Communication #323 from D. Radford Shanklin, Emeritus Professor, University of Tennessee, Memphis, and Library Reader, Marine Biological Laboratory, Woods Hole

Citation: Shanklin, D.R.[1,2], Shokouh-Amiri,M.[2], Placental hypervascularity does not cause perinatal brain injury. *J.Invest.Med.* 59:636, 2011

[1] Marine Biological Laboratory
[2] Department of Pathology and Laboratory Medicine, University of Tennessee, Memphis

Source: Eastern Section, American Federation for Medical Research, April 26-27, 2011

Format: PowerPoint Poster and Presentation converted to PDF with brief added remarks for clarification of the PPP frames and topical introduction

Introduction:

Developmental biologists are occasionally blessed by the result of what have been called *experiments of nature* and those studying human developmental biology are sometimes favored by the additive events of *clinical management*, albeit sometimes unfortunately inadvertent. This remarkable descriptive experience is one such, a developmental state plus a critical sequence of events in the clinical management of the birth of dizygotic, mixed sex twins, near term.

Background

The clinical diagnostic category *cerebral palsy* includes a wide range of morphologic and functional abnormalities. The cause or causes remain fundamentally unclear. It is important to note the very dramatic increase in clinical application of abdominal surgical delivery since about 1970, on the presumed evidence of "fetal distress" suggested by electronic fetal heart monitoring, has failed to diminish the prevalence of cerebral palsy. Unfortunately, obstetrical malfeasance remains an occasional critical factor in some cases (not to be discussed here). Many clinicians and pathologists have looked to placental abnormalities for some insight to this scenario. Of all the human organs commonly subjected to microscopic study the placenta remains a kind of *terra incognita* to most professionals. Its large relative size (it is the largest fetal organ) is one reason. Nevertheless, some observers have fixated on placental hypervascularity (erroneously termed *chorangiosis* by a few - erroneously because etymologically chorangiosis refers to a paraneoplastic condition related to the *chorangioma*, a vascular tumor of the placenta), as cause.

Argument

The assignment of placental hypervascularity as cause ignores the probable functional consequence of an increased maternofetal vascular exchange surface, a state likely to enhance oxygen and carbon dioxide exchange, and for nutrient uptake, and waste product dismissal. The special anatomy of the primate hemochorial placenta includes the development of a secondary capillary network which migrates within the placental villi to a station immediately subjacent to the epithelial cover of the villi, the trophoblast, which is the exchange layer at the maternofetal interface. This is called the paracapillary network. It begins approximately at the start of the second trimester of human gestation and the equivalent time frame in other primates. It is usually complete by the midpoint of the third trimester. Its growth parallels and provides for rapid fetal growth in the third trimester.

The case

A 36 year old primigravida went into labor in the 38th week of gestation. She had mild elevated blood pressure but no other clinical issues had arisen beyond awareness she was carrying twins, a fact known since about the 20th week. Normal, unaugmented labor delivered the first twin, a female weighing 2479 grams, with a separate placenta weighing 510 grams, for a placental:fetal weight ratio (P:F ratio) of 0.2057 (normal for 37-38 weeks). This child responded immediately and later showed normal growth and development over an observed period of three years. To facilitate the delivery of the second twin, before the uterus had accommodated to the change in content volume, the obstetrician manually ruptured the amnion of the second twin. As the physician's hand was removed from the uterus the umbilical cord of the second twin prolapsed beyond the introitus. Attempts to replace it failed, further traumatizing the cord per se. There was added delay in setting up for and performing an abdominal section, the minimum recorded time was 25 minutes (range per the record, 25-31 minutes). The second twin was a 2791 gram male with very low Apgar scores and a separate placental weight of 500 grams for a P:F ratio of 0.1791, also normal for 37-38 weeks. He developed severe cerebral palsy, spastic type, and mental retardation. The initial placental diagnosis on his placenta was "chorangiosis."

Subsequent consultative study of both placentas and umbilical cords revealed moderate to marked placental hypervascularity of both and occluding thromboses of the umbilical vein and one artery in the placenta of the second born male twin. The thrombi contained fresh platelets and eosinophiles, markers of recent thrombosis consistent with the time interval of cord prolapse.

The consultative report commented on the logical point: if "chorangiosis" was the causal factor then both twins should have had at least some degree of perinatal brain injury. The only clinical distinction between these twins was the event, prolapse of cord and delayed delivery. The only pathological distinction was the bidirectional blockage of umbilical blood flow for twin #2.

