described during the entire examination, failure to maintain the stable association for a minimal portion of the examination, or failure to reorganize after the acoustic stimulation? Did meeting this definition during one of the serial evaluations place the fetus in the "disorganized fetal state" category, or did this require disorganization during all the examinations? How many examinations were performed, and over what range of gestation? How long were the examinations? By what gestation was regulation considered delayed?

In addition, there is some question as to what is normal, since a normal drug-free group was not evaluated with the neurobehavioral profile. In Nijhuis et al.'s original work,[1] before 38 weeks, coincidence, or simultaneous occurrence, of 1F and 2F state parameters occurred only 55% to 65% of the entire observation time, with the observation period lasting 112 minutes on the average. They suggested that these periods of coincidence occurred by chance and did not represent organized behavioral states because of the lack of simultaneous change of the state variables. Only with the synchronization of these changes, which developed around 36 to 38 weeks, could true behavioral states be defined. One can see how a preterm fetus, without periods of coincidence of parameters a considerable portion of the time, might be at risk for being classified as "disorganized." This is especially true if the fetus is delivered preterm, as were 25% of the fetuses in the study of Hume et al.

Further clarification of the definitions of "organized" and "disorganized" fetal states, as well as comparison with the fetal neurobehavioral profiles and neonatal outcomes of drug-free controls, would greatly enhance this investigation of the effects of cocaine on the developing central nervous system.

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Reply

To the Editors: The questions raised by Drs. Tabor and Soffici are insightful criticisms of our work. The issues addressed point out the potential for confusion concerning the terminology used to define the abnormal fetal behavior observed in our cocaine-exposed subjects. The pioneering work by Prechtl, Nijhuis, and Arduini and their colleagues (references 8, 9, 12, 14, and 15 of our article) were used in the formulation of our tool. The classification of fetal behavioral states follows that of Nijhuis, as stated. Our study design involved serial ultrasonographic observations (four to eight per subject) of at least 30 minutes' duration during the course of prenatal care. We scored the behavior observed from 28 weeks on to term. The fetal behavior observed included the acquisition and coordination of components of behavior into the defined states, as described by Nijhuis, and the ability and character of fetal reaction to acoustic stimulus, as well as atypical behavior not observed in normal subjects or described by others. Delay of state organization was scored as abnormal if stable state regulation failed to be appreciated by term (>38 weeks).

The confusion of terminology is significant, and Drs. Tabor and Soffici are entitled to a clarification of our use of "organized" and "disorganized." Normally organized and regulated fetal behavior follows the synchronization of components into stable states by 36 to 38 weeks of gestation. The "disorganized" classification applied to fetuses who had delay of organization, bizarre or atypical behavior, or disrupted behavior in response to stimulation. Three fetuses exhibited sustained hyperpnea plus lack of stable state organization, three fetuses exhibited recurrent yawning and abnormal response to stimulation, and three fetuses were hypertonic and hyperirritable, while four were never observed to attain organized state behavior by term gestation. The atypical fetal behaviors were present in those infants scored as being more severely affected as neonates.

The fetal response to stimuli mimics the "all-or-none" or "wired" neonate born with active cocaine intoxication. These neonates are very difficult to arouse, but once so they are very difficult to console. Bradycardia, ballistic fetal activity, and lack of habituation in response to acoustic stimulation were the fetal antecedents to such abnormal neonatal neurobehavior. We have shown our video recordings to many observers of various levels of ultrasonographic or neurobehavior sophistication and all agree in scoring the abnormal cases—the behavior really looks unusual. The need for a prospective study with normal control subjects is apparent and is under way. The use of video recording to score the fetal behavior affords a blinded evaluation to address the criticism of the subjective nature of this interpretation. The results of a larger-prospective longitudinal cohort study are needed to validate the fetal neurobehavioral profile's usefulness and reliability in a clinical setting.

I appreciate the interest in our work.

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Preeclampsia—An endothelial cell disorder plus "something else"?

