



Introduction

Cite this article: Burton GJ, Moffett A, Keverne B. 2015 Human evolution: brain, birthweight and the immune system. *Phil. Trans. R. Soc. B* **370**: 20140061. <http://dx.doi.org/10.1098/rstb.2014.0061>

One contribution of 13 to a discussion meeting issue 'Human evolution: brain, birthweight and the immune system'.

Subject Areas:

evolution, health and disease and epidemiology, physiology, developmental biology

Keywords:

obstetric dilemma, brain, evolution, placenta, birthweight

Author for correspondence:

Graham J. Burton
e-mail: gjb2@cam.ac.uk

Human evolution: brain, birthweight and the immune system

Graham J. Burton^{1,2}, Ashley Moffett^{1,3} and Barry Keverne^{1,4}

¹Centre for Trophoblast Research, and ²Department of Physiology Development and Neuroscience, University of Cambridge, Cambridge CB2 3EG, UK

³Department of Pathology, University of Cambridge, Cambridge CB2 1QP, UK

⁴Sub-Department of Animal Behaviour, University of Cambridge, Cambridge CB23 8AA, UK

The large size of the human brain at birth is one of the defining features of our species, and yet comes at a price. Among the primates, humans have particularly difficult births, with high rates of maternal and fetal morbidity and mortality. Approximately 287 000 maternal deaths occurred in 2010 worldwide, and complications during delivery, including obstructed labour, were significant contributors. This situation is widely assumed to have arisen because of the need for compromise between development of the large brain and the biomechanics of bipedalism, which impose constraints on the dimensions of the pelvis. These two opposing demands constitute what is often referred to as the 'obstetric dilemma'. In this Theme Issue, a broad multidisciplinary approach is taken to review this concept, considering recent advances in our understanding of the evolution of the human brain, bipedalism and how development of the large brain is supported *in utero*.

The issue opens with a review of the ontogeny of the brain in Pleistocene hominins by Hublin *et al.* [1]. They reveal that the high level of encephalization critical to the human adaptive niche emerged among hominins in the course of the past 2 Myr. Central to their discussion, and to the concept of the obstetric dilemma, is the balance between pre-natal and post-natal growth of the brain. Large brains obviously require greater energy investment, with an extended period of growth post-natally to avoid obstetric constraints. Current evidence indicates that brain ontogeny evolved along different pathways in different Pleistocene hominins; for example, the Neanderthal pathway was distinct from that of extant humans, which evolved relatively recently.

In the next contribution, Maslin *et al.* [2] consider how the changing climate and tectonics in East Africa over the past 10 Myr created a uniquely complex, and environmentally highly variable setting that shaped hominin evolution. They postulate that alternating periods of extreme humidity and aridity may have driven hominin speciation, encephalization and dispersals out of Africa. Furthermore, they emphasize that changes in brain size should be considered within the broader context of changes in life history, body size and dimorphism, adaptation to long-distance running, and social behaviour.

Turning to the evolution of the human pelvis, Gruss & Schmitt [3] consider how mechanical requirements for locomotion, childbirth and thermoregulation have often conflicted. In our earliest bipedal ancestors, fundamental changes in the shape of the pelvis associated with a change in function of the gluteal muscles facilitated walking. The result was a pelvis that had a broad internal cavity, and this form was maintained with minor adaptations for 3–4 Myr. It was not until *Homo sapiens* evolved approximately 200 000 years ago that the anatomically modern pelvis with a more circular birth canal emerged, in association with a narrow body shape needed to facilitate heat dissipation.

Trevathan [4] develops this theme and describes how the modern female pelvic configuration necessitates rotation of the fetus during birth to accommodate first the head and then the shoulders. The end result is that the infant emerges facing the opposite direction from the mother, placing a premium on having assistance at delivery to clear the infant's airways. The author then discusses recently reported observations of births in monkeys and apes in order to compare the process in human and non-human primates, highlighting similarities and differences. These include internal and external rotation, the use of the hands by mothers and infants, reliance on assistance and the developmental state of the neonate.

