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Are animal models useful or confusing in understanding the human feto-maternal relationship? A debate☆

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ABSTRACT

The proposition "This house agrees that the proper study of man is woman" was debated. For those negating the proposition, the alternative was that "animal models are useful in understanding the human feto-maternal relationship." Evidence for the proposition emphasized molecular and structural differences between the human and animal placenta and placentation. Evidence against the proposition and in favor of the alternative focused on functional and structural homologies, emphasizing that different molecules could be used in humans to achieve similar functional effects seen in animal (e.g., mouse) models. It was agreed that one always needed to test the validity of animal data by studying humans. The advantages and limitations of animal models were discussed.

1. Introduction

At the June 1860 Evolution Debate at Oxford University, the proposition that man and woman were created as unique creatures by God, distinct from animals was set against the new idea proposed by Darwin that man and woman had evolved from animal species by a process of natural selection of mutants that had a survival advantage. The absence of many details of the steps in evolution notwithstanding, those favoring Darwin prevailed. Subsequently, much has been learned from the study of animals that appears relevant to understanding human anatomy and physiology.

There are three types of models that scientists use in an attempt to understand humans: conceptual models, mathematical models, and analog models. Conceptual models may outline a series of events in a physiological process, and experiments to test and reject the model are then proposed and carried out. Mathematical models examine how closely real events can be predicted using mathematical formulae. Analog models look for clues in a physiological event such as pregnancy in a mouse or rat, or other animal species, and then apply this information to the human condition. Animals such as mice are inexpensive, have short pregnancies, have a hemochorial placenta and immune system similar to humans, and allow direct testing for cause and effect that cannot be done in humans. On the other hand, direct extrapolation of mouse data to humans has proven inappropriate: whatever model one chooses to study, there is an associated cost. Although animal models provide clues as to what to look for in humans, it is necessary to validate animal data by collecting human data. Cause and effect in humans can only be tested in predictive clinical trials.

Three speakers participated in the debate, the proposition for which was "This house agrees that the proper study of man is woman," and a brief summary of their arguments follows in the order in which they arose in the debate.

☆ Based on presentations at the 11th Congress of the European Society for Immunology of Reproduction, Budapest, Hungary, March 20, 2014.

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2. Dr. Udo Markert: only humans have human placentas

Dr. Markert from the Placenta Lab. in Jena, Germany, presented the results of studies on microRNAs (miRNAs) in the human placenta carried out by his post-doctoral fellow (Markert et al., 2014). miRNAs can modulate the expression of many genes at a time, and miRNAs are detectable in the blood and exert regulatory effects. Particular emphasis was placed on a cluster of miRNAs on chromosome 19 produced by trophoblasts. These miRNAs were associated with a variety of pregnancy disorders including preeclampsia, intrauterine growth restriction, and preterm delivery. Importantly, these miRNAs were not found in other species. It was asserted that studying trophoblast-derived miRNAs in animal models did not provide information relevant to humans. The data will be submitted in an independent paper by Dr. Markert's post-doctoral fellow.

3. Dr. Gerard Chaouat: reproductive immunology: the only good model for humans is. . .homo sapiens

For the Budapest meeting, I proposed a round table on the model of what had already been organized in Toronto and Rhodes for recurrent abortion immunotherapies, but this time on the question raised by Charlie Loke: the best model for studies of human pregnancy for an immunologist remains the human female. This gave rise to the Budapest format. Ironically enough, both myself and David Clark are still working, including at the bench, with mice (Clark et al., 2013), and while taking opposite positions in this meeting, we still work together on the very same model. Thus, it was a bit of "jeu de role," but as such, it was great fun, even though it was (I was) also serious. I have tried to include some of the fun elements in this paper.

