

SELECTED PAPERS
ON
PLANNED
PARENTHOOD

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VOLUME
2

**Drugs for Anti-Implantation
& Termination
of Early Pregnancy**

抗着床与抗早孕药物

Selected Papers on Planned Parenthood

Vol. 2

**Drugs for Anti-Implantation
& Termination
of Early Pregnancy**

1975

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着床

本文叙述了哺乳类动物孕卵着床过程的一般特征。较详细地阐述了灵长类、啮齿类、兔类的胚胎的发育,透明带的作用,着床时胚泡和子宫内膜的关系,以及胚泡在子宫内定居等问题。文章有助于了解不同哺乳类动物孕卵着床中各自的特点。

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着床研究

着床是哺乳类动物生殖的基本过程,不同物种的着床过程有很大区别。本文比较系统地总结了作者对于大鼠着床机制的实验研究,将大鼠着床过程分为两个阶段,对其具体内容作了概括性描述。文中并按研究工作开展的时间顺序,叙述了有关着床机制的一些概念的提出、发展和修正的过程。

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在交配后给药才能防止妊娠,其主要作用机制可能是通过对子宫内膜的直接作用,特别是降低内膜的碳酸酐酶和血液供应,使发育中的卵不能排出二氧化碳和维持正常的酸碱度。

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β 氨基乙醇类的抗生育活性

本文报导某些 β -氨基乙醇化合物对大白鼠的抗生育作用, 其中 α -(3-环戊烯基氨基)-乙醇, α -(异丙基氨基)-乙醇能分别抑制大白鼠着床前后的胚胎发育。对于结构与活性的关系, 作者认为基中的“羟基”和“乙撑”基团必不可少, 取代的 N-烷基的结构或性质对其生物活性极敏感。

Once-A-Month Vaginal Administration of Prostaglandins E_2 & $F_{2\alpha}$ for Fertility Control 233用前列腺素 E_2 和 $F_{2\alpha}$ 每月一次阴道内投药作为生育控制

本文介绍了对 12 例月经过期 2—7 天的妇女 (其中 8 例小便妊娠试验为阳性), 用 PGE_2 或 $PGF_{2\alpha}$ 乳糖片放在阴道内促使月经来潮。 $PGF_{2\alpha}$ 乳糖片每片含 $PGF_{2\alpha}$ 50 mg, 而 PGE_2 乳糖片每片含 PGE_2 20 mg。放在阴道后穹窿中, 每隔 4 小时放一片, 共放二次。其中 10 例在放药后 1—6 小时开始有阴道流血。对 2 例无流血者, 次日再放一片, 其中一例有流血, 另一例无效。12 例于一周后随访, 其中仅无流血的一例尿妊娠试验仍为阳性, 其余 11 例呈月经样流血持续至 3—4 天。

本文还探讨了 PG 催经的机制, 作者认为给药途径简便, 妇女可以自己使用, 因此可考虑作为催经抗早孕的方法。

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本文介绍了对 22 例月经过期 2 周内的妇女, 用 $PGF_{2\alpha}$ 5 mg 宫腔内一次冲击法给药, 作为非手术性的人工流产方法。试验结果表明: 其中 20 例完全流产。因为在给药前应用了镇静药组, 所以副反应小, 易为受药者接受。

文中还以激素的测定, 子宫的描绘说明引产药物冲击后孕酮水平的下降与用药效果的关系, 作为药物抗早孕的理论根据。

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PHYSIOLOGY OF IMPLANTATION

IMPLANTATION

By

Richard J. Blandau

Embryo-endometrial interrelationship leading to implantation has been a subject of great interest to developmental biologists for decades. Although considerable understanding of the process has evolved for several laboratory animals, it is not incorrect to state that it is still impossible to define precisely the exact temporal, physiological and biochemical parameters that lead to successful nidation for any mammal, much less the primates.

Anyone attempting to summarize what is known concerning implantation phenomena on a comparative basis is soon impressed with the diversity of opinion as to how the various factors, systemic, blastocystic, and endometrial, interact in nidation. Specific information remains vague and unsatisfactory. The considerable species differences in the manner in which implantation is accomplished but adds to the dilemma and aggravates the uncertainty.

A uniform feature of the fertilized ovum after it enters the uterine cavity is its transformation into the blastocyst. The morula forms a cavitation that enlarges and expands rapidly to line the zona pellucida. Certain of the cells gather at one pole and form the inner cell mass from which the embryo develops. The layer of epithelial cells on the inside of the zona pellucida comprises the trophoblast. When primitive mesoderm lines the trophoblast, it becomes the chorion.

