Chapter 1
Introduction

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Abstract Establishment and maintenance of pregnancy in a number of mammalian species depends upon a tightly regulated interaction between the semiallogeneic conceptus and the maternal uterine endometrium. The term "Maternal Recognition of Pregnancy" is attributed to Roger V. Short's paper titled "Implantation and the Maternal Recognition of Pregnancy" which was published in proceedings from the 1969 Symposium on Foetal Autonomy. Professor Short's landmark paper stimulated increased interest in elucidating how the conceptus signals its presence to assure maintenance of the corpus luteum beyond the normal length of the estrous or menstrual cycle to allow pregnancy to be established and maintained. Ten years following publication of Professor Short's paper, a Ciba Foundation Symposium entitled "Maternal Recognition of Pregnancy" brought together leading scientists to discuss the multiple mechanisms and pathways by which different viviparous species establish a successful pregnancy. The present volume on "Regulation of Implantation and Establishment of Pregnancy in Mammals" brings together current reviews from leading experts to address the diversity of mechanisms by which species establish and maintain pregnancy. Implantation in mice, dogs, pigs, cattle, sheep, horses, primates, humans and species in which embryonic diapause occurs are discussed. Reviews will provide current knowledge on the role of endometrial steroid receptors, adhesion factors, cytokines, interferons, steroids, prostaglandins, growth factors and immune cells involved with regulation of conceptus development.

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Establishment and maintenance of pregnancy in a number of mammalian species depends upon a tightly regulated interaction between the semiallogeneic conceptus and the maternal uterine endometrium. The term "Maternal Recognition of Pregnancy" is attributed to Roger V. Short's paper titled "Implantation and the Maternal Recognition of Pregnancy" which was published in proceedings from the 1969 Symposium on Foetal Autonomy (Short, 1969). Professor Short's landmark paper stimulated increased interest in elucidating how the conceptus signals its presence to assure maintenance of the corpus luteum beyond the normal length of the estrous or menstrual cycle to allow pregnancy to be established and maintained. To gain an historical perspective on maternal recognition of pregnancy, I recommend that every graduate student and young investigator involved with reproductive biology read his review paper. The following quote, taken from the introduction of Professor Short's paper, indicates that the establishment of pregnancy involves more than a simple biological pathway to "rescue" the corpus luteum from regressing during pregnancy and outlines the fundamental questions regarding pregnancy recognition signaling mechanisms which researchers today continue to investigate across a diverse variety of species.

> The maternal organism first becomes aware of the presence of an embryo in the uterus in diverse ways. In most mammals, this critical piece of information must be relayed to the mother at an early stage of gestation, and we will begin by considering in general terms both the nature of the message and the mode of its transmission. We shall then be in a position to investigate variations on the basic pattern, species by species.
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> One of the first outward and visible signs that an embryo has made its presence felt in the uterus is when the corpus luteum of the cycle becomes transformed into a corpus luteum of pregnancy, and estrous or menstrual cycles cease to recur. Let us therefore examine this luteotropic action of the conceptus in a little more detail. Can the stimulus be initiated by the embryo before it has achieved an anatomical union with the endometrium? Is the stimulus itself mechanical in nature, giving rise to afferent neural stimuli to the hypothalamus, which in turn bring about the release of luteotropic hormone(s) from the anterior pituitary, or does the conceptus have a hormonal action, elaborating its own luteotropic substances? In those species in which the endometrium of the nonpregnant uterus seems to produce a luteolytic factor, how does the embryo act to neutralize this effect? These are some of the questions to which we must attempt to the find the answers. Furthermore, it may be a mistake to concentrate all our attention on luteal maintenance as the first premonition of a pregnancy; fundamental differences between the pregnant and nonpregnant animal may begin to become apparent soon after fertilization, and in a number of species, the lifespan and secretory activity of the corpus luteum is unaffected by pregnancy. Undoubtedly much still lies outside our comprehension in this most fascinating area of investigation (Short 1969).