The presentation

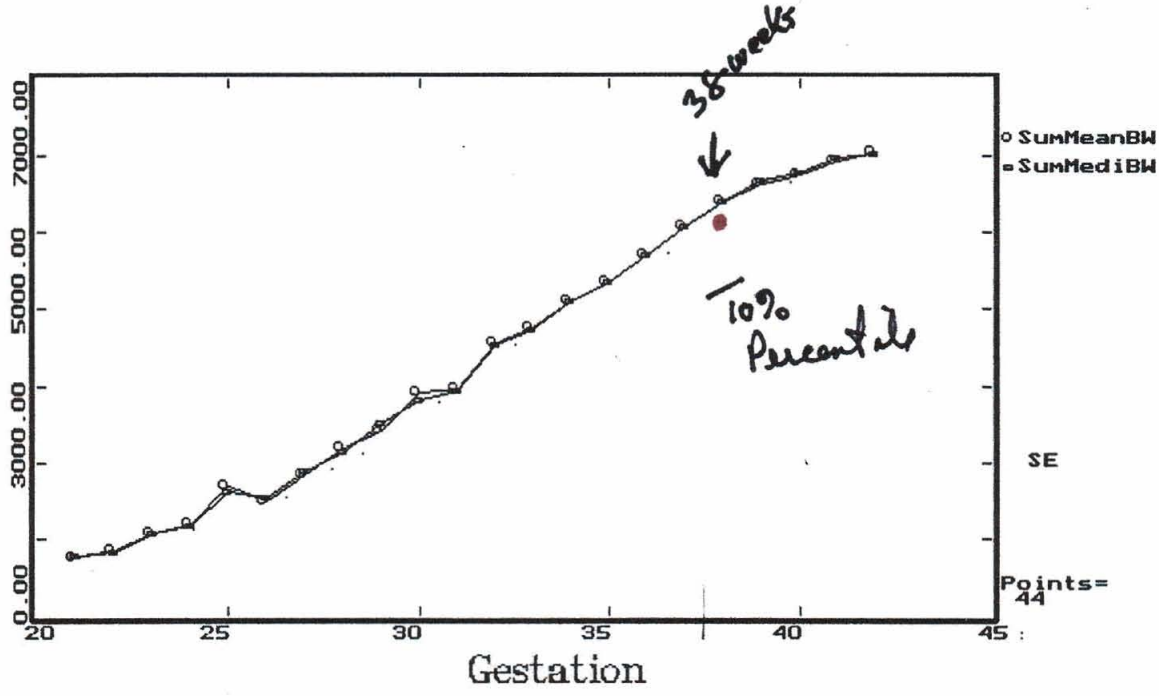
1. Title page and authors disclaimer
2. Graph of combined birth weight of caucasian twins, showing this set to be very close to the conjoint mean-median plot
3. Photomicrograph of normal late third trimester human placental tertiary villi, indicating their density per villus and size
4. Umbilical cord thrombi, male second twin
5. Representative hypervascular villi from placenta of brain injured male second twin
6. Representative hypervascular villi from placenta of normal female first twin
7. Representative hypervascular villi from a placenta delivered at high altitude (Denver)
8. Diagram showing origin of paracapillary vascular network; adaptative increased growth begins with the origin of these vessels
9. Table of data from University of Tennessee perinatal pathology service showing the high frequency of hypervascularity in twin gestations; discussion
10. Selected references
11. Abstract from the meeting