In the next review, Wells [5] notes that there is variability in the severity of obstetric complications across human populations today. Importantly, Wells proposes that the obstetric dilemma is not fixed, and can be renegotiated in response to growth trends driven by ecological change. He points out that fetal growth is only weakly regulated by genes, and is largely dependent upon maternal allocation of nutrient resources. The supply of these resources is dependent on the environment and the mother's own needs. Hence, both short- and long-term changes in maternal nutrition may have a profound impact on the obstetric dilemma through their effects on maternal size and fetal growth.

The maternal nutrients must pass to the fetus, however, and so Burton & Fowden [6] consider the role of the placenta as the maternal–fetal interface. Although principally considered an organ of exchange, the placenta performs a wide variety of other functions that integrate maternal supply and fetal demands. It secretes numerous hormones that have profound effects on maternal metabolism and physiology, increasing maternal stores of nutrients early in pregnancy and mobilizing them to meet fetal demands later. The placenta also acts as a selective barrier, detoxifying xenobiotics and inactivating maternal stress hormones in order to provide a stable milieu in which the fetus can develop. Perturbations of these functions can all impact on fetal growth.

The placenta is the most morphologically variable of mammalian organs, and in the next contribution, Gundling & Wildman [7] consider its evolution. Four major characteristics are discussed: placental shape, maternal–fetal interdigitation, intimacy of the maternal–fetal interface and the pattern of maternal–fetal blood flow. In addition to interspecific anatomical variation, there is also variation in placental anatomy and function within species. Much of this intraspecific variation occurs in response to different environmental conditions such as extreme temperatures, altitude and maternal nutrition.

This theme is developed further by Elliot & Crespi [8], who employ a novel genomic approach to understanding the evolution of placental invasiveness. The human placenta is the most invasive of all species, and this characteristic has often been associated with the development of the large brain at birth. It comes at a price, however, in terms of complications of pregnancy, such as the hypertensive disorder pre-eclampsia, that are almost unique to the human. The authors demonstrate that during evolution, less invasive placental forms have been selected for avoiding these complications. They recommend a novel comparative functional-evolutionary approach for the study of genetically based human disease and mammalian diversification.

A spectrum of placental invasiveness is displayed even among the primates, a topic reviewed by Carter *et al.* [9]. One of the key functions of the invasion is remodelling of the maternal spiral arteries within the wall of the uterus to ensure an optimal blood supply to the placenta. Remodelling involves the loss of smooth muscle from the walls of the arteries, which subsequently dilate and lose their vasoreactivity. Trophoblast invasion and arterial remodelling are seen to the greatest

extent in the human, and failure of either results in growth restriction of the fetus and pre-eclampsia in the mother.

The importance of uterine and placental blood flow for fetal growth is considered by Browne *et al.* [10], who use adaptations to high altitude as an experiment of nature. High altitude is associated with a reduction in birthweight of approximately 100 g per 1000 m of elevation, but the effect is greater in non-indigenous compared with indigenous populations. These authors demonstrate using ultrasound-generated indices that uterine blood flow is increased in indigenous women at high altitude compared with lowland controls, whereas in non-indigenous migrants it is reduced. They speculate that uterine artery blood flow is not only an important supply line, but also a trigger for stimulating the metabolic and other processes regulating fetal–placental metabolism and growth.

Placental invasion does, however, pose important immunological challenges as the invading trophoblast interact with cells of the maternal immune system. This topic is reviewed by Sharkey and colleagues [11], who show that certain genetic interactions between the polymorphic HLA-C antigens expressed on the invading trophoblast cells and the highly variable killer-like immunoglobulin receptors on the maternal uterine natural killer cells predispose to complications of pregnancy, including growth restriction and pre-eclampsia. The mechanisms involved are uncertain at present, but interactions with the cells of the innate immune system are thought to regulate trophoblast invasion and spiral artery remodelling.

