Stress Processes in Pregnancy and Preterm Birth

Christine Dunkel Schetter

University of California, Los Angeles

ABSTRACT—*Preterm birth (PTB) is of epidemic proportions in the United States, particularly among African Americans. Its consequences range from risk of infant mortality to life-long disease and disability. Stress is a contributor to preterm labor and delivery. This article summarizes research on stress as a risk factor for PTB. As is evident in considering the complex mechanisms, psychological science has much to contribute to addressing this important health issue.*

KEYWORDS—*stress; pregnancy; birth; preterm; women's health*

Preterm birth (PTB) is defined as birth occurring before 37 weeks gestation, whereas normal gestation is 40 to 42 weeks. About 1 in 8 births in the United States are preterm. These high rates of PTB have persisted for decades and are still on the rise. Moreover, there are persistent disparities in PTB between racial and ethnic groups in the United States. Black women deliver their babies preterm at nearly twice the rate of White women and at higher rates than other major U.S. ethnic groups, and this partially accounts for the high rates in the United States. PTB has been referred to by authorities as a "quiet epidemic" (McCormick & Behrman, 2006), because the public lacks awareness of the problem. Half to two thirds of infants born preterm are low birth weight (LBW, defined as 2500 grams or less). Babies born early weigh less because they have had less time to grow in the womb; by the same token, fetuses that are not growing normally are more likely to be born early, possibly as an adaptive mechanism. However, some pathways leading to early delivery are distinct from the pathways leading to LBW.

The potential consequences of PTB for children born too early and for their families are enormous, beginning with an increased risk of neonatal and infant mortality. Improvements in neonatal intensive care have resulted in better survival rates, but the risk of complications remains. Preterm infants are at risk of respiratory, gastrointestinal, immune, central nervous system, and sensory problems. Longer-term risks affecting especially those born very early (earlier than 32 weeks) include growth problems, learning difficulties, cerebral palsy, and mental retardation. Costs associated with PTB (such as medical care, parental loss of work, and special education for children) are estimated at $26 billion a year in the United States.

Poor women are especially at risk of PTB. The constellation of low socioeconomic status, African American race, and other demographic factors (i.e., teenage and unmarried mothers) poses high risk. However, many women of other backgrounds deliver preterm, and prediction of PTB on the basis of demographic and medical factors alone is poor (Lu & Halfon, 2003). Therefore, research on PTB has turned to multidisciplinary approaches that emphasize interactions of psychosocial, sociocultural, and biomedical processes to better understand the pathways to PTB, delineate high-risk groups, and develop prevention programs.

STRESS, AFFECTIVE STATES, AND PTB

Stress is defined as external demands that tax or exceed the adaptive capacity of an organism. When appraised as stressful, demands result in behavioral, emotional, cognitive, and biological responses with numerous potential adverse consequences for mental and physical health. Stressors may be acute or discrete events or chronic and ongoing difficulties, and individuals differ in their tendency to perceive situations as stressful, making "stress" a slippery construct to measure. Researchers have utilized each of these conceptualizations in their attempt to untangle potential links between stress and PTB,

Very early research on psychosocial factors and PTB focused on prenatal maternal anxiety, conceptualized as either a dynamic state or a stable trait. Subsequent research focused on the role of general emotional distress, not on specific emotional states. Later prospective studies examined both anxiety and depression but found no consistent evidence of associations of depression with PTB. Instead, depression is more often a risk factor for LBW.

Address correspondence to Christine Dunkel Schetter, Department of Psychology, 1285A Franz Hall, UCLA, Los Angeles, CA 90095-1563; e-mail: dunkel@psych.ucla.edu.

@DIR 1637 | CDIR | 1637 | B | Dispatch: 24.7.09 | Journal: CDIR | CE: Bindu
Journal Name | Manuscript No. | Author Received: | No. of pages: 5 | PE: Archana/ananth

In contrast, research indicates that anxiety during pregnancy is an independent risk factor for PTB. The prospective studies are quite consistent in finding that anxiety concerning the pregnancy itself is associated with the timing of delivery. This usually refers to anxiety or worry about the impending birth and about the health of the child. One large prospective study found that pregnancy-related anxiety at 24 to 29 weeks predicted PTB in a sample of 1,962 women, after adjustments for alcohol and tobacco use (Dole et al., 2003). Particularly important is that this held up when preexisting medical conditions were controlled and when only the women who did not have medical induction were examined (i.e., spontaneous preterm labor). Controlling for high-risk conditions of pregnancy rules out the possibility that these conditions, or anxiety concerning them, are responsible for effects of stress on PTB.