Placental hypervascularity does not cause perinatal brain injury

D. Radford Shanklin, M.D.[1,2]
M.Shokouh-Amiri, M.D[2]

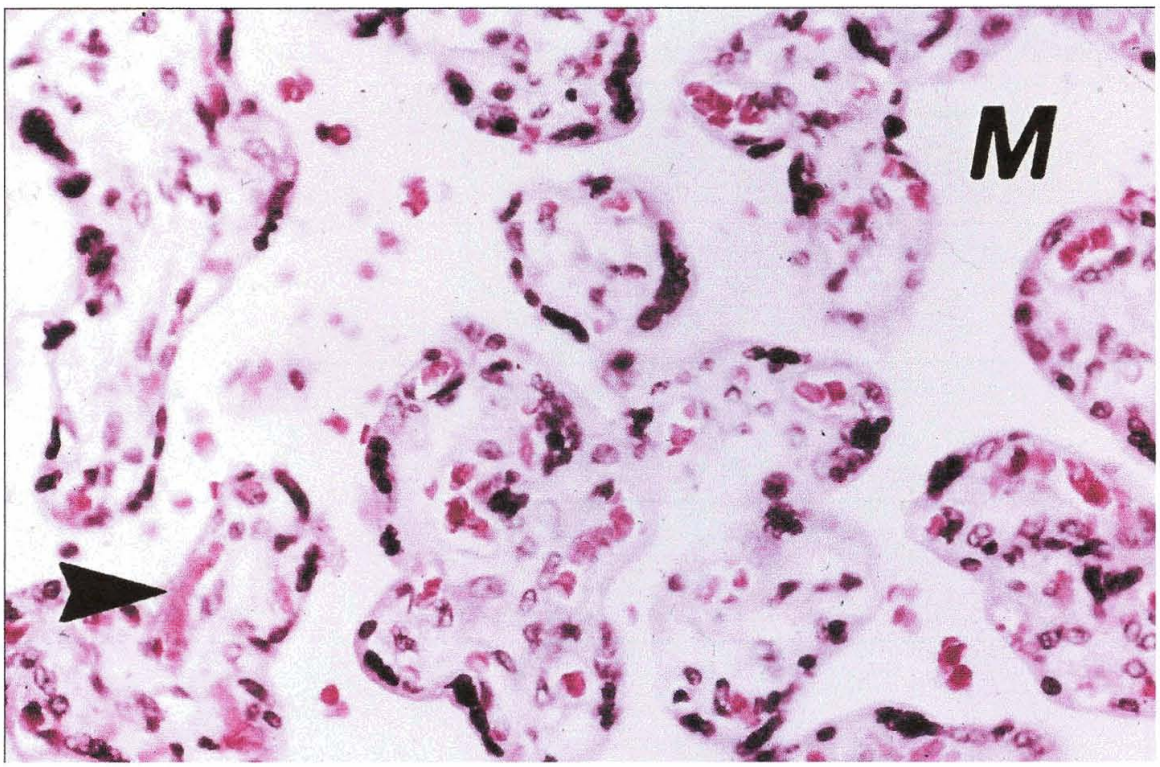
[1] Marine Biological Laboratory
[2] University of Tennessee, Memphis

The authors have no interests to declare

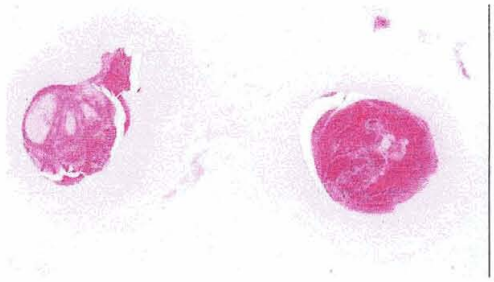


Total mean and median twin birth weights by gestation

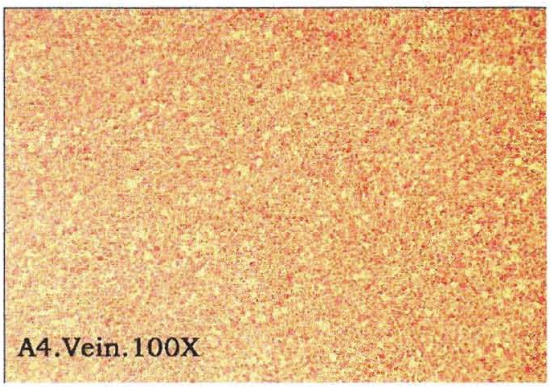
Large databases may contain skewed information. One way to check the distribution is a simultaneous plot of the means and medians. Here, with 22 time point intervals, from over 5,000 twins, is a plot of the tabular data in Baldwin, VJ, *The pathology of multiple pregnancy*, 1994, p. 135. These are the combined weights of twin sets. The two points slightly off the mainly linear trend, at 25 and 31 weeks, are statistical bookends to a period of instability in human fetal growth indices seen in many databases. The timing of labor in the index case, 38 weeks is noted by an arrow and the red dot indicates the position of the twins of this report relative to the Baldwin curve. This is well above the 10th percentile line of the larger database. Baldwin's data are Canadian and the ethnic origin of the index case is consistent therewith.



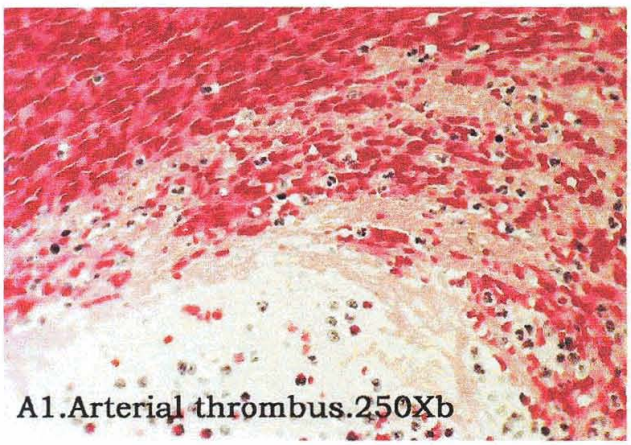
Hematoxylin & eosin stain of terminal tertiary villi, normal human placenta. Original magnification 250X. The arrow at the left points to an anucleate *bare* zone in the synctiotrophoblast along an extended stretch of a fetal placental paracapillary, a common feature of mature human placentas. *M* refers to the maternal intervillous space, here fairly drained of maternal blood. Note the close proximity of the paracapillaries to the undersurface of the trophoblast. These villi show little stroma indicative of the absence of disorders such as immune reactions, infections, or abnormal fluid accumulation.

