

SELECTED PAPERS
ON
PLANNED
PARENTHOOD

计 划 生 育 专 题 论 文 选 集

VOLUME

4

**Steroidal Hormonal
Contraceptive Agents**

甾体激素避孕药

Selected Papers on Planned Parenthood

Vol. 4

**Steroidal Hormonal
Contraceptive Agents**



March 1975

Abstracts

摘 要

Physiology of Menstruation

月经生理

2

本文综述了月经周期中子宫内膜的变化,讨论了控制月经的内分泌因素,并概述了正常月经周期中激素的变化及其生理意义。文中较详细地介绍了 Markee 将子宫内膜组织移植于猴眼前房直接观察的工作。

Regulation of the Human Menstrual Cycle

人体月经周期的调节

22

本文综述了正常月经周期中卵巢形态与激素的周期性变化。作者将周期中的形态学变化分为四个时相:1)初级的卵泡生长,2)卵泡的成熟与闭锁,3)排卵期,4)黄体化与黄体。将周期中的激素变化也分为四个时相:1)初级的卵泡生长,2)卵泡成熟与闭锁、甾体生成,3)排卵期,4)黄体的生命和死亡。文中引用了大量实验资料,作了较为详尽的叙述。

文章的最后部分简单地介绍了一种新的研究途径:考虑到月经周期的调节非常复杂,其正常功能有赖于许多变数的相互作用,作者发展了一种月经周期的工程分析,用非线性的代数学和微分方程,明确地描述周期中各个激素与形态成分的特性。

The Hypothalamus & Control of Ovulation

丘脑与排卵控制

37

哺乳类动物的排卵过程(分反射性和自发性二种)均受神经内分泌的控制,其中包括丘脑对垂体和卵巢功能的影响以及血中促性腺激素和卵巢激素在血中浓度的变化对丘脑和垂体的反作用,即所谓垂体功能的反馈调节,它促进或抑制排卵过程,并造成灵长类动物正常的月经周期。克罗米粉诱发排卵和甾体类避孕药抗排卵的作用机制都是由于影响了这种反馈机制,其主要作用部位是在丘脑。

Pituitary & Gonadal Hormones in Women During Spontaneous & Induced Ovulatory Cycles

在妇女自发与诱发排卵周期中的脑下垂体与性激素

47

文章首先描述观察指标的标准。详细介绍正常月经周期和短月经周期中的 FSH 和 LH 的曲线变化,以及相应的 17-羟基黄体酮、黄体酮、基础体温的变化。

文中比较了正常周期与短周期之间 FSH、LH, 以及两者的分泌特点和比率上的差异。作者在文中还暗示 17-羟基黄体酮作为观察指标的意义。

最后作者阐述了 F 丘脑、垂体、性腺激素之间的调节关系,也讨论了目前测定性激素、FSH 和 LH 方法上存在的一些问题。

Hormonal Regulation of Sperm Capacitation

精子获能的激素调节

109

本文综述了免精子获能与各种激素之间的关系。扼要叙述了促性腺激素对免精子获能的影响;精子在动情、去卵巢与假孕兔子宫内的获能;精子在孕激素处理过的兔子宫内的获能等。尽管不同作者所得实验结果不一致,但有许多证据支持精子在假孕或孕酮处理过的兔子宫内的获能受到抑制的观点。此外,免精子在输卵管内获能,不论在假孕兔或在去卵巢而用雌激素或孕酮处理过的兔上均可完成,但在去卵巢而不给予激素处理的兔上则不能完成。不过这些报告尚有待重复。作者主张在人和其它动物上进一步研究精子获能的激素调节。

卵子着床的激素需要

本文阐述了大鼠卵子着床过程依赖于两种卵巢激素的顺序性相互作用。子宫内腺需在孕酮至少 48 小时准备的基础上,于妊娠第 4 天在微量雌激素的作用下,才能着床成功。

去卵巢的大鼠以不同顺序给予孕酮和雌激素处理的资料显示:孕酮—雌激素时间关系的变化会影响子宫内腺对雌二醇的摄取和 RNA 的合成。

从非雌激素化子宫在延缓着床过程中对胚泡生长停止作用的研究中,推测在延缓阶段,子宫内腺对胚泡具有主动抑制作用。

最近实验还提示了非雌激素化子宫的抽提上清液中,含有一种能在体外抑制大鼠和兔子胚泡对 RNA 前身物摄取的因子。

Developments in Steroidal Hormonal Contraception

149

甾体激素避孕药的发展

本文综述了甾体激素口服避孕药的化学结构,各种甾体避孕药生理活性的差异,作用方式,内分泌影响,毒性作用以及最近的一些进展,此外还讨论到这类药物将来发展的可能性。

New Developments in Anti-Fertility Drugs: Clinical Perspectives

155

抗生育药物的新进展:临床观察

本文叙述了新的避孕方法的一些用法及其优缺点和对今后十年进展的估计。

新的避孕方法包括有:口服配伍的雌激素和孕激素、注射配伍的雌激素和孕激素、口服孕激素、注射孕激素、子宫内放置孕酮、同房后用药、下丘脑释放因子的抑制、前列腺素、宫内节育器、杀精子的药物、女性绝育法和男性绝育法。