The trophoblast of the blastocyst is a remarkable membrane that has not received the attention which it deserves: 1) It develops various kinds of attachment cone that initially anchor the blastocysts to the maternal endo-

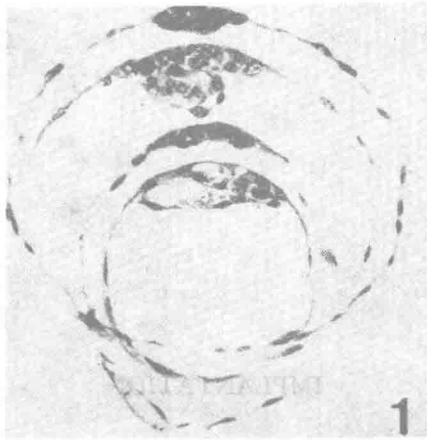


Fig. 1.

Sections of four different free blastocysts recovered from the uteri of the *Macaca mulatta* to show particularly the variations in size and appearance of the normal pre-implanted embryos. $\times 200$ (Courtesy Heuser & Streeter 1941).

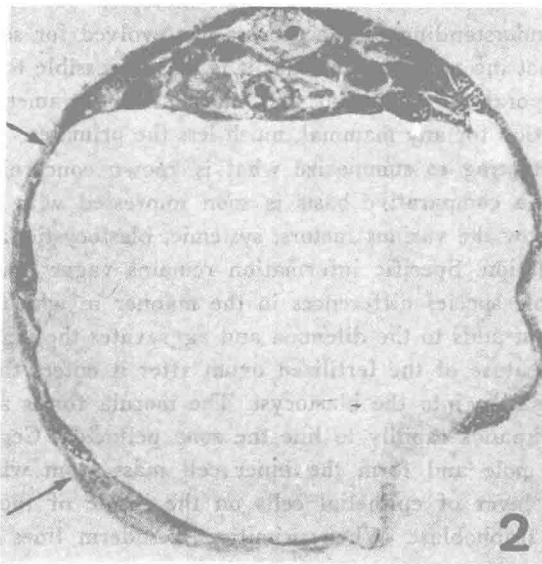


Fig. 2.

Section through an 8-day macaque blastocyst. Note the various cells comprising the inner cell mass, the single layer of trophoblast cells, and the remnants of the zona pellucida (arrows). $\times 250$ (Courtesy Heuser & Streeter 1941).

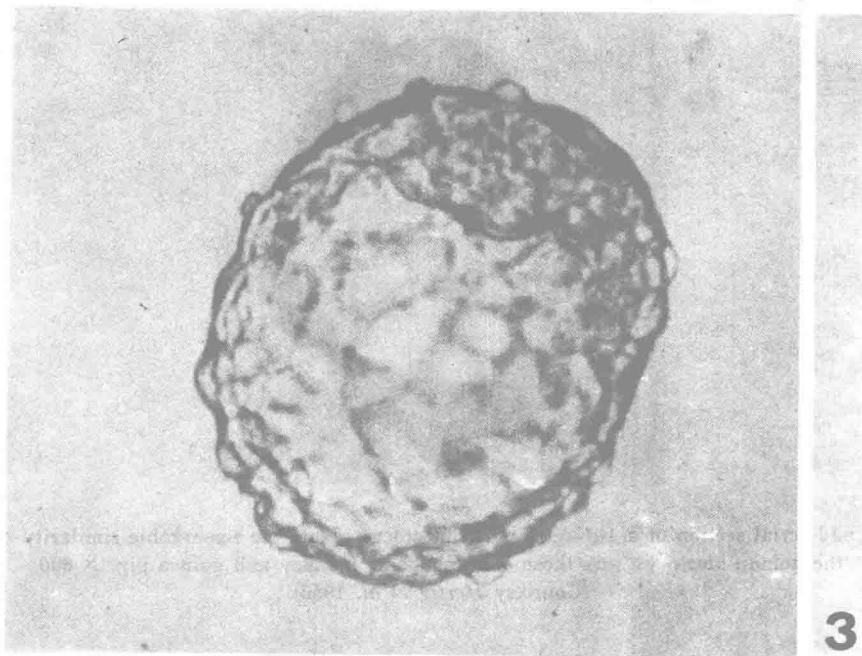


Fig. 3.