Many studies on stress and PTB have focused on the effects of major life events such as divorce, death in the family, or job loss. Of the handful of rigorous studies on life events in pregnancy, a majority report significant associations of some aspects of life events with PTB. One large prospective study assessed life events at 20 weeks gestation in a cohort of 2,432 Danish women and found that severe life events during pregnancy predicted PTB, with maternal age, cohabitation, and education controlled (Nordentoft et al., 1996).

Studies of chronic forms of stress are fewer. One team of researchers studied 237 homeless women interviewed at 78 shelters or meal programs (Stein, Lu, & Gelberg, 2000). Severity of homelessness, especially the percent of one's lifetime spent homeless, predicted preterm birth, controlling for how much the baby weighed at birth and for many other variables (substance use, trauma and distress, prior birth complications, ethnicity, income, and medical risk). Results of investigations on perceived stress—another approach to examining chronic strain—are mixed, with some studies showing significant effects on PTB, but typically when combined with other stress measures. A relatively small number of studies have assessed daily stressors or "hassles," with no significant results.

Another small group of studies involved women who experienced a catastrophic event during pregnancy. One illustrative study assessed the impact of the 2001 terrorist attack at the World Trade Center on 300 nonsmoking women in New York City who were pregnant at the time (Lederman et al., 2004). Women who were in the first trimester at the time of the bombing delivered their infants significantly earlier than did women who were further along in pregnancy. Similar effects were found in another study of 40 women who experienced a major earthquake in their first, second, or third trimester or postpartum (Glynn, Wadhwa, Dunkel Schetter, Chicz-DeMet, & Sandman, 2001). The later in pregnancy the earthquake occurred, the longer was gestation; the longest gestations occurred among women who had already delivered at the time of the event (i.e., those unexposed to the stressor). Although there are some conflicting findings, both of these studies suggest that major trauma early in pregnancy can lead to earlier delivery.

Finally, researchers have investigated sources of chronic strain arising from social contexts such as work. Results have been somewhat consistent in showing significant associations of either occupational stress or physical strain with greater risk of PTB. This topic has often been framed as an issue of whether employment during pregnancy is itself risky, without consideration of the specific characteristics of a woman's job. Research has not adequately accounted for type of work activities, hours worked, when in pregnancy women work, work environment, or cognitive and emotional strain, all of which must be considered. When these factors are quantified, we may learn that some employed women are at risk of adverse birth outcomes and that others are not. In addition, the neighborhood in which a woman lives is also gaining attention as a source of chronic strain.

FINDINGS IN OUR LABORATORY

For the past 20 years, our lab has been engaged in collaborative research on stress and PTB (http://health.psych.ucla.edu/CDS/). Initially, we focused on determining if there was any evidence for stress as a contributor to earlier delivery, lower birth weight, or other adverse outcomes. Our group was one of the first to prospectively assess stress as a multidimensional construct repeatedly over the course of pregnancy and to untangle the effects of stress on timing of delivery, controlling for birth weight and medical risk. In a multiethnic sample of 130 low-income women, Lobel, Dunkel Schetter, and Scrimshaw (1992) found that a stress composite including perceived stress, state anxiety, and distress about life events independently predicted both earlier delivery and lower birth weight, controlling for medical risk. When attempting to replicate these results in a larger sample of 1,100 Mexican immigrants, Mexican American, and Black women, we found that stress predicted earlier delivery, controlling for medical risk factors but not lower birth weight (Zambrana, Dunkel Schetter, Collins, & Scrimshaw, 1999).