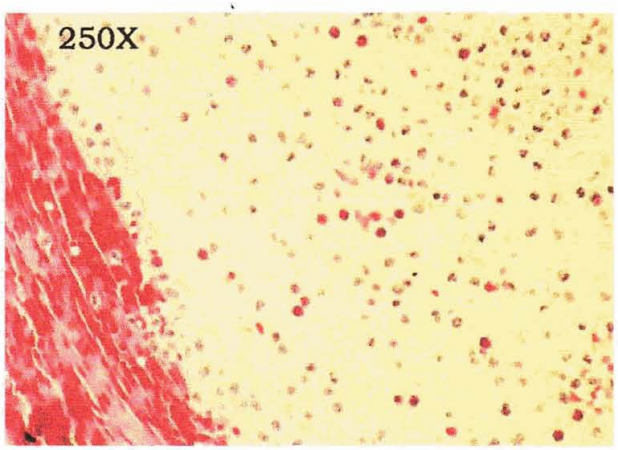


Whole mount of the umbilical vein and one umbilical artery of the male twin, occluded by fresh thombi

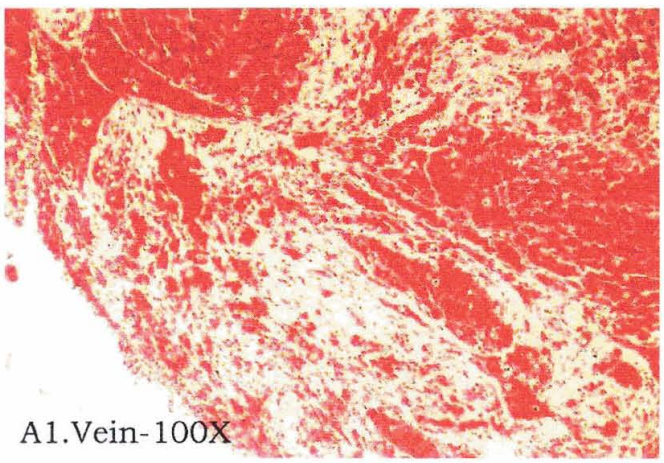


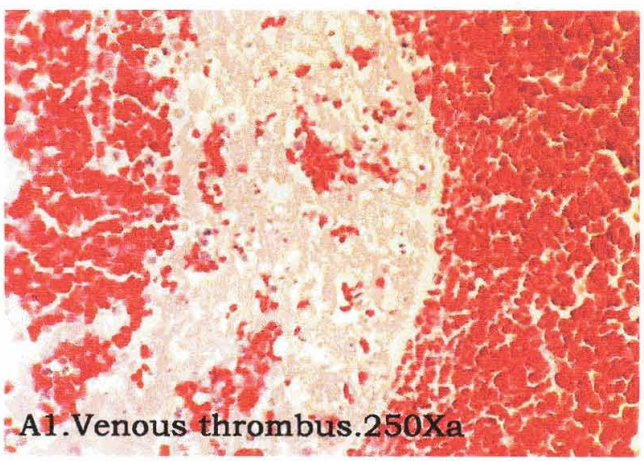
Normal trapped blood in umbilical vein of female first twin





