced placental perfusion with numerous maternal factors indicates that various causal factors may have different degrees of importance among individuals. Although this increases the complexity of the scientific endeavor, it raises the possibility that specific causes in specific women may be treatable. The similarities to the pathophysiology of cardiovascular disease in later life are intriguing. It is likely that the study of both disorders might provide complementary insights. There is abundant evidence that the pathophysiological changes of preeclampsia are present long before the clinical presentation of the disorder, which probably explains why all management of overt preeclampsia other than delivery is only palliative. This indicates that future successful therapies will require the institution of therapy before clinically evident disease.\textsuperscript{44} Thus, predictors of preeclampsia with high sensitivity and moderate specificity will be useful initially in the conduct of clinical trials and perhaps eventually for therapy.\textsuperscript{23}

**Gaps in Understanding**

Although the understanding of preeclampsia has grown enormously, it is important to point out that several postulates, including the linkage of the two stages of preeclampsia by oxidative stress, remain hypotheses requiring further testing. If oxidative stress provides this linkage, how do the evanescent free radicals formed in the intervillous space result in systemic endothelial activation? There are numerous candidates proposed as intermediaries in this process, including stable products of lipid peroxidation (eg, malondialdehyde),

**TABLE 2. Evidence of Oxidative Stress in Preeclampsia**

<table>
<thead>
<tr>
<th>Category</th>
<th>Markers</th>
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<tbody>
<tr>
<td>Circulating markers</td>
<td>Nonlipid markers</td>
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<tr>
<td></td>
<td>Antibodies to LDL</td>
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<tr>
<td></td>
<td>Ascorbate oxidizing activity</td>
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<tr>
<td></td>
<td>Increased nitrosothiols</td>
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<tr>
<td>Lipid markers</td>
<td>Lipid oxidation products</td>
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<tr>
<td></td>
<td>Antibodies to oxidized LDL</td>
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<tr>
<td>In systemic maternal tissues</td>
<td>Increased nitrotyrosine residues in blood vessels</td>
</tr>
<tr>
<td></td>
<td>Activated neutrophils and monocytes</td>
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<tr>
<td>In decidua</td>
<td>Atheros with lipid-laden macrophages</td>
</tr>
<tr>
<td></td>
<td>Increased lipid peroxides</td>
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<tr>
<td></td>
<td>Increased isoprostanes (8 iso PGF2α)</td>
</tr>
<tr>
<td></td>
<td>Protein carbonyl</td>
</tr>
<tr>
<td>In placenta</td>
<td>Nonlipid markers</td>
</tr>
<tr>
<td></td>
<td>Increased xanthine oxidase in invading trophoblast cells</td>
</tr>
<tr>
<td></td>
<td>Increased nitrotyrosine resides in fetal blood vessel</td>
</tr>
<tr>
<td>Antioxidants</td>
<td>Reduced superoxide dismutase</td>
</tr>
<tr>
<td></td>
<td>Reduced glutathione peroxidase</td>
</tr>
<tr>
<td>Lipid markers</td>
<td>Increased malondialdehyde</td>
</tr>
<tr>
<td></td>
<td>Increased lipid peroxide</td>
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<td></td>
<td>Protein carbonyl</td>
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\textsuperscript{62} Reduced superoxide dismutase (SOD) is an enzyme that catalyzes the dismutation of superoxide radicals to hydrogen peroxide and oxygen. It is a key antioxidant enzyme that helps to prevent oxidative damage. \textsuperscript{70} Reduced glutathione peroxidase (GSH-Px) is an enzyme that catalyzes the reduction of hydrogen peroxide to water and organic peroxides. It is involved in the detoxification of many xenobiotics. \textsuperscript{72} Reduced glutathione peroxidase (GSH-Px) is an enzyme that catalyzes the reduction of hydrogen peroxide to water and organic peroxides. It is involved in the detoxification of many xenobiotics. \textsuperscript{73} Reduced glutathione peroxidase (GSH-Px) is an enzyme that catalyzes the reduction of hydrogen peroxide to water and organic peroxides. It is involved in the detoxification of many xenobiotics.
and neutrophils or monocytes activated directly in the inter-villous space or by material (placental fragments or cytokines) from the hypoxic placenta. Furthermore, the identification of angiotensin antibodies with the capability to activate NADPH oxidase with subsequent free radical formation in women with preeclampsia suggests a very different origin for oxidative stress. In addition, the role of oxidative stress, although attractive, can only be shown to be causally important by the demonstration in clinical trials that preventing oxidative stress prevents preeclampsia. It must be borne in mind that preeclampsia has been characterized as the “disease of theories,” none of which has stood the test of time. Indeed, although this review has stressed a current and very plausible hypothesis, it would be remiss not to summarize other postulates under consideration. These include abnormalities in the mother’s circulatory adaptations to pregnancy, maternal endothelial dysfunction secondary to cytokines, altered autocrine systems, vitamin and mineral deficiencies, infectious agents similar to those linked to atherosclerosis, impairment of the normal barriers against the importation of fetal and trophoblastic material into the maternal circulation, and a combination of these factors with those described in detail above. This emphasizes the value and need for clinical trials that incorporate mechanistic studies to increase understanding further.

