The first observations that placental bed defects were potentially linked to clinical outcomes such as preeclampsia (PE) were made nearly 50 years ago. This study followed prior findings that the placental clearance of radio-labeled saline was significantly decreased in women with hypertensive gestations. Histological examination of placentas and placental bed biopsies obtained from complicated gestations and compared with normotensive controls were performed in hopes to discern histopathologic causes for clinical outcomes. Decades of research into placental histopathology have held fast to certain dogma; defects in spiral artery remodeling and trophoblast invasion are characteristic of hypertensive disorders of pregnancy and fetal growth restriction (FGR). These 2 processes, deemed essential for normal pregnancy, are mechanistically not understood. Our current understanding of spiral artery remodeling and trophoblastic invasion is that they are highly inter-related, but separate processes. Regulation is likely multifactorial, including genetic, immune, maternal, fetal, endocrine, and cardiovascular influences. Temporal regulation is known, making timing of study and sampling a large issue, particularly in women. Typically, samples are only available as terminations in first trimester, before presentation of maternal disease, or at term, well after disease presentation. There is no opportunity for serial sampling, which is an understandable limitation, to our current knowledge, in humans. Data from animal models have yielded important findings, although the potential for translational application to humans is questionable. Even in studies of animals with hemochorial placentation, several differences are apparent. Perhaps the best studied are mice, with short (19–20) day gestations and significant decidual spiral artery remodeling. In mice, specialized terminally differentiated lymphocytes called uterine natural killer cells are primarily responsible for arterial remodeling in this species. Trophoblastic invasion in mice is relatively shallow and is temporally restricted to late gestation, generally considered a minor contributor to arterial remodeling. In rats, invasion of trophoblast is more robust, extending deep into the myometrium in normal gestations.

In a rat model of PE, trophoblast invasion was observed to be more extensive than control gestations at term. Mice with impaired spiral artery remodeling remained normotensive throughout gestation without development of proteinuria or fetal growth restriction. The range of genetically manipulated rodents available for study has undoubtedly broadened our knowledge; however, whether impaired spiral artery remodeling is the cause or consequence of the complicated pregnancy is still unclear. Thus, to gain better understanding of human complications of pregnancy, we require more careful study of humans. Currently, there is no standard practice for collection of placenta or placental bed biopsies. This leads to a serious limitation for the entire field: sampling bias. Each research group tends to follow their own protocol and definitions, and indeed some investigators have written methods for others to follow. Nonetheless, published studies often will not specify either placenta or placental bed (or worse, confuse the two). Subtypes of extravillous trophoblasts are frequently not classified properly into endovascular, interstitial, and intramural. The significance of proper use of terminology to describe anatomic divisions such as myometrium, decidua, and placenta may have impact on how we view research results.

In the current issue of Hypertension, Lyall et al present a detailed histological examination of placental bed biopsies in normal and complicated pregnancies using modern immunohistochemistry techniques. Placental bed biopsies were collected during cesarean section from uncomplicated pregnancies, preeclamptic women, and gestations complicated by severe FGR and were studied for spiral artery remodeling and extravillous cytotrophoblast behavior and then correlated to several clinical outcomes. One of the main findings is that across all groups, there is little difference in decidual spiral artery remodeling or extravillous trophoblast invasion; this is contrary to many published studies that report significant defects in decidual spiral arteries in both PE and FGR. Conversely, in myometrial spiral arteries, remodeling was incomplete in PE and FGR biopsies. This was evidenced by preservation of the medial wall, which was completely disrupted in uncomplicated gestations. Importantly, myometrial vessels from cases with severe abnormalities in uterine artery Doppler and with preterm delivery had the most dramatic impairment of myometrial vessel remodeling. The authors also determined no major interstitial trophoblast invasion abnormalities in samples from PE women; this finding is also contrary to published literature. However, in FGR biopsies, Lyall et al observed greater amounts of interstitial trophoblast invasion compared with both normal and PE samples. This important observation distinguishes FGR and PE as 2 unrelated processes. Furthermore, the implication is that impaired spiral artery remodeling and alterations in
trophoblast invasion are insufficient to cause maternal signs and symptoms of PE. It remains likely that placental defects are pathophysiologic responses to some other factor, rather than a trigger. Although leaders in the field of placental histology carefully performed this study, there are a few limitations. The sample sizes are small, and it would be desirable to have more samples than what were obtained in the FGR group. The PE group, in general, had normal umbilical and uterine artery Dopplers; this is notable because increased pulsatility index is a sensitive predictor of preterm PE. In light of this, the authors might have considered inclusion of plasma biomarkers, such as angiogenic factors, which more closely correlate to adverse maternal and fetal outcomes than clinical diagnostic criteria that rely on nonspecific signs and symptoms. Finally, more pathologic features should have been examined, including atherosis and syncytial knots, both of which are associated with PE and FGR.

This publication has several important implications for future studies. First, we need to shift the focus from decidual pathology to myometrial pathology. Literature examining placental bed biopsies almost unanimously supports myometrial impairment in PE and FGR, whereas reports of decidual pathology are mixed. It may be time to alter the rigid thinking that decidual spiral arteries are the culprit for impaired blood flow to the placenta. Taken together with prior studies, this work suggests that lack of intramural trophoblasts in the myometrial vessels rather than defective interstitial trophoblast invasion may be the primary abnormality in PE and FGR. Rather than focusing on trophoblast invasion studies in cell culture that model interstitial invasion, we need to adopt better in vitro models to recapitulate the vascular changes noted in the myometrium. In this regard, in vitro models developed by Cartwright et al and Dunk et al allow adequate manipulation of the myometrial system. Both groups use biopsy samples to dissect out myometrial arteries for various experiments. Results revealed that myometrial arteries in vitro are capable of being invaded by trophoblasts as well as undergo remodeling. Ultimately, what are the implications of a relative defect in myometrial vascular trophoblast invasion in PE and FGR? Experts in the discipline are uncertain but theorize that the 2 may have a similar end point: impedance to placental blood flow. If myometrial arteries retain muscular walls, indeed this remains likely. However, is this hindrance to flow cause or consequence of disease? This remains the question. In both PE and FGR, the insult has already occurred well before we are able to clinically detect or study the process. This is the enduring problem; we are trying to understand the end points of a disease, not knowing when or where to look.

Disclosures
S.A. Karumanchi is a coinventor on multiple patents for preeclampsia markers and reports service as a consultant to Roche, Siemens, and Beckman Coulter and has financial interest in Aggamin LLC. S.D. Burke reports no conflicts.

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