The key points for the Loke position, which we will come to, were discussed in Loke and King (2000) as well as in Moffett and Loke (2006):

(a) Although the rodent placenta is hemochorial, it differs from the human placenta in its anatomical structure and depth of invasion, most notably with regard to the second wave of trophoblast invasion in humans that is defective in those developing preeclampsia, the "shallow" invasion depicted by Pijnenborg's group (Naicker et al., 2003).
(b) The expression of MHC alloantigens is different in human and mouse trophoblast.
(c) Class IB MHC HLA-G or HLA-G-like expression is seen only in humans and some – but not all – great apes, as there is no real consensus that HLA-G-equivalent candidates in rodents fulfill this role.
(d) The only quasi-equivalent models for humans are some of the great apes, which are genetically close, but most if not all are endangered and thus protected species. Even AIDS studies have been limited by this fact. The other monkey species are genetically too unlike humans.
(e) The repertoire of NK cell receptors in mice and humans differs drastically.
(f) Resorption in mice is not fully equivalent to human miscarriage.

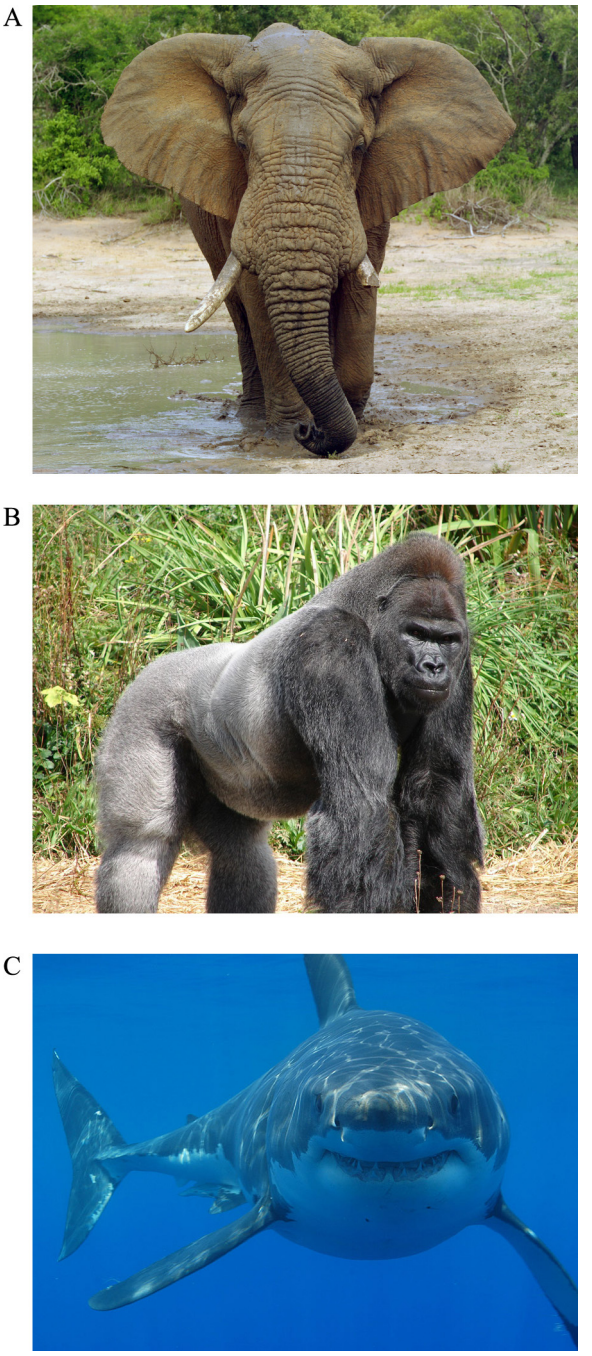

Fig. 1. Danger model, not in Matzinger style. A is the African Bush Elephant (Loxofdonta Africana), Kruger National Park, South Africa, author Gotot13 November 2008. B is Jock the Gorilla from Jock, the Gorilla by Antony from Glousester, U.K. 19 August 2006, 13:47. C is Great white shark (Carcharodon carcharias) off South Africa Fecha 10 de marso de 2009, 13:00, Fuente Greate White Shark Cage Diving, author Hermanus Backpackers.

Let us begin the discussion. There are animal models and animal models. Some animal models pose practical difficulties for safe study, such as those seen in Fig. 1. Even so, all these animal models are being studied. There are amongst them animal models that tell us something,