A free baboon blastocyst recovered from the uterine cavity at 8 days (estimated fertilization age). (Courtesy *Kraemer & Hendrickx 1971*).

metrium; 2) It acts as a selective membrane that controls materials entering the blastocoelic cavity; 3) It plays a role in controlling the rate of protein metabolism in blastocysts in which implantation is delayed; 4) It is important in the escape of the embryo from the zona pellucida and accomplishes this by a variety of mechanisms in different species; 5) At the appropriate time in development it is transformed into the syncytial trophoblast that, by its adhesiveness and cytolytic capabilities, invades the living maternal endometrial stroma; 6) It may play a critical role in interposing an immunological barrier between foetus and maternal tissues; and 7) With time it will produce and secrete both protein and steroid hormones and develop into a complex endocrine organ, the placenta.

Although blastocysts vary greatly in size and rate of development, they are basically alike in all mammals (compare Figs. 1, 2, 3, 4, 5 & 6). Why blastocysts assume the shape and form that they do in the various mammalian species is unknown. The blastocyst remains free in the uterine lumen for a variable period of time (rat and mouse, 36 to 48 h; guinea pig, 6 days; macaque, 9 days; baboon, 7 to 8 days; cat, 13 days and human, at least 5 to 6 days). In cases of

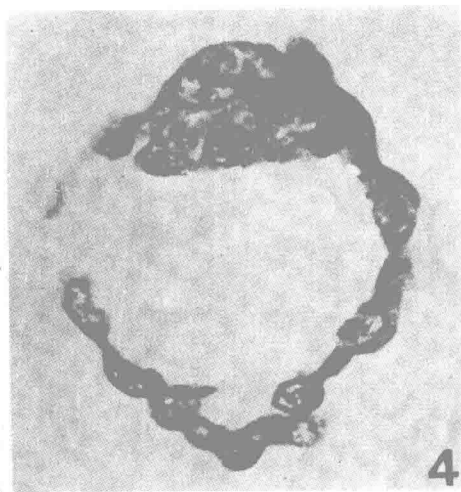


Fig. 4.

A mid-serial section of a 107-cell human blastocyst. Note the remarkable similarity of the human blastocyst and those of the baboon, monkey and guinea pig. $\times 600$.
(Courtesy Hertig *et al.* 1956).

delayed implantation nidation may be deferred for days or for even as long as 10 months (European badger, *Meles meles*). Under conditions of delayed implantation the appearance of the blastocysts remains largely unchanged.

Blastocyst development in the non-human primate

Considerable information on the development and appearance of the blastocysts is available for a few primates, namely, the baboon, *Papio cynocephalus* (Hendrickx 1971); lesser bush baby, *Galago senegalensis senegalensis* (Butler 1959); and macaque, *Macacus rhesus* (Heuser & Streeter 1941).

A series of four different macaque blastocysts, in section, is shown in Fig. 1 (Heuser & Streeter 1941). All of these were still free within the uterine cavity and were recovered on the 8th and 9th days after ovulation and fertilization. Unfortunately all of the blastocysts recovered in this series were fixed in

Fig. 5 a & b.

Guinea pig blastocysts found attached to the antimesometrial border in freshly opened cornua on the 6th day after ovulation. They were fixed *in situ*, removed *en bloc*, sectioned and stained. In »a« shrinkage artifact has lifted the blastocyst away from the epithelium. Except for the area of attachment cone the zona pellucida (arrows) is still intact. In »b« note the alterations in the superficial epithelium below the attachment cone and the early invasion of the endometrial stroma by the trophoblastic syncytium. M – embryonic macrophage.



Bouin's fixative, the acid component of which causes the zona pellucida to depolymerize and largely disappear. Heuser and Streeter picture an 8-day blastocyst still invested by remnants of the zona pellucida (Fig. 2). They maintain that it would be impossible for the blastocyst to make effective contact with the maternal epithelium unless the zona pellucida were shed. This interpretation of the status of the zona pellucida at the time of attachment may not necessarily be correct in light of the fact that in certain animals, such as the guinea pig (*Spee* 1883; *Blandau* 1949a) and perhaps also in *Citellus tridecemlineatus* (*Mossman* 1937), the zona pellucida may remain largely intact during the early stages of attachment except at the sites of formation of the attachment cone (Fig. 5). When blastocysts of approximately the same stage of development are examined in detail in either living or fixed conditions, one is impressed with the considerable differences in size, shape, and stage of development. These variations in blastocyst size have been reported in a number of animals [macaque (*Heuser & Streeter* 1941), baboon (*Hendrickx* 1971), mouse (*Rumery & Blandau* 1971), rat (*Tachi et al.* 1970), etc.].