In a subsequent study, we determined that prenatal anxiety (a combination of state anxiety and pregnancy anxiety), assessed by interview at 22 to 28 weeks, was associated with gestational age in 230 Hispanic and White women (see Fig. 1), controlling for sociodemographic, medical, behavioral, and other psychosocial risk factors (Rini, Dunkel Schetter, Sandman, & Wadhwa 1999). We replicated these findings in another study with a sample of 282 women who were assessed twice in pregnancy (Mancuso, Dunkel Schetter, Rini, Roesch, & Hobel, 2004) using a different measure of pregnancy anxiety. In that study, "pregnancy-specific anxiety" at 28 to 30 weeks significantly predicted gestational age. Further analyses explored which of three stress indicators (state anxiety, pregnancy anxiety, perceived stress) was most predictive of timing of delivery. Pregnancy anxiety was the only significant predictor when all three psychosocial indicators were compared. Assessments of pregnancy anxiety as

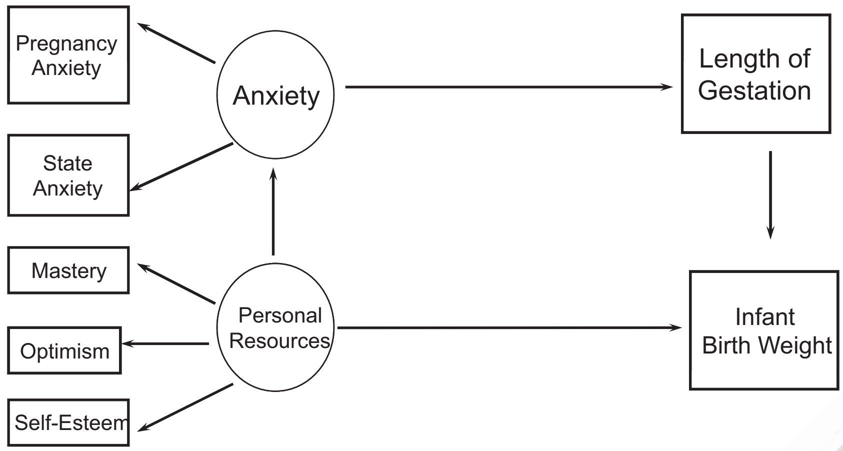

Fig. 1. **The adverse effects of anxiety (pregnancy specific and general state anxiety) on length of gestation, controlling for demographics and medical risk factors (not shown) and the beneficial effects of personal resources (mastery, optimism, and self esteem) on infant birth weight (Rini, Dunkel Schetter, Sandman, & Wadhwa, 1999).**

early as 18 weeks predicted PTB (Roesch, Dunkel Schetter, Woo, & Hobel, 2004). Our programmatic studies suggest that anxiety about one's pregnancy is an independent risk factor for PTB, possibly due to its effects on hypothalamic pituitary axis (HPA) function. Effect sizes range from small to moderate across studies.

BIOPSYCHOLOGICAL, PSYCHOSOCIAL, AND SOCIOCULTURAL MECHANISMS OF PTB

Three broad and interrelated pathways from stressors to PTB have been delineated (see Fig. 2). First, maternal perceptions of stress can activate the HPA system, which is implicated in the onset of labor. Corticotrophin-releasing hormone (CRH) is a neuropeptide released by the pituitary in response to stress that sets in motion a cascade of other neuroendocrine effects, preparing the body to manage acute stress. When elevated chronically, it indicates dysregulation of the stress system, which can affect the fetus adversely. In human pregnancy, CRH is also expressed in the placenta and is thought to play a central role in both fetal maturation and onset of labor. Maternal CRH of placental origin increases exponentially over the course of normal pregnancy, but it is elevated earlier and increases faster in pregnancies that end in preterm labor. The term "placental clock" refers to this phenomenon (McLean et al., 1995). Our findings suggest that CRH may mediate the effect of maternal anxiety on PTB (Mancuso et al., 2004).

Second, stress can alter neuroendocrine modulation of immune function, leading to increased susceptibility to inflammation and infection (Wadhwa, Culhane, Rauh, & Barve, 2001). This inflammatory pathway is thought to be responsible for a majority of cases of PTB (50% of those delivering at 28 weeks or less). Inflammation may be present in pregnancy or prepregnancy. Various forms of infection including genital infections (e.g., bacterial vaginal infection, known as BV), intrauterine infection, systematic maternal infections, and periodontitis (gum disease) may pose risk of PTB. High levels of proinflammatory immune markers such as cytokines and prostaglandins in response to infection play a central role in this pathway and their effects in pregnancy are presently under investigation.