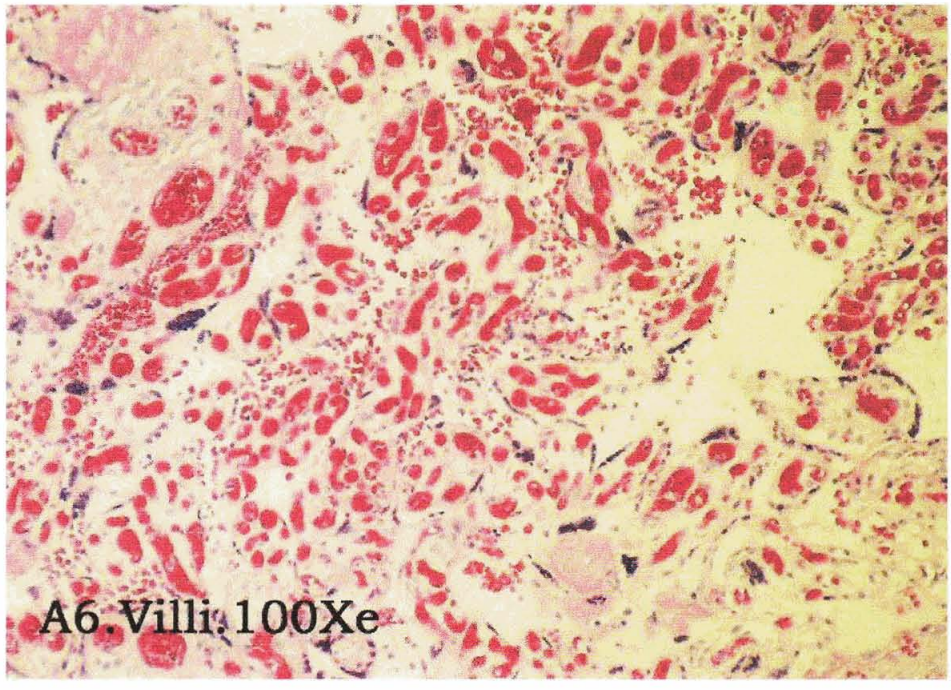
Thrombosis of one umbilical artery with numerous intact platelets and eosinophilic leukocytes

