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Classics revisited: C. J. van der Horst on pregnancy and menstruation in elephant shrews

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ABSTRACT

Background: Menstruation occurs only in higher primates, some bats, the spiny mouse and the elephant shrew. Our knowledge of the latter species is due to work by C. J. van der Horst.

Findings: Changes in the uterine stroma are initially similar in fertile and infertile cycles and are confined to a small area. In pregnant animals, the presence of the conceptus causes further development to an implantation chamber. In infertile cycles an outgrowth of highly glandular stroma (a polyp) appears. With decline of the corpora lutea it is shed in a process equivalent to menstruation. Van der Horst described the further development of the placenta and a decidua pseudocapsularis in pregnant animals. In addition he built a unique collection that has thrown light on embryonic development and placentation in other South African mammals.

Conclusions: The changes in endometrial stromal cells during the menstrual cycle appear similar between primates and the elephant shrew and deserve to be studied at the molecular level.

1. Introduction

Human reproduction has many unique features [1]. One is menstruation, the shedding of decidua at the end of an infertile cycle with accompanying loss of blood. Decidualization involves a change in the size, shape and properties of the connective tissue cells of the endometrium (stromal fibroblasts) in preparation for embryo implantation [2]. In most mammals, decidualization does not occur until there is an embryonic signal. But in humans decidualization is triggered by a maternal signal in the second half of the menstrual cycle. The decidua will be useful if there is a pregnancy, but otherwise is shed.

Menstruation is known to occur in haplorrhine primates (Old World monkeys and apes) and some Neotropical primates. It has also been documented in phyllostomid and molossid bats [3] and the Cairo spiny mouse (*Acomys cahirhinus*) [4]. However, the best-known example of menstruation in non-primates concerns a distantly related order, the elephant shrews or sengis (Macroscelidea). In the 1940's, when human menstruation was poorly understood, Professor C. J. van der Horst of the University of the Witwatersrand proposed using elephant shrews as a model. To this end, he published an impressive body of research. In the meantime, a breeding colony of rhesus macaques (*Macaca mulatta*) had been established at the Carnegie Institution of Washington [5]. It was used to give a detailed description of the changes in the endometrium during the menstrual cycle and in pregnancy and to explore the physiological basis for these events in primates [6,7]. This was considered a better model for human reproduction and work on menstruation in elephant shrews was not pursued after van der Horst's death.

In addition to describing reproduction in the Eastern rock elephant shrew (*Elephantulus myurus*), van der Horst made significant observations on the early development and placentation of South African mammals. His work was extended by scientists working on his extensive collection. These contributions are reviewed below and his work on elephant shrews discussed in the light of renewed interest in the decidualization process and its role in the evolution of placentation in eutherian mammals [8–10].

2. Brief biography

Cornelius Jan van der Horst was born 11 May 1899 in Nieuwer-Amstel (now Amstelveen). He studied botany and zoology at the University of Amsterdam, where early influences included the botanist Hugo De Fries and the zoologist Max Weber [11–16]. His doctoral thesis from 1916 was on the motor nuclei and tracts of the fish brain [17]. In the same vein, he collaborated with the Swedish zoologist Nils Holmgren to describe the central nervous system of the Queensland lungfish (*Neoceratodus forsteri*) [18]. He studied corals under the tutelage of Stanley Gardiner of Cambridge University and in 1920 participated in a marine biological expedition to the Caribbean island of Curaçao. This led to publications on corals and acorn worms (Hemichordata: Enteropneusta). In 1925 he became Deputy Director of the Central Institute for Brain Research in Amsterdam, but in 1928 moved

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Fig. 1. Professor C. J. van der Horst on a field trip to Inhaca Island, Mozambique in 1938. A. Together with Mary Ruth McEwan a lecturer from his department. B. With a group of students. Photos courtesy of Dr. Vivienne Williams, School of Animal, Plant and Environmental Sciences, University of the Witwatersrand.

to Johannesburg.

Max Weber, who had visited South Africa in 1894-5, encouraged van der Horst's interest in its fauna. With Stanley Gardiner as intermediary, he was offered and accepted a post as senior lecturer in the zoology department of the University of the Witwatersrand [19]. He succeeded to the chair of zoology 4 years later. At Johannesburg van der Horst continued his work in marine biology, taking students on field trips to Inhaca Island off the coast of Mozambique (Fig. 1) and publishing a weighty tome on the hemichordates [20]. Yet soon he became intrigued by the unique mammalian fauna of South Africa and this led him to study their reproduction.