Third, stress may increase high-risk behaviors. Although many health behaviors have been studied, only a few are clearly

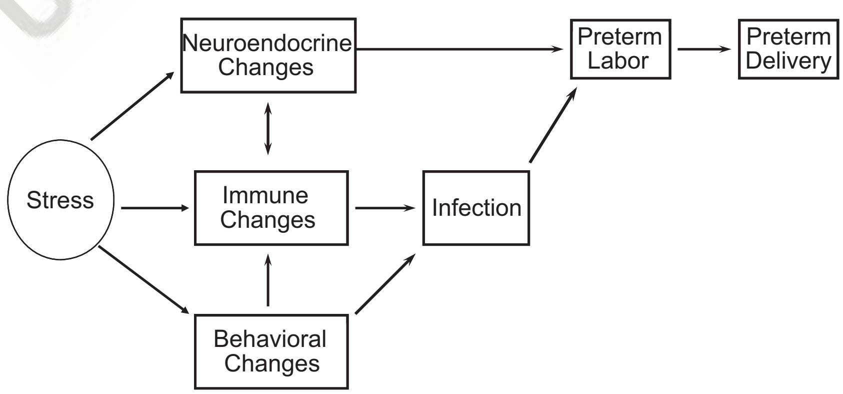

Fig. 2. **Hypothesized explanatory mechanisms for stress–preterm delivery effects. Stress contributes to preterm birth via neuroendocrine, immune, and behavioral pathways.**

associated with increased risk of PTB. Among the health behaviors most strongly associated with PTB is cocaine use. Lifestyle factors such as amount of physical activity (too little or too much) and diet (fasting, lack of vitamins) have also been implicated in behavior pathways to PTB.

Emerging research suggests that both a genetic susceptibility and gene–environment interactions play roles in PTB. Stress is thought to be a factor in these interactions and the pathways are believed now to vary depending on how early a preterm birth is. Clearly, the pathogenesis of PTB involves complex interactions of genetic, environmental, psychobiological, social, and behavioral factors (Behrman & Butler, 2006).

CULTURE, RACE, AND ETHNICITY IN PTB

African American women have unique experiences of stress, yet there is not enough research on this issue in pregnancy. The pressing need to reduce racial disparities in adverse birth outcomes in the United States has led to new theories and research directions on the pregnancies of Black women, especially on the role of racism and discrimination (Giscombe & Lobel, 2005; Hogue & Bremer, 2005). Racism is interpersonal and institutional discrimination or unfair treatment based on a person's race or ethnicity. Perceived racism has been assessed in a handful of case-control and prospective studies of pregnancy. In general, research suggests that racism may be a potent stressor that occurs throughout the lifetimes of African American women and that contributes to ethnic disparities in PTB. Further research is imperative, however, to determine the specific forms of racism, to test cumulative and time-specific effects, and to elaborate the pathways. For example, research on cognitive and behavioral methods of responding to racism may mediate effects of racism on the outcomes of African American women's pregnancies.

Our lab's recent focus has been on ethnic, racial, and cultural risk and resilience factors, including perceived racism in African Americans (Parker Dominguez, Dunkel Schetter, Glynn, Hobel, & Sandman, 2008) and familism in Latinas (Campos et al., 2008). The emerging pattern suggests that these factors are linked to fetal growth during pregnancy (LBW, not PTB), perhaps by influencing health behavior. Cultural values, for example, can facilitate better nutrition and medical care. Chronic strains such as racism, on the other hand, may contribute to riskier health behaviors as responses to a steady stream of socioeconomic disadvantage and discrimination over a lifetime. We continue to search for cultural influences on stress, resilience, and PTB. Pregnancy anxiety appears to be a stronger predictor of PTB for Latinas compared to other groups, but as yet we do not know why.

CONCLUSIONS AND FUTURE DIRECTIONS

Research on stress and PTB is moving forward at a very fast pace. However, human experimental and intervention studies that could provide causal evidence either have not been done or have been inconclusive. Furthermore, prenatal intervention trials that attempt to improve outcomes with multiple components do not generally use advanced methodologies for isolating the effects of stress reduction from other psychosocial effects, nor do they examine the mediating processes involved, to determine which components successfully reduced stress, which did not, and why.

