Endocrinology of Embryo-Endometrium Interactions:
A Hundred Years of Fascinating Discoveries

Alexandre Psychos
Hospital Bicetre, Batiment INSERM
94876 Kremlin-Bicetre, France

Only a hundred years ago, when Fernand Lataste (1891) discovered lactational delayed implantation, no one was able to suggest a rational explanation. Fifty years went by before Krebseiet (1941) and Weichert (1942) reported that this intriguing phenomenon could be due to low estrogen secretion.

At the time of Lataste's discovery, Mathias Duval, known for his studies on the human placenta, described egg-implantation and ovarian involvement in his book "Cours de Physiologie" published in 1692. He said, "The fertilized ovum arriving into the uterus induces by its presence hypertrophy of the uterine mucosa from which results the decidua; at the same time there occurs in the ovary, due to an act of sympathy (in French: act sympathique) or a reflex difficult to explain, the characteristic evolution of corpora lutea of pregnancy."

These few lines summarize the background of knowledge from which the pioneers of our field started, at the beginning of this century, to add further information, answering two fundamental questions:

- Are the corpora lutea necessary for the normal evolution of pregnancy?

  A positive answer was given by Ludwig Fraenkel who first demonstrated the importance of corpora lutea, by a series of elegant experiments.

- Is the modification of the uterine mucosa observed during pregnancy, dependent on the presence of a fertilized ovum?
The negative answer to this question was given by Pol Bouin, with his classical work with Ancel, on pseudopregnant rabbits; by Leo Loeb, with the experimental induction in the guinea pig of a decidual transformation (deciduoma) of the uterine mucosa.

I will refer again to these main discoveries, while following the pathway which from Mathias Duval's "sympathy" led us to the "hormonal" concept.

We also owe to Fernand Lataste (1892), the first description of the cyclic changes occurring in the vaginal epithelium. However, it took some 25 years until Charles Stockard and George Papanicolaou at Cornell University rediscovered this phenomenon in the guinea pig, by a simple technique, the vaginal smear, the key to the discovery of the estrogenic hormone (Stockard and Papanicolaou, 1917). Joseph Long and Herbert Evans, at the University of California, inspired by Stockard and Papanicolaou's paper, then started to study vaginal cytology during the cycle in the rat and published their findings in their classical monograph (Long and Evans, 1922).

It was now the turn of a young instructor in Anatomy at Washington University, Edgar Allen, to be inspired by the reading of Long and Evans' monograph. He collected follicle fluid from sow ovaries and injected it into ovariectomized mice. By using the vaginal smear method, characteristic of estrus, he could thus read his results within a day. It seems that Edgar Allen met Edward Doisy at St Louis on the occasion of a joint effort to form a faculty baseball team. In March 1923, Allen reporting his findings to Doisy, and speculated that the ovarian-vaginal relationship he observed could be of hormonal nature. The two young men decided to work together. Doisy started purifying the follicular fluid, observed that the estrogenic potency was found in the lipid fraction and obtained soon after the partial purification of the estrogenic hormone (Allen and Doisy, 1923; 1924).

At this point we have to give credit to a Doctor of Medicine and Maître de Conférences at the Sorbonne in Paris: Henri Iscovesco. In 1912 he had already reported to the Société de Biologie that one of the lipid fractions he prepared from sow ovaries contained a substance which, injected into young rabbits, caused marked growth of their uterus. In a longer article two years later, Iscovesco made known that the active substance was soluble in alcohol, ether and petroleum ether, but not in acetone. He also reported that using this substance in his gynaecological practice, he obtained satisfactory results in dysmenorrhea, amenorrhea and hypogonadism (Iscovesco, 1912; 1914). Henri Iscovesco must also be considered as a pioneer and precursor of modern times from another point of view. It seems that he did a commercial use of his extract, and I guess that he was the founder of the Pharmaceutical company which bears his name today.

For English-speaking scientists an invaluable guide had appeared in 1910 in Cambridge: the book of Francis Marshall "The Physiology of Reproduction". Marshall and Jolly (1905), then in Edinburgh, had injected an anestrous bitch with a saline extract of ovarian tissue from another bitch that was