In the 8- and 9-day unattached macaque blastocyst both the trophoblast shell and the inner cell mass show some differentiation. The trophoblast may be differentiated into 1) the polar trophoblast (*i. e.*, in the region of the inner cell mass), which very early may become multi-layered (Figs. 7a & b), and 2) the continuous single layered trophoblast cells that line the zona pellucida and form the boundary for the blastocoele cavity (Figs. 2 & 7a). The inner cell mass is composed of two types of cells, large lightly staining cells (formative cells), and flattened epithelial cells that have delaminated from the inner cell mass and now constitute the endoderm (Fig. 2). The cells comprising the various constituents of the 8- and 9-day blastocyst may be summarized:

8-day blastocyst

polar trophoblast cells	56
cavity wall trophoblast cells	58
formative cells (embryonic)	14
endodermal epithelial cells	12
Total	140 cells

9-day blastocyst

polar trophoblast cells	95
cavity wall trophoblast cells	224
formative cells (embryonic)	32
endodermal epithelial cells	24
Total	375 cells

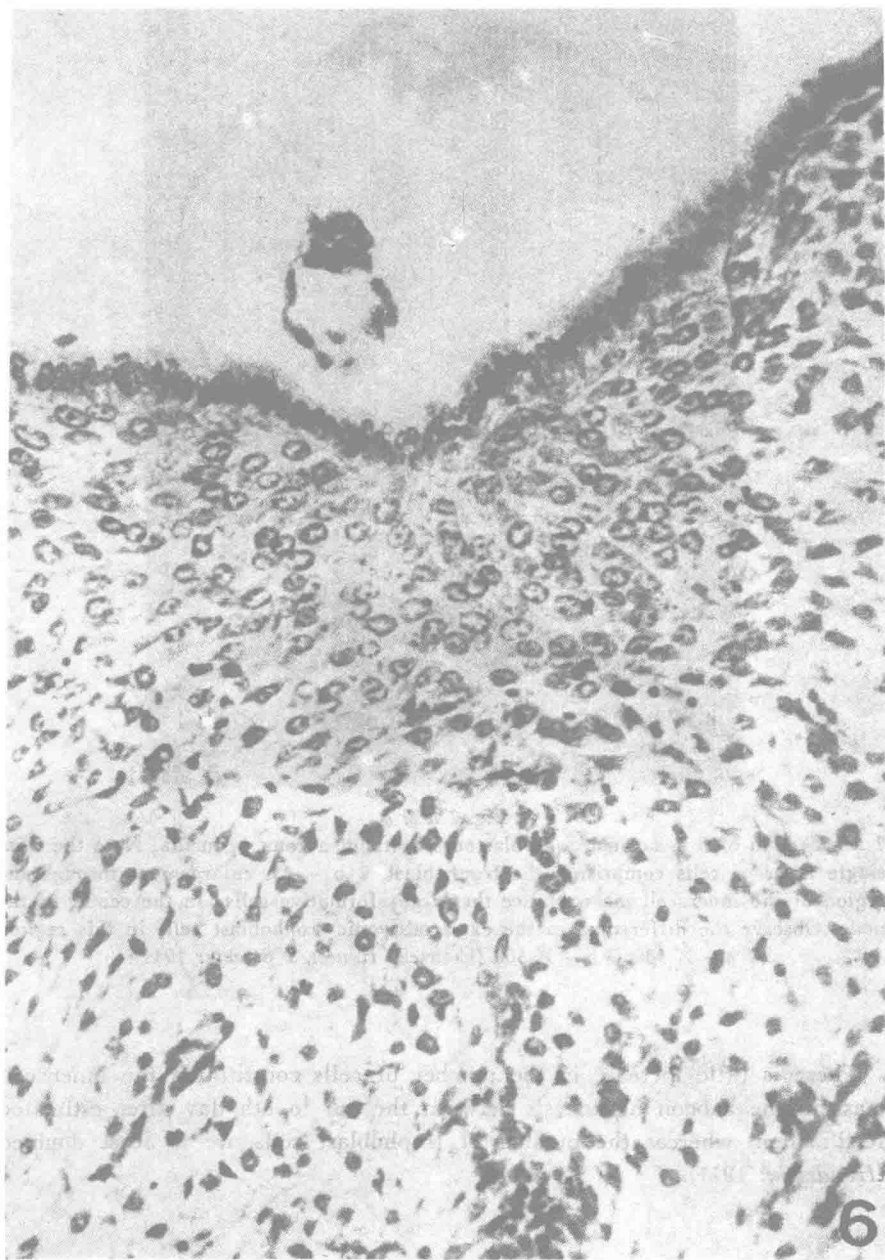


Fig. 6.

A section through the initial site of attachment of a rat blastocyst recovered late on the 4th day after ovulation. The blastocyst has initiated an early decidual response. There is no obvious alteration of the superficial epithelium. The zona pellucida is gone.