There is also a need for better theoretical analyses to guide research. One promising topic is the intensity and duration of distinct emotional states and their consequences for physiology and for PTB. New findings may emerge if we focus our inquiry on the role of anxiety and its specific biological consequences. Another avenue is to focus more on specific times in pregnancy. Emerging research indicates that emotional, endocrine, and cardiovascular stress reactivity diminishes over the course of gestation until the time of birth (Glynn, Dunkel Schetter, Hobel, & Sandman, 2008) suggesting a masking of responses to protect the fetus. If the physiology of pregnancy and the psychological terrain in which a pregnancy occurs is altered very early in gestation, then developing a healthy population before pregnancy as a form of primary prevention becomes the goal of maternal and child health policy.

This challenge requires psychological scientists—both students and seasoned researchers—to work in collaboration across disciplines and within communities. Our group is working on only a limited set of issues, but we are encouraged that research is increasing in the United States and other countries. Psychological science has much to contribute to this intriguing interdisciplinary endeavor.

Recommended Reading

Behrman, R.E., & Butler, A.S. (Eds.). (2006). (See References). Comprehensive and scholarly volume on the etiology, consequences, and recommendations for prevention of preterm birth by leading interdisiciplinary scientists composing the Institute of Medicine Committee on Preterm Birth.

Beydoun, H., Saftlas, A.F. (2008). Physical and mental health outcomes of prenatal maternal stress in human and animal studies: A review of recent evidence. *Paediatric and Perinatal Epidemiology*, *22*, 438–466. Recent review of a broad range of studies (including animal and human studies) linking prenatal stress to many physical and mental health outcomes and drawing conclusions for public health policy.

Coussons Read, M. (2003). Neural-immune consequences of environmental and psychological stress in pregnancy. *Recent Research in Developmental Life Science*, *1*, 113–130. An excellent review of alterations in maternal immune function resulting from prenatal stress and of neural immune interactions as they influence maternal and infant outcomes such as stress responsivity and immune function in the developing infant.

Savitz, D., & Dunkel Schetter, C. (2006). Behavioral and psychosocial contributors to preterm birth. In R.E. Behrman & A.S. Butler (Eds.), *Preterm birth: Causes, consequences and prevention* (pp. 87–123).Washington DC: National Academy Press. A review, requested by the Institute of Medicine, covering the major findings

@WUS CDIR 1637.PDF 24-Jul-09 15:45 127953 Bytes 5 PAGES (~operator~gs7avishkar)

@DIR 1637

on health behaviors and psychosocial factors contributing to PTB and drawing conservative conclusions from the research.

Acknowledgments—The contributions of several individuals to this work are acknowledged: To my first collaborator, Susan Scrimshaw, PhD, a superb medical anthropologist working in international public health who sparked the research trajectory that followed; to my first student, Marci Lobel, PhD, whose courage to work in uncharted territory was sustaining; to Ruth Zambrana, PhD, a medical sociologist, who first directed my attention to the power of socioeconomic status to shape a pregnancy; to Curt Sandman, PhD, at the University of California, Irvine, whose long term collaboration is much valued; to Calvin Hobel, MD, Distinguished Chair of Maternal Fetal Medicine at Cedars Sinai Health Center, whose wisdom and passion for obstetrics and the role of stress in PTB has always inspired me; and to current collaborators, Laura Glynn, PhD, Michael Lu, MPH, MD, Loretta Jones, MA, and Tyan Parker Dominguez for keeping the fires of passion burning. Thanks also to our Community Child Health Network and National Institute of Child Health and Human Development funders who, through community-based participatory research processes in five sites, are offering us promise of better research in child and maternal health. Thanks to my current lab group and Christine Rini, PhD, for feedback on early drafts of this paper, and to Stacy Eisenberg, Courtney Hooker, and Rassilee Sharma for administrative assistance.

REFERENCES

Behrman, R.E., & Butler, A.S. (Eds.). (2006). *Preterm birth: Causes, consequences and prevention*. Washington DC: National Academy Press.

Campos, B., Dunkel Schetter, C., Abdou, C., Hobel, C.J., Glynn, L.M., & Sandman, C.A. (2008). Familialism, social support, and stress: Positive implications for pregnant Latinas. *Cultural Diversity and Ethnic Minority Psychology*, *14*, 155–162.

Dole, N., Savitz, D.A., Hertz-Picciotto, I., Siega-Riz, A.M., McMahon, M.J., & Buekens, P. (2003). Maternal stress and preterm birth. *American Journal of Epidemiology*, *157*, 14–24.

Giscombe, C.L., & Lobel, M. (2005). Explaining disproportionately high rates of adverse birth outcomes among African Americans: The impact of stress, racism, and relation factors in pregnancy. *Psychological Bulletin*, *131*, 662–683.