Ten years following the publication of Professor Short's paper, a Ciba Foundation Symposium entitled "Maternal Recognition of Pregnancy" (Ciba Foundation Symposium, 1979) brought together leading scientists to discuss the multiple mechanisms and pathways by which different viviparous species establish a successful pregnancy. The diversity of mechanisms to establish and maintain luteal function alone are clearly evident from the following species variation: (1) in the bitch, the corpora lutea (CL) are maintained for the length of pregnancy whether or not mating occurs; (2) in mice and rats, a sterile mating extends the lifespan of the CL from 4 to 12 days through vaginal stimulation by the erect penal spines (Fig. 1.1) that

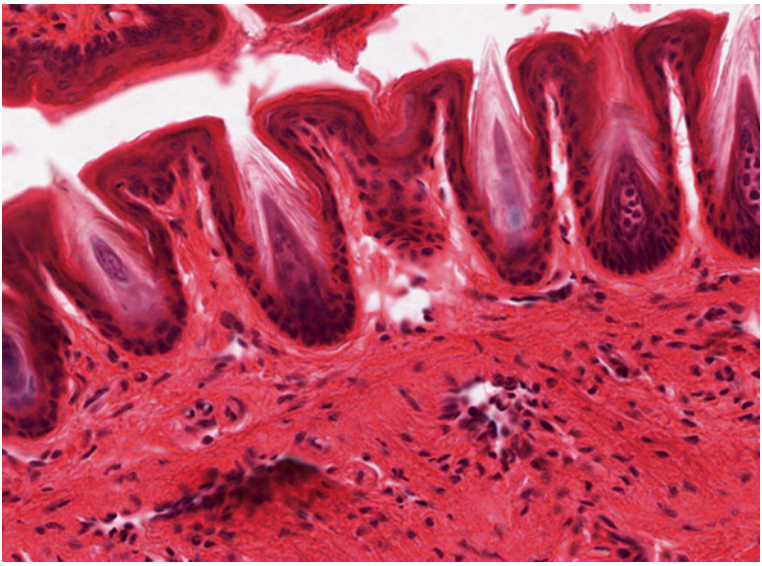

Fig. 1.1 Penile spines of the glans penis of rats stimulate the vagina of the female during mating to extend CL lifespan beyond a normal 4-day estrous cycle. If maternal recognition of pregnancy is considered extending CL function beyond the estrous cycle, the penile spines could be considered one of the earliest signaling mechanisms evoked even before fertilization. However, establishment of a pregnancy by viable blastocysts/conceptuses involves a more elaborate interaction between the maternal endometrium and implanting conceptus. Note that the short estrous cycle, mating-induced CL extension, and the ability to induce embryonic diapause place mice and rats among the more efficient and prolific species of mammals for reproduction

induce the diurnal release of prolactin; (3) in humans and subprimates, release of a conceptus-derived factor (chorionic gonadotrophin, CG) acts directly on CL to maintain function; and (4) the release of conceptus-derived factors indirectly inhibits the release or production of luteolytic pulses of prostaglandin F2α (luteolysin) from the endometrium. Of course, PGF2α had not been identified as a luteolytic hormone at the time of Short's paper. However, maternal recognition of pregnancy involves considerably more than extending luteal function. The attaching or implanting conceptus must stimulate adequate maternal blood flow to the placenta for transfer of oxygen and nutrients and induce the maternal endometrium to provide the spatiotemporal pattern of secretions and nutrient transport mechanisms necessary for continued development and survival of the conceptus throughout pregnancy while altering the maternal immune system to prevent rejection of the semiallogeneic conceptus.

Over the past few decades, technological advances in transcriptomics, proteomics, metabolomics, and glycomics along with the ability to selectively knockout genes of interest has greatly advanced our understanding of maternal-conceptus interactions that are essential for the establishment and maintenance of a successful

pregnancy. This knowledge provides a foundation from which to build research endeavors to help resolve infertility, embryonic loss, and recurrent abortion in humans, captive wild animals, and important farm species. The present volume on "Regulation of Implantation and Establishment of Pregnancy in Mammals" brings together current reviews from leading experts to address the diversity of mechanisms by which species establish and maintain pregnancy. Implantation in mice, dogs, pigs, cattle, sheep, horses, primates, humans, and species in which embryonic diapause occurs are discussed. Reviews will provide current knowledge on the role of endometrial steroid receptors, adhesion factors, cytokines, interferons, steroids, prostaglandins, growth factors, and immune cells involved with regulation of conceptus development. This knowledge provides a foundation for the development of strategies to resolve infertility, embryonic loss, and recurrent abortion in humans, captive wild animals, and important farm animal species in the future.

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