The relation of preeclampsia to long-range cardiovascular disease has important implications. Women who have had preeclampsia have increased risk of cardiovascular disease in later life compared with women who have had normal pregnancies. This has been interpreted as indicating similar risk factors for preeclampsia and later life cardiovascular disease. However, the nature of this relation remains to be established, and data on women who have been examined before, during, and after a preeclamptic pregnancy do not exist. The alternative possibility that preeclampsia leads to cardiovascular disease in later life or even that normal pregnancy has a beneficial long-range cardiovascular effect cannot be excluded based on current data. The public health implications of these possibilities are quite different and merit careful consideration.

Management of Chronic Hypertension
As women in developed countries delay childbirth, the impact of chronic hypertension will increase because the prevalence of hypertension increases with age. It is likely that in the near future, as many as 5% of women who become pregnant will have preexisting hypertension. Clinicians do not have sufficient evidence to know which pharmacological therapy is best, when to begin treatment, how vigorously to treat, or whether to stop treatment and hope that the hypotensive effect of normal pregnancy will be enough to control blood pressure. The only trial for treatment of hypertension during pregnancy with adequate infant follow-up (7.5 years) was performed over 25 years ago with a drug (alpha-methyldopa) now rarely used in nonpregnant patient. Past clinical trials also have not supported a beneficial effect on pregnancy outcome of treating mild hypertension. There has been no reduction in perinatal mortality, placental abruption, or superimposed preeclampsia. All of these trials are subject to criticism, including small numbers, starting the drug too late in pregnancy, or flawed study design. Nonetheless, no other data are available. Because of the unknown long-term effects on the infant of any treatment, these studies have led to recommendations to treat only on the basis of blood pressure sufficiently elevated to pose potential acute risk to the mother. Whether this is the appropriate strategy is not clear. Small and frequently poorly designed studies have recently suggested that therapy of mildly elevated blood pressure may prevent progression to preeclampsia. Even for women with blood pressure elevation sufficient to justify therapy for their own benefit, it is not clear whether treatment is beneficial or detrimental for the fetus. In several studies, treatment of hypertensive women resulted in an increased risk of growth restriction in their infants. It is not known whether this is the inevitable consequence of lowering blood pressure during pregnancy or whether it is due to excessive blood pressure decreases or to specific drugs.

Dietary and other lifestyle changes have been shown in nonpregnant women to substantially lower blood pressure in the short term, both in hypertensive and nonhypertensive individuals. For example, in the Dietary Approaches to Stop Hypertension (DASH)–Sodium Study, the combination of the DASH diet and lower sodium intake (65 mmol/24-hour urinary excretion) reduced systolic blood pressure by 11.5 mm Hg in hypertensive over 4 weeks, compared with a typical American diet. Whether such blood pressure reduction can be achieved safely in hypertensive pregnant women is not known and should be evaluated.

These questions can only be resolved with well-designed, relatively long-term clinical trials. Pharmaceutical companies have not been eager to test drugs in this small market with a high potential for litigation. These studies nonetheless must be carried out.

Recommendations for Research
Specific recommendations were developed by Working Group members and assigned priorities by using standard techniques for obtaining group consensus. In developing recommendations, the Working Group considered the merits of competing scientific questions, the maturity of hypotheses for clinical testing, and the availability of scientific resources. The research questions deemed to be of the highest priority and the proposed scientific strategies are summarized below.