Glynn, L.M., Dunkel Schetter, C., Hobel, C.J., & Sandman, C.A. (2008). Pattern of perceived stress and anxiety in pregnancy predicts preterm birth. *Health Psychology*, *27*, 43–51.

Glynn, L.M., Wadhwa, P.D., Dunkel Schetter, C., Chicz-DeMet, A., & Sandman, C.A. (2001). When stress happens matters: Effects of earthquake timing on stress responsivity in pregnancy. *American Journal of Obstetrics and Gynecology*, *184*, 637–642.

Hogue, C.J.R., & Bremmer, J.D. (2005). Stress model for research into preterm delivery among black women. *American Journal of Obstetrics and Gynecology*, *192*, S47–S55.

Lederman, S.A., Rauh, V., Weiss, L., Stein, J.L., Hoepner, L.A., & Becker, M. (2004). The effects of the World Trade Center event on birth outcomes among term deliveries at three lower Manhattan hospitals. *Environmental Health Perspectives*, *112*, 1772–1778.

Lobel, M., Dunkel Schetter, C., & Scrimshaw, S.C.M. (1992). Prenatal maternal stress and prematurity: A prospective study of socioeconomically disadvantaged women. *Health Psychology*, *11*, 32–40.

Lu, M.C., & Halfon, N. (2003). Racial and ethnic disparities in birth outcomes: A life-course perspective. *Maternal and Child Health Journal*, *7*, 13–30.

Mancuso, R.A., Dunkel Schetter, C., Rini, C.M., Roesch, S.C., & Hobel, C.J. (2004). Maternal prenatal anxiety and corticotropin-releasing hormone associated with timing of delivery. *Psychosomatic Medicine*, *66*, 762–769.

McCormick, M., & Behrman, R. (2006). The quiet epidemic of premature birth: Commentary on a recent Institute of Medicine Report. *Ambulatory Pediatrics*, *7*, 8–9.

McLean, M., Bisits, A., Davies, J., Woods, R., Lowry, P., & Smith, R. (1995). A placental clock controlling the length of human pregnancy. *Nature Medicine*, *1*, 460–463.

Nordentoft, M., Lou, H.C., Hansen, D., Nim, J., Pryds, O., Rubin, P., & Hemmingsen, R. (1996). Intrauterine growth retardation and premature delivery: The influence of maternal smoking and psychosocial factors. *American Journal of Public Health*, *86*, 347–354.

Parker Dominguez, T., Dunkel Schetter, C., Glynn, L.M., Hobel, C., & Sandman, C.A. (2008). Racial differences in birth outcomes: The role of general, pregnancy, and racism stress. *Health Psychology*, *27*, 194–203.

Rini, C.K., Dunkel Schetter, C., Sandman, C.A., & Wadhwa, P.D. (1999). Psychological adaptation and birth outcomes: The role of personal resources, stress, and sociocultural context in pregnancy. *Health Psychology*, *18*, 333–345.

Roesch, S.C., Dunkel Schetter, C., Woo, G., & Hobel, C.J. (2004). Modeling the types and timing of stress in pregnancy. *Anxiety, Stress, and Coping*, *17*, 87–102.

Stein, J.A., Lu, M.A., & Gelberg, L. (2000). Severity of homelessness and adverse birth outcomes. *Health Psychology*, *19*, 524–534.

Wadhwa, P.D., Culhane, J.F., Rauh, V., & Barve, S.S. (2001). Stress and preterm birth: Neuroendocrine, immune/inflammatory, and vascular mechanisms. *Maternal and Child Health Journal*, *5*, 119–125.

Zambrana, R.E., Dunkel Schetter, C., Collins, N., & Scrimshaw, S.C. (1999). Mediators of ethnic-associated differences in infant birth weight. *Journal of Urban Health*, *76*, 102–116.

Author Query Form

Journal	**CDIR**
Article	**1637**

Dear Author,

During the copy-editing of your paper, the following queries arose. Please respond to these by marking up your proofs with the necessary changes/additions. Please write your answers clearly on the query sheet if there is insufficient space on the page proofs. If returning the proof by fax do not write too close to the paper's edge. Please remember that illegible mark-ups may delay publication.

Query No.	Description	Author Response
.	No Queries	