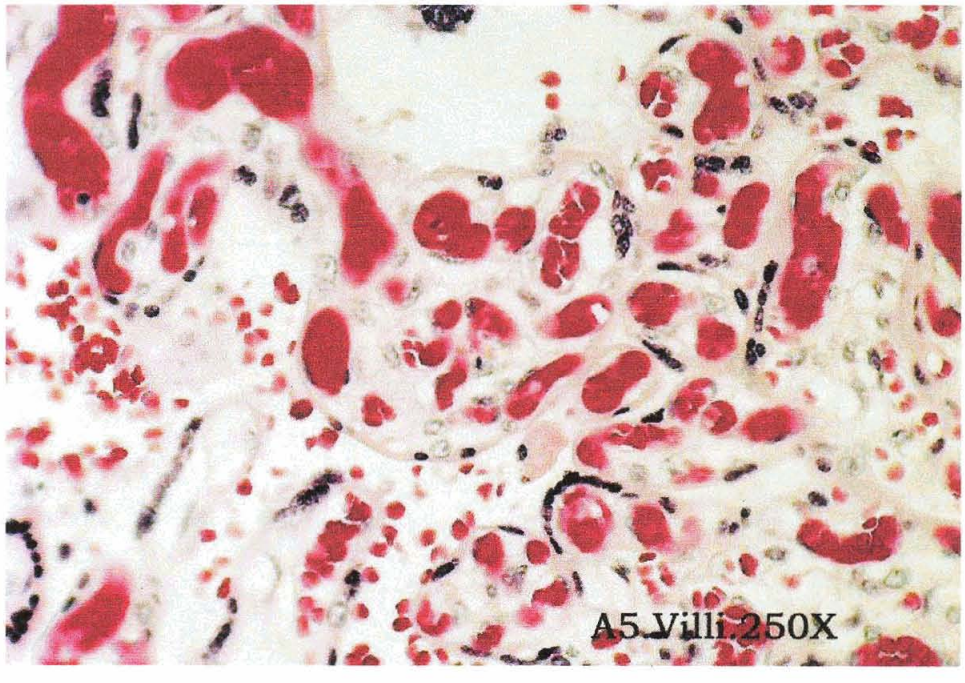




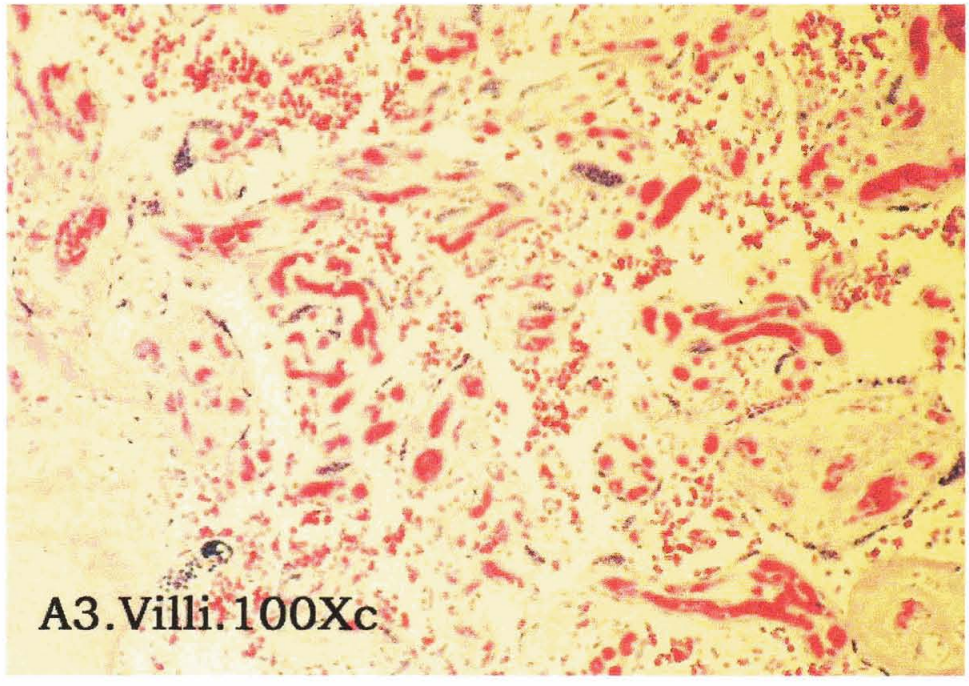
Thrombosis of the umbilical vein

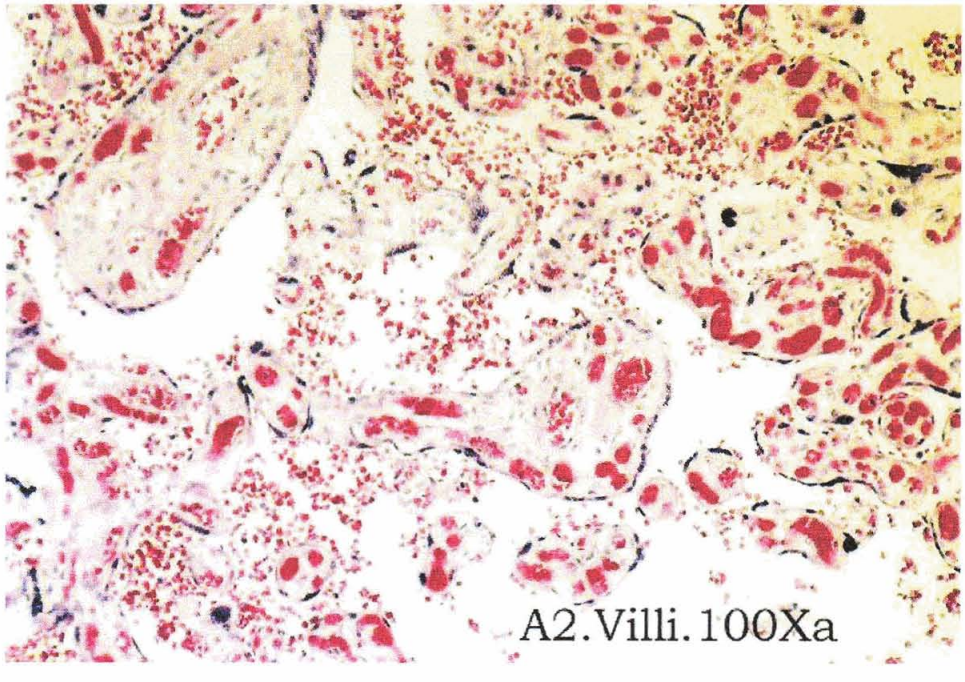
Representative hypervascular villi from the placenta of the injured second twin, male