Finally, fetal growth is also regulated by imprinted genes, and recent advances have revealed important insights into genetic and epigenetic links between the regulation of placental and brain growth. Moore *et al.* [12] discuss the role of genomic imprinting, using the insulin-like growth factor family as an example of a key regulator. Manipulating expression of these growth factors modulates fetal weight, and can have transgenerational effects, and so in genomic and genetic analyses, it is important not to overlook parent-of-origin effects.

Together, these contributions lead us to re-evaluate the obstetric dilemma. The large human brain at birth appears to be a relatively recent development, selected for by rapid environmental changes in the African climate and permitted by deep placental invasion that allows intimate access to the maternal circulatory system. Coevolution of the placenta and the maternal immune system ensured that the invasion is regulated, with the placenta integrating signals of maternal supply and fetal demand. Imprinting arose coincidentally with the evolution of placentation, and enables dosage of genes influencing resource allocation to be acutely regulated in response to environmental cues. These dynamic interactions may explain why the incidence of obstructed labour and other pelvic constraints is variable across different contemporary populations, and provide deeper insight into the evolution of human reproduction.

We thank all the authors for their thoughtful contributions, the Royal Society for supporting the meeting and Helen Eaton for compiling this issue.

References

- Hublin J-J, Neubauer S, Gunz P. 2015 Brain ontogeny and life history in Pleistocene hominins. *Phil. Trans. R. Soc. B* **370**, 20140062. (doi:10.1098/rstb.2014.0062)
- Maslin MA, Shultz S, Trauth MH. 2015 A synthesis of the theories and concepts of early human

- evolution. *Phil. Trans. R. Soc. B* **370**, 20140064. (doi:10.1098/rstb.2014.0064)
3. Gruss LT, Schmitt D. 2015 The evolution of the human pelvis: changing adaptations to bipedalism, obstetrics and thermoregulation. *Phil. Trans. R. Soc. B* **370**, 20140063. (doi:10.1098/rstb.2014.0063)
 4. Trevathan W. 2015 Primate pelvic anatomy and implications for birth. *Phil. Trans. R. Soc. B* **370**, 20140065. (doi:10.1098/rstb.2014.0065)
 5. Wells J. 2015 Between Scylla and Charybdis: re-negotiating resolution of the 'obstetric dilemma' in response to ecological change. *Phil. Trans. R. Soc. B* **370**, 20140067. (doi:10.1098/rstb.2014.0067)
 6. Burton GJ, Fowden AL. 2015 The placenta: a multifaceted, transient organ. *Phil. Trans. R. Soc. B* **370**, 20140066. (doi:10.1098/rstb.2014.0066)
 7. Gundling Jr WE, Wildman DE. 2015 A review of inter- and intraspecific variation in the eutherian placenta. *Phil. Trans. R. Soc. B* **370**, 20140072. (doi:10.1098/rstb.2014.0072)
 8. Elliot MG, Crespi BJ. 2015 Genetic recapitulation of human pre-eclampsia risk during convergent evolution of reduced placental invasiveness in eutherian mammals. *Phil. Trans. R. Soc. B* **370**, 20140069. (doi:10.1098/rstb.2014.0069)
 9. Carter AM, Enders AC, Pijnenborg R. 2015 The role of invasive trophoblast in implantation and placentation of primates. *Phil. Trans. R. Soc. B* **370**, 20140070. (doi:10.1098/rstb.2014.0070)
 10. Browne VA, Julian CG, Toledo-Jaldin L, Cioffi-Ragan D, Vargas E, Moore LG. 2015 Uterine artery blood flow, fetal hypoxia and fetal growth. *Phil. Trans. R. Soc. B* **370**, 20140068. (doi:10.1098/rstb.2014.0068)
 11. Moffett A, Hiby SE, Sharkey AM. 2015 The role of the maternal immune system in the regulation of human birthweight. *Phil. Trans. R. Soc. B* **370**, 20140071. (doi:10.1098/rstb.2014.0071)
 12. Moore GE *et al.* 2015 The role and interaction of imprinted genes in human fetal growth. *Phil. Trans. R. Soc. B* **370**, 20140074. (doi:10.1098/rstb.2014.0074)