George H. Findlay, in an affectionate portrait of his mentor, wrote that van der Horst "looked like a sedate, benign Hollander, who might be seen anywhere sitting quietly in a church pew" [14]. He was far from talkative and "students surmised he had lost the habit of speaking through being surrounded at home by a large and purely female family!" [14]. Van der Horst had married Katherina Jacoba Aletta Vergouwen in 1918 and they had four daughters. C. J. van der Horst died on 10 October 1951 at the age of 62.

3. Reproduction in the elephant shrew

C. J. van der Horst penned as many as 35 papers [21] on reproduction in the Eastern rock elephant shrew (*Elephantulus myurus jamesoni*). Many were written in collaboration with Joseph Gillman (1907–1981) mentor of the anthropologist Phillip V. Tobias (1925–2012) and Nobel laureate Sydney Brenner (1927-present) [22]. Perhaps due to their exhaustive nature, there has been little follow up on these studies other than a paper by Tripp [21] and separate studies of placentation. Only the salient features will be mentioned here.

3.1. Ovulation and corpus luteum formation

E. myurus can carry one fetus in each horn of the uterus. Therefore it is remarkable that many more ova are discharged from each ovary; van der Horst and Gillman suggested as many as 60 [23] and Tripp calculated a mean of 49 [21]. Four other species of Elephantulus have normal ovulation rates, while polyovulation occurs to various degrees in *E. brachyrhyncus*, *E. edwardii*, *Macroscelides probiscideus* and *Petrosaltator rozeti* [21]. The only other eutherian mammal with such excessive ovulation is the plains viscacha (*Lagostomus maximus*) [24]. In *E. myurus*, luteinization of the granulosa cells commences prior to ovulation and there is eversion of the mature corpus luteum [23,25].

3.2. Implantation and decidua formation

Van der Horst and Gillman correlated changes in the uterus with the events of the oestrous cycle [26] and early pregnancy [27]. Oestrus was characterized by extensive oedema involving the whole thickness of the endometrium and by leucocyte invasion. Following ovulation, the oedema subsided and the leucocytes disappeared. Instead there was proliferation of the endometrial stromal cells. There then appeared a site of localized oedema in a small area on the mesometrial side of each horn. This sequence was common to early pregnancy and infertile cycles.

Fertilized ova were found to enter the uterus at the one, two or four cell stage. The occurrence of a vesicular blastula at the four-cell stage is unusual for eutherians, but has been reported in the streaked tenrec (*Hemicentetes spinosus*), another afrotherian [28].

One such blastula localized to the implantation site in each horn and only this developed past the four-cell stage. A small thimble-like cavity then formed to accommodate the embryo. This was followed by changes in the uterine epithelium, which started to degenerate, and in the stroma where generalized oedema was followed by enlargement of the stromal cells to form decidual cells. There was dilatation of the accompanying glands. Although the implantation site was predetermined, completion of the decidual reaction required the presence and further development of the embryo.

3.3. Placentation

Within the implantation cavity, the embryo developed to a blastocyst, although it was first after differentiation of the polar trophoblast that attachment began [29]. At first the syncytiotrophoblast penetrated no further than the basement membrane of the uterine epithelium. By this time an amniotic cavity had been formed and endoderm had lined the distended yolk sac (Fig. 2A). Subsequently, trophoblast invaded the decidua and opened the maternal capillaries. However, uterine glands supplied the embryo with histotrophe through the first half of pregnancy. Further stages in development of the chorioallantoic placenta were described in detail by van der Horst [29] and will not be repeated here. The definitive placenta was discoid, labyrinthine and haemochorial with a substantial spongy zone. A yolk sac persisted to term though diminished in size after expansion of the allantois and exocoelom.

Initially, the walls of the implantation cavity formed a decidua parietalis, but this did not persist. Instead outgrowths of the lateral wall formed an extensive "decidua pseudocapsularis" with prominent glands, which separated the embryo and its membranes from the main uterine cavity (Fig. 2B). The decidua capsularis later disintegrated bringing the allantochorion in contact with the uterine epithelium to form an extensive paraplacenta. This interesting arrangement was subsequently described in other elephant shrews, including *M. proboscideus* [30], *E. rufescens* [31], *Rhynchocyon chrysopygus* [32] and *Petrodomus tetradactylus* [33] (Fig. 3).

Another feature described by van der Horst was the appearance of giant cells with granulated cytoplasm that formed a sheath around the maternal arteries and penetrated to their lumen. It was later shown for