To the Editors: We enjoyed the article by Roberts et al. (Roberts JM, Taylor RN, Musci TJ, et al. Preeclampsia: An endothelial cell disorder. Am J Obstet Gynecol 1989;161:1200-4). This work brings up to date the ideas of Page[1] (he also worked in San Francisco) and Beker.[2] Their concept was one of uteroplacental ischemia as the underlying pathophysiologic characteristic of preeclampsia. We agree with the idea that the clinical

syndrome of preeclampsia arises when placental perfusion is poor. In some instances there may be underlying vascular or autoimmune disease.[3, 4] We suggest that in many primigravid women the poor placental perfusion resulting from a failure of secondary trophoblast invasion seems to be related to a genetic,[5, 6] or possibly immunogenetic,[7] susceptibility. Roberts et al. do not offer any explanation either for the fact that preeclampsia is commonest in primigravid patients or for the protective effect of a first pregnancy.[8] Does this not suggest an involvement of the immune system,[9] and if so, how?

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Reply

To the Editors: Drs. Liston and Kilpatrick correctly point out that our hypothesis extends the role of reduced placental perfusion in the development of the multisystemic syndrome of preeclampsia, a concept originally proposed by the late Professor E. W. Page of this department. Our proposal provides a rationale for the communication of this abnormality in the intervillous space to the many organ systems involved in the syndrome. As pointed out, we feel that endothelial cell injury-activation by an agent(s) produced by poorly perfused trophoblast could explain the systemic abnormalities observed in preeclampsia. Our hypothesis does not differentiate the several causes of reduced perfusion but predicts that they converge to a common pathway, resulting in the production of this bioactive agent(s).

It was not our purpose to explain how this reduced perfusion is initiated in first-pregnancy preeclampsia. We, as others, unfortunately have no direct information to identify the inciting pathogenetic event in this enigmatic disease. As Drs. Liston and Kilpatrick have demonstrated, there is good evidence that the "something else" described in their letter involves a combination of genetic and immunologic factors.

We feel strongly that any candidate as the intiating cause(s) of preeclampsia must account for reduced trophoblastic invasion, genetic predisposition to the disorder, and the protective effect of exposure to paternal antigens, usually by a previous pregnancy. These phenomena may derive sequentially from the same primary process. For example, the immunogenetic dissimilarity of mother and father, or mitigation of maternal immune "aggression" by previous exposure to paternal antigens, could influence the production of factors (e.g., blocking antibodies, activators of suppressor cells, etc.) that immunologically protect the trophoblast. If these factors are not present in a requisite amount, trophoblastic invasion may be retarded as part of an allogeneic rejection phenomenon. Alternatively, it is possible that independent mechanisms interact to produce preeclampsia. In this scenario a genetically determined abnormality of trophoblast function reducing placental invasiveness might lead to preeclampsia only in the first pregnancy because it compounds a subtle form of the immunologic compromise proposed above. There are obviously numerous other combinations of independent factors (including preexistent microvascular disease) that could converge to generate the syndrome.

Recent advances in our understanding of the fetal-maternal interface, such as the recognition of unique placental major histocompatibility antigens[1] and the characterization of enzymes involved in trophoblastic invasion,[2] should accelerate our understanding of the complexities of normal and abnormal placentation and ultimately will allow the precise identification of "something else."

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Possible therapeutic applications of cordocentesis

To the Editors: We read with interest the journal articles by Drs. Economides and Nicolaides et al. concerning antenatal detection of different metabolic disturbances in small-for-gestational-age (SGA) fetuses in samples obtained by cordocentesis.[1-4] The data provided by these authors suggest reduced glucose supply as a reason for reduced growth,[1] and show lower fetal insulin/glucose ratio,[2] and elevated fetal glycine/valine ratio,[3] in SGA fetuses. Most recently they showed that fetal hypertriglyceridemia may be used as a marker for hypoxemia in SGA fetuses.[4]

Intrauterine growth retardation is second only to prematurity in its association with perinatal morbidity and mortality. It may well be time to rekindle interest