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Editorial

Kurt Benirschke: In Memoriam

Dr. Kurt Benirschke, M.D., world-renowned placental pathologist, passed away on September 10, 2018, at the age of 94.

Kurt received his medical degree from the University of Hamburg in 1948 and immigrated to the United States in 1949. Following residency training at Harvard Medical School, Kurt worked as a pathologist at the Boston Lying-in Hospital (now part of Brigham and Women's Hospital), where he discovered his love of the placenta. He continued his studies in reproductive and placental biology at Dartmouth, where he was chair of the Department of Pathology from 1960 to 1970. He was subsequently recruited by University of California San Diego's (UC San Diego) newly-established medical school, where he developed a genetics laboratory and ran the autopsy service. At the same time, he quickly became active in the San Diego Zoo's conservation program, lobbying for the creation of the Center for Research of Endangered Species (CRES), with its associated novel biorepository for long-term preservation of eggs, sperm, and other tissues of endangered species. Today, the renamed San Diego Zoo Institute for Conservation Research is the largest of its kind, with cell samples from nearly 1000 taxa, many of which are either extinct or severely endangered.

At UC San Diego, Kurt was heavily involved in research, teaching, and clinical practice. He authored more than 500 original publications and over 30 books, including “Pathology of the Human Placenta,” currently in its 6th edition. He served as Pathology Department Chair from 1976 to 1978, and also played a key role in the creation of the Center for Academic Research and Training in Anthropogeny (CARTA).

While he formally retired as professor emeritus in 1994, “Dr. B,” as he was affectionately called by staff and trainees at UC San Diego, remained active as a consultant to the autopsy and perinatal services. I was therefore fortunate to be able to learn from him during my first four years at UC San Diego. He surprised me on my very first day at work, by walking into my office and officially welcoming me to the Department. He continued to amaze me at the biweekly Perinatal M&M conferences, where he would show interesting cases, both from our autopsy service as well as from the San Diego Zoo: at the first such conference that I attended, he showed a placenta from a vampire (that is, a vampire bat, as I learned a few minutes into the presentation …. !). At the same conference, he continually astounded both his colleagues and trainees by referring to recently-published journal articles (and their page numbers) relevant to the presented cases. Dr. B also set a very high bar for teaching, grossing placentas with residents on a weekly basis and personally overseeing and participating in most autopsies.

The week before he suffered a stroke in March 2012, he called me into his office and handed me a manuscript, stating, “Here are the most important issues left to explore in placental pathology.” It was early in the morning on a very busy day, so I remember joking: “Will they hold until tomorrow?!” These questions represent not only his deep and broad knowledge of placental biology and its implications for pregnancy health, but also his methodical thinking, based on meticulous observations. They further show Dr. B's genuine commitment to the future of our field, even while knowing that his ability to be a part of that future was limited. Some of these questions have already begun to be addressed; nevertheless, with Dr. B's passing, these questions seem even more urgent; therefore, it is most fitting to present them to the readers of *Placenta*, in the hopes that they inspire new avenues of research.

Principal unknown aspects of human placentation

Kurt Benirschke, M.D. (2012)

This review discusses six aspects of human placentation, whose mechanisms are being unraveled, and could be resolved by experimental studies. They are as follows:

1) Villitis of unknown etiology (VUE) and the potential chimerism of the fetus and its possible future consequences, especially whether maternal cells keep living in the fetus forever;
2) The vascular support of the decidua capsularis and its relationship to the decidua vera;
3) Extravillous trophoblast and the production of ‘major basic protein’ (MBP);
4) The reason for the maintenance of some portions of the decidua basalis. Why does in the normal placentation a placenta accreta not form?
5) The mechanism of the development of placenta percreta;
6) The derivation of cell-free DNA in the maternal circulation and its possible immune relationship and other consequences.

1. *Villitis of unknown etiology*

Villitis of unknown etiology (hereafter VUE) is a relatively common entity found in the human placenta. We have examined the frequency of VUE in our 9334 placentas examined since 2000 and found it to be 4.5%. This contrasts with villitis due to cytomegalovirus infection (CMV), which is also a common entity. Plasma cells are ***not*** involved in VUE and while there is obliteration of villous capillaries in both, the common sequel of CMV infection, hemosiderin deposition, is absent in VUE. Altshuler et al. have drawn attention to the common condition of CMV infection in a major symposium [1]. On the other hand, we have shown conclusively that in patients with recurrent VUE, the infiltration of cells are composed primarily of ***maternal*** T-cells [2].

VUE is often the cause of fetal growth restriction and, when it is severe, it may also cause fetal demise. Most commonly, the inflammation begins at the basal plate of the villi. Here, the villous connective

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tissue is exposed to the maternal decidua and thus, to the mother's NK cells. Much less commonly, VUE is also focally distributed throughout the villous tissues. Because VUE is frequently recurrent in a sibship, the possibility arises that a mismatch of HLA antigens exists and that this might be expressed in the villous stromal tissues. While HLA-G is expressed on the *trophoblastic* surfaces that also have access to maternal lymphocytes in the intervillous space, this antigen can thus be 'recognized' as being harmless. It is known that *fetal* lymphocytes takes place are present in the maternal circulation, where these cells can indeed proliferate and become the cause of systemic sclerosis (scleroderma and perhaps other autoimmune conditions) [3]. Whether the converse (the proliferation of ***maternal*** T-cells in the fetus) occurs is still unknown, and remains a challenge for future studies. I have suggested that *male* fetuses need to be studied, particularly fetuses with placental VUE, and that these **maternal** (46, XX) lymphocytes will need to be evaluated and identified. Ultimately these individuals should also be followed for the possible development of similar autoimmune conditions.

