Introductory remarks on the milieu of the egg and the early embryo

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Extensive experimental work on the developmental biology of the mammalian embryo (Burki, 1986; Hogan *et al.*, 1986; Rossant & Pedersen, 1986) was made possible by the discovery of usable culture methods that were perfected about 20 years ago for the mouse and, to some extent, the rabbit (Biggers, 1987). This work on preimplantation embryo development has far outstripped the study of the microenvironments encountered by an embryo as it moves along the female genital tract to the uterus. This fact is perhaps surprising, since the culture media used to study development are substitutes for these environments. There are three reasons for this lack of attention to the composition of the genital tract secretions during the initial stages of pregnancy. Firstly, the available culture media are adequate for much of the developmental work to proceed. Secondly, the paucity of the secretions makes it very difficult to obtain samples for biochemical analysis. For example, the composition of the uterine secretions has received relatively little attention, although those interested in animals which implant superficially had speculated for years that the histotrophe produced in these species has a nutritional role (Amoroso, 1952). Thirdly, the oviduct has been traditionally thought of as a superfluous organ that acts only as a conduit for the embryo as it passes from the site of fertilization to the uterus. This view was particularly fostered by the results of the Estes operation, which was discussed by Hunter (1977), and later by Adams (1979) at the last Symposium held by the *Society for the Study of Fertility* on the milieu of the ovum. This operation, first described by Dudley in 1900 and later by Estes in 1909, was the method sometimes used until the 1960s to treat sterility due to tubal occlusion (Biggers, 1984). The ovary, attached to its pedicle, was moved into the uterine cavity where it was hoped ovulation would occur. It was argued that because a few pregnancies occurred following this operation the passage of the preimplantation embryo through the oviduct was unnecessary and that the oviduct is not involved in the nurture of the embryo. Biggers (1979) has pointed out that this clinical evidence is particularly weak to reach such a conclusion.

There are good reasons to believe that the environment, including that provided by the oviduct, is important throughout preimplantation development. Embryos of many species cannot be cultured in media which support mouse and early rabbit and human development (Bavister, 1987). For example, the rat and hamster are difficult to culture through the early cleavage divisions; the rabbit blastocyst will not expand properly *in vitro* and the differentiation of its germinal disc is impaired; and the pig blastocyst will not elongate *in vitro*.

A useful way of identifying the areas of research needed to understand in part the biology of early pregnancy is to use the methods of systems analysis (Biggers, 1981). Four general areas of research can be recognized.

- (1) The development of the embryo, which involves irreversible processes. This area is the subject matter of mammalian developmental biology.
- (2) The physiological exchanges between the embryo and its microenvironment.
- (3) The physiological exchanges between the mother and the microenvironment.
- (4) The flows of fluid along the genital tract, which may be in either direction and allow adjacent microenvironments to influence each other.

With the exception of the irreversible developmental processes, these areas are all concerned ultimately with the physiology of molecular transport. Some information is beginning to accumulate about the nature of the exchanges between the embryo and its environment. One of the most important steps concerns the change in transport mechanisms produced by compaction so that the embryo can regulate the composition of its extracellular fluid, first explicitly stated in 1971 by this year's Amoroso Lecturer—Allen Enders. In the past 16 years a series of sodium transport systems has been shown to develop sequentially in the expanding rabbit blastocyst (Biggers *et al.*, 1988). Another set of transport systems that also develops in the mouse and rabbit is concerned with amino acid transport (Kaye, 1986). This symposium will focus on the third component of the overall system—the maternal control of the microenvironment of the preimplantation embryo, particularly in relation to oviduct secretions, the transfer of materials between uterine capillaries and the uterine lumen and the formation and action of uterine secretions.

A truism stated at the turn of the century by the distinguished American biologist E. V. Wilson is that embryogenesis begins in organogenesis. The normal growth and development of the ovum into the largest cell of the body is clearly of importance to future development, and the materials for this growth must come from the mother. During this period the ovum appears to acquire special metabolic characteristics which affect the initial stages of development (Biggers *et al.*, 1967; Brinster & Harstad, 1977), as well as passing through interrupted stages of meiotic and cytoplasmic maturation (Schuetz, 1985).

At present the composition and physiological roles of the microenvironment of the mammalian ovum are poorly understood. In the preantral follicle, the ovum is in direct contact with a layer of cells which rest on a basement membrane. The nearest blood vessels to the oocyte are on the outside of this basement membrane. The passage of materials to the ovum in the preantral follicle thus involves the vectorial transport of molecules across an epithelium. The antral follicle forms when fluid that has been transported across the epithelial granulosa cells accumulates. Many substances collect in the follicular fluid, some in high concentrations. In general physiological terms we are therefore concerned with cavity formation and fluid accumulation in a closed, compliant system. The nature of the influxes and effluxes which maintain these levels is virtually unknown for any of these substances. Whether the composition of the antral fluid is an indicator of the microenvironment of the oocyte, which is enclosed by the cumulus cells, is controversial. At a recent meeting on the primate ovary at the Oregon Primate Research Center, Dr David Baird described the follicular fluid as a Pandora's box. Future research is needed to decide whether such scepticism is justified.

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