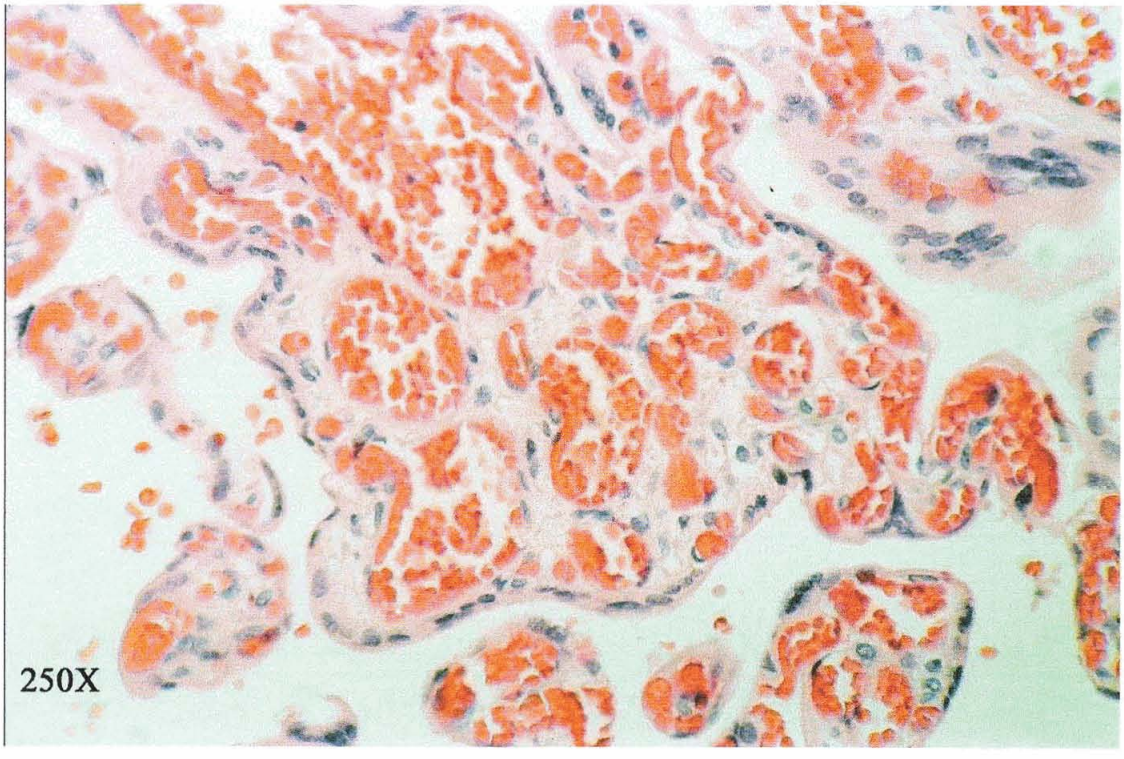


Representative hypervascular villi from the placenta of the normal, uninjured first twin, a female





Representative hypervascular villi from a term placenta with a normal healthy child delivered vaginally in Denver, Colorado



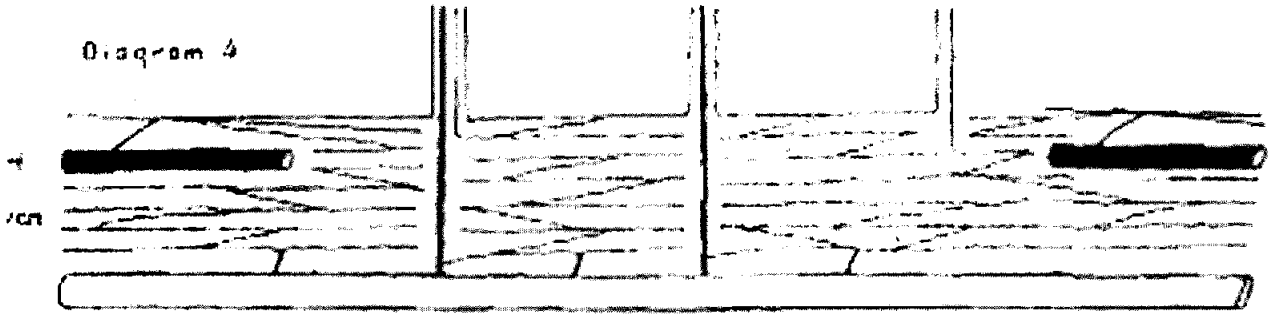


Diagram 4. *The three types of vascularization of the chorionic villi.*
art. artery
v. vein
p.v.c.n. paravascular capillary network

From: Bøe, F. Studies on the vascularization of the human Placenta. *Acta Obstet.Gynecol.Scand.* 32[Supp. 5]:1-92, 1953.

Frequency of placental villus hypervascularity, high risk file, University of Tennessee, Memphis

Placental status	Number of cases	Hypervascularity (%)	Number of infants with hypoxic-ischemic encephalopathy
Singletons	100	17 (17%)	None
Twins	25	11 (44%)	None

The anatomical pathology service of the University of Tennessee, Memphis, includes a perinatal autopsy service and a high risk pregnancy placental registry. When the index case came to our attention in early 2008, we reviewed the placental registry expressly for cases showing the kind and degree of hypervascularity found in the index case. The table gives the results of 125 such placentas. The early human placenta has a plasticity of growth overall, with a marginal expansion known as *placenta extrachorialis*; from these observations a similar adaptive capacity appears to be operative at the level of the tertiary chorionic villi. Multiple gestation is a metabolic challenge to maternal resources. The result here may well be a consequence of the vascuolgenic effects of hypoxia-inducible protein in the placenta or the fetus. Our study provides no information on the point.