How Does Preeclampsia Develop, andDoes It Confer Future Cardiovascular Risk?
It is accepted that abnormal implantation of the blastocyst and abnormal placental bed remodeling or other causes of reduced placental perfusion are prerequisites for preeclampsia, but the mechanistic links between this step and the development of preeclampsia many weeks later are not known. Moreover, little work is currently being done in this area. Mechanistic studies should be encouraged, both independently and as part of ongoing or future longitudinal studies to determine the cell biology and physiology that links reduced placental perfusion to the maternal syndrome of preeclampsia. Studies could focus on basic pathological mechanisms, the natural history of vascular changes in pregnancy, perfu-
Women with chronic hypertension who become pregnant are residua of the preeclampsia syndrome. How Should Chronic Hypertension in Pregnancy Be Treated? and thus are risk factors or occur only after delivery. Maladies in cardiovascular function that can be identified could make the important distinction of whether the abnormalities in cardiovascular function that can be identified several years after preeclampsia occurred before the pregnancy and are thus risk factors or occur only after delivery and thus are residua of the preeclampsia syndrome.

How Should Chronic Hypertension in Pregnancy Be Treated? Women with chronic hypertension who become pregnant are treated with α-methyldopa, based on a single study completed many years ago that had long-term follow-up of the offspring to demonstrate fetal safety of the treatment. Although some antihypertensive agents such as ACE inhibitors are contraindicated in pregnancy, there are a number of alternate antihypertensive agents that should be studied. A clinical trial of antihypertensive treatment in pregnancy should be conducted to evaluate blood pressure control, fetal growth and safety, and genetic variation in response to therapy.

Will Antioxidant Therapy Safely Prevent Preeclampsia? Treatment and prevention trials have been disappointing to date. However, several recent studies that have suggested causal links between oxidative stress, depletion of vitamin C, low levels of the endogenous vasodilator nitric oxide, and the development of preeclampsia indicate that there may be a role for antioxidant vitamins in the prevention of preeclampsia. A clinical trial should be undertaken testing the hypothesis that antioxidant vitamins can reduce the risk of preeclampsia, reduce maternal and fetal mortality rates, and increase birth weight. Such clinical trials also should incorporate study of biomarkers and other measures of risk factors and determine predictors and early pathophysiological changes of preeclampsia in low-risk and high-risk populations.

How Should Research Capabilities Be Developed? Career development programs should be encouraged to enhance the research capabilities of scientists interested in hypertensive disorders of pregnancy. A major goal of career development programs should be to increase the involvement of scientists with diverse research backgrounds and capabilities in the study of hypertensive disorders of pregnancy. A focused effort would improve the skills of individuals working in this area and bring new researchers and skills to bear on the study of hypertensive disorders of pregnancy.

Appendix

Roster: Working Group, High Blood Pressure in Pregnancy Chair: James M. Roberts, MD, Director, Magee-Women’s Research Institute, and Professor and Vice Chair (Research), Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh. Members: Phyllis August, MD, Professor of Medicine, Obstetrics and Gynecology, Chief, Hypertension Division, Weill Medical College of Cornell University; Matthew W. Gillman, MD, S.M., Associate Professor, Department of Ambulatory Care and Prevention, Harvard Medical School/Harvard Pilgrim Health Care; Marshall Lindheimer, MD, Professor, Departments of Obstetrics and Gynecology and Medicine, The Pritzker School of Medicine, University of Chicago; Leslie Myatt, PhD, Professor of Obstetrics and Gynecology, University of Cincinnati, College of Medicine; Christopher W.G. Redman, M.A., M.B., Bchir, Nuffield Department of OB/Gyn, Headington, Oxford; Baha Sibai, MD, Professor and Chairman, Department of Obstetrics and Gynecology, University of Cincinnati College of Medicine; Kenneth Ward, MD, Professor, Obstetrics and Gynecology and Human Genetics, University of Utah; Michelle Williams, ScD, Professor of Epidemiology, Department of Epidemiology, University of Washington; Representative, NHLBI Public Interest Organization: Anne E. Garrett, Executive Director, Preeclampsia Foundation.

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