2. Vascular support of the decidua capsularis

When the embryo implants into the decidua it becomes 'interstitially' implanted and the defect is closed by a '*Schlusscoagulum*.' [4] Virtually no endometrial (decidual) proliferation takes place at that time. Nevertheless, in the small available space of the uterus, the expanding blastocystic cavity of the embryo is in direct contact with the opposite side of the uterus and it is possible that the decidua vera ultimately fuses with the decidua capsularis; but whether the vascular support may be of the future decidua capsularis in the placental membranes remains unknown. After all, when the placenta is delivered, the 'membranes' always possess a membranous decidua capsularis of different quantities. This decidual tissue covers the 'membranes' and it contains an abundance of maternal blood vessels. Indeed, on occasion, one finds typical atherosis in these maternal vessels, suggesting that the normal endovascular trophoblastic invasion is inadequate to transform these arterioles. While it may be difficult to undertake, an injection of uterine arteries with plastic materials may be needed in hysterectomy specimens so as to clarify this current riddle. It may thus be possible to demonstrate whether the vascular supply of the decidua capsularis ultimately comes from the decidua vera and thus from the uterine circulation.

3. Extravillous trophoblast and major basic protein

At present it is unclear just when the extravillous trophoblast (EVT) is set aside from the trophoblastic shell [4] that surrounds the implanting embryo. It is certain, however, that the EVT differs remarkably from the Langhans' trophoblast and its ultimate syncytium formation under the influence of 'syncytin.' The EVT invades the decidua basalis and the superficial myometrium at the implantation site; and the spiral arterioles of the decidua basalis are invaded as well. It is thus responsible for the transformation of the spiral arteriolar wall [5] to enable the future intervillous circulation not to be subject to maternal hypertensive states.

Studies carried out at Mayo Clinic have shown that the EVT is responsible for the production of the major basic protein (MBP), the protein that is also contained in the granules of the eosinophilic leukocytes [6–9]. Excessive amounts of MBP are occasionally formed to obstruct the intervillous circulation, causing fetal demise; this differs from blood coagulation products, which can cause similar obstruction of the intervillous space. An especially characteristic form of placental disease is 'maternal floor infarction' that may also cause fetal demise [10]. In such cases the maternal serum contains a larger quantity of MBP that disappears after the delivery of the placenta. It is currently unknown whether the presence of MBP in the serum of pregnant mothers has an immune regulatory effect or why normal levels of this protein disappear after delivery.

4. Maintenance of decidua basalis and development of placenta accreta

Why is there a decidua basalis at all and why does the trophoblast not continue to destroy it, thus leading to a placenta accreta? There is little doubt that the trophoblast 'eats' the endometrium in early gestation [11]. But what prevents it from removing ***all*** of the decidua? It is possible that the extravillous trophoblast becomes suddenly 'active' and takes over; alternatively, it is also possible that the original polyploid trophoblast has now differentiated into two lineages, and with that, the destruction of the endometrium (the decidua basalis) comes to an end. It may be possible that immune-regulatory factors are also involved.

5. Development of placenta percreta

The topics of placenta accreta/percreta are closely related to that of the previous topic. It has now become evident that placenta percreta and placenta accreta have increased substantially, while they had occurred only rarely in the past experience of obstetricians. Placenta accreta often complicates a placenta previa because the endocervical mucosa does not undergo decidualization. Therefore, it would appear that a decidua basalis is **necessary** for a 'normal' implantation. It has also become evident that prior 'deep' curettage of the uterus is often followed by the development of a placenta accreta.

A recent review [12] explores the placentas accreta that are the sequelae of 'classical' (fundal) Cesarean sections. However, with the remarkable increase in recent years of ***low*** Cesarean section deliveries, the mechanism of placenta percreta has become more explicable. After all, when the uterus involutes immediately after delivery, it reduces the hypertrophy of myometrial fibers; there is no proliferation of muscle fibers, which are destined to merely atrophy and the surgical defect is 'closed' by scar tissue. When the next pregnancy comes along and distends the uterus again, this connective scar tissue thins (including the peritoneal adhesions that may have formed), and it becomes very delicate. If the placenta happens to implant over this scar tissue, the possibility of a placenta percreta becomes a probability, often requiring hysterectomy (sometimes associated with severe blood loss). Some years ago, it became popular to close a Cesarean Section incision with a single-layer of resorbable sutures in order to reduce the length of closure time and thus, the length of anesthesia time. Bujold et al. [13] have now conclusively shown that a double-layered closure is significantly more preventive of the development of a placenta percreta.

6. Maternal cell-free DNA

While it is not certain that much syncytiotrophoblast is regularly being deported from the placenta and then destroyed in the lung [14], it then also may liberate cell free-DNA (cfDNA). This **could** also stimulate some immune response against the placental trophoblast. Moreover, there are currently speculations that this cfDNA could be useful for the prenatal diagnosis of trisomies; appropriate studies are being carried out now.

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