Discussion

The oxygen tension of human fetal tissues has been estimated, in the main, by inference from the difference between umbilical artery and umbilical vein values determined by blood samples. The oxygen content of a mammalian fetal lung, in the rabbit, has been determined by direct oxygen probes in a restricted operative field flooded by nitrogen [Exper.Mol.Pathol. 89:36-45, 2010] to be 10-12 Torr. This is a measure of the probable maximum which evolves over gestational time by the maturation of the fetal placental circulation. When the metabolic sink expands through fetal growth some accommodation seems essential and a mechanism for this has to be in place and functional as the need arises. As a falsifiable hypothesis, so called chorangiosis, which is at best counterintuitive, is ruled out by this remarkable case. Pathogenetic conclusions are not always based on statistical significance and can be established by logic and inference. The term *pathognomonic* applies here in the negative sense. When applied in a positive way it means, essentially, something so fully characteristic of a condition that it is easily recognized as the only possible conclusion to the query. Here, in the negative sense, the histomorphological fact is present but the presumed consequence is absent. Thus, a natural experiment, *dizygous twins* with no connection between their attendant placentas, has provided the test modality for ruling out one pathogenesis of perinatal brain injury whilst identifying the actual cause, iatrogenic umbilical vascular thrombosis . If a state of placental vasculogenesis is a factor in perinatal brain injury, then it would be a lack of the hypervascular adaptation or some other interference with the normal progression of the vascular network of the hemochorial placenta of primates, including humans. The impossibility of direct repetitive data collection from early and midgestational human placenta, due to proper ethical concerns, does mean that such information can be collected only slowly and by associational factors, a future project not addressed by this study.

References

Chorangiosis:

Shanklin, D.R., Tumors of the placenta and umbilical cord, 1990, B.C. Decker Inc, Philadelphia, ISBN 1-55664-236-9, p. 106-111.

Placenta extrachorialis:

Scott, J.S., Placenta extrachorialis (Placenta marginata and placenta circumvallata): a factor in antepartum haemorrhage. J.Obstet.Gynaecol.Brit.Emp. 67:904-918, 1960.

Shanklin, D.R. amd Sotelo-Avila, C., The pathogenesis and significance of placenta extrachorialis. Lab.Invest. 15:1111, 1968.

Development of the paracapillary system:

Bøe, F., Studies on the vascularization of the human placenta. Acta Obstet.Gynecol.Scand. 32[Supp. 5]: 1-92, 1953.

PLACENTAL HYPERVASCULARITY DOES NOT CAUSE PERINATAL BRAIN INJURY

Radford Shanklin, M.D., F.R.S.M.,[1,2] and Mohammad Shokouh-Amiri, M.D.[1]

[1] Department of Pathology and Laboratory Medicine, University of Tennessee, Memphis 38163
[2] Marine Biological Laboratory, Woods Hole, Massachusetts 02543

Purpose of Study: To refute the assertion that "chorangiosis" is a causal factor in perinatal hypoxic brain injury.

Methods Used: Critical analysis of an index case and review of pertinent archival autopsy, placental, clinical, and epidemiological data.

Summary of Results: Dizygotic twins at 38 weeks with separate placentas: twin A, a 2479 gram female, was healthy after vaginal delivery. Five minutes later when the amnion of twin B was ruptured artificially, the cord prolapsed and could not be repositioned. Some 25 minutes later a 2791 gram male was delivered by section. Brain injury was noted soon afterward and subsequent development was marked by severe cerebral palsy and mental retardation. Initial diagnosis of twin B's placenta was "chorangiosis," overlooking fresh thrombi blocking the umbilical vein and one umbilical artery. Subsequent assessment revealed the same change in twin A's placenta. Archival records had 18/500 (3.5%) stillborns and 17/418 (4.07%) newborns with central placental hypervascularity. Of 125 recent consult placentas there were 17/100 singleton and 11/25 (44%) twin placentas displaying this change. Of 229 section deliveries there were 0/42 stillborns and 5/187 newborns with this vascular pattern. Another set of 625 autopsies revealed none with both hypoxic encephalopathy and this placental finding. This structural change is the same often seen in placentas from high altitude such as in Denver. Cerebral palsy occurs less often in Colorado than in other American states, per epidemiological data.

Conclusions: Central villous hypervascularity is an adaptation of placental development prior to midgestation through exaggerated growth of the paracapillary network and is not a pathogenetic agent or process.

Cite as *Journal of Investigative Medicine*, 59:636, 2011 (P#29)