Endocrine Properties & Mechanism of Action of Oral Contraceptives

159

口服避孕药的内分泌性质与作用机制

文中概述口服避孕药中孕激素类化学构造的特点与生物学活性。其作用机制主要是丘脑中促性腺激素释放因子的释放受到抑制,使垂体中促性腺激素的分泌降低到最低限度,其中雌激素使 FSH 的分泌减少,滤泡不能成熟,孕激素使滤泡破裂所需的 LH 高峰消失,但 FSH 的抑制是主要的。

The Effect of Drugs on Egg Transport

169

药物对卵子运行的影响

卵在输卵管内的运动,以及峡部—壶腹部和子宫—输卵管接头的作用处于精细的激素控制之下,并受卵巢切除、外源性激素和一些合成的与天然物质的影响。本文对合成的甾体雌激素、前列腺素和其它影响平滑肌药物(如利血平)等对卵子运行的影响进行了讨论。这些化合物中的某一些加速卵子运行,使其提早到达子宫,造成卵子变性。而另一些则阻碍卵子运行,称之为“输卵管闭锁”,这种作用通常发生在峡部—壶腹部接头处。某一种化合物的作用是使卵子运行受阻还是加速,则有赖于用药剂量水平和所使用的动物品种。

本文讨论了几种化合物的作用机制,着重说明了这些知识如何有助于理想避孕药的设计。

Oral Contraceptive Activity of Danazol in the Rhesus Monkey

185

口服新药 Danazol 对恒河猴的避孕作用

Danazol 可抑制啮齿动物,恒河猴及人类的垂体促性腺分泌,此系新的类固醇药物,无雌激素及孕激素活性但有雄激素活性。本篇系报导其对恒河猴是有效的口服避孕药。

第一实验:6 只成熟的雌恒河猴,在月经第 11—16 天交配,5 只在第一周期中妊娠,第 6 只是在第二周期妊娠。故这些动物模型是可以用作快速衡量药物的口服避孕效果的。

第二实验:18 只雌恒河猴服用 Danazol,每天为 200—400 毫克共 90 天,则全部未孕。如剂量为 100 毫克,则 6 只中有 1 只在第 1 周期妊娠。如为 50 毫克,则 5 只中在第 1, 2, 3 周期中共有 4 只妊娠。14 只对照组中,12 只于第 1 周期中妊娠,1 只于第 2 周期,另一只则在第 3 周期妊娠。故每天用药 200 毫克,可阻止恒河猴受孕。因其无雌激素及孕激素活性,比现有的口服避孕药更有优越性。

新药 Danazol 对垂体促性腺的抑制作用

Danazol 是类固醇化合物。啮齿类动物口服后,对垂体促性腺功能有着显著的抑制作用。本篇系报道老鼠、兔子口服此药后的内分泌活动。

成熟雌鼠用药后,经阴道涂片,发现卵泡期天数百分率随剂量增大而减少,剂量增大后,肾上腺重量减少。将成熟的雌鼠的右侧卵巢切除后,灌输此药,并作阴道涂片,发现卵泡期天数受到抑制,对侧卵巢代偿性的增大也受到抑制。成熟雄鼠用药后剖割,发现前列腺体、贮精囊、及睾丸等的重量减轻。阉割的雄鼠用药后,对上述器官的刺激是小的,而对肛门的重量则有增加。未成熟的雌鼠用药后,子宫重量可有增加。对卵巢切除后的雌鼠,阴道粘膜无角化改变,应用大剂量 Danazol 后,用 Clarberg 法测定,无孕素活性。在受精后次晨,每天用 200 毫克,共 6 天,则可完全阻止妊娠。

口服 Danazol 后,有显著垂体-性腺轴的抑制作用。该药物无雌素及孕素活性。并具有弱的雄素活性。如经注射给药,上述作用更为明显,作者建议可作重要临床应用。

Oral Contraceptives: Therapeutics versus Adverse Reactions, with An Outlook for the Future. I & II.

197

口服避孕药: 疗效与毒性 (附展望)

本文分两部分。第一部分,首先从丘脑、垂体、卵巢三者的相互关系阐明了妇女正常月经周期的激素变化,介绍了各类甾体口服避孕药的化学结构、服用情况和作用原理;然后,就付作用中的血栓症作了比较详细的总结。第二部分,叙述了其他的付作用,包括肿瘤和增生过盛,对碳水化合物和脂类代谢以及肝功能的影响等。最后指出了甾体避孕药的展望。

Coordinated Studies of the Effects of Oral Contraceptives

233

口服避孕药作用的综合研究

本文是美国关于口服避孕药医学影响的一个调查报告。它提供了资料,证实口服避孕药对于增加血栓症和中风的可能性。对于增加乳腺癌的可能性未被证实。服用口服避孕药的妇女似乎对宫颈结构不良有倾向性。此外,还对 18,000 名服药和未服药的妇女进行了各种临床测定,证明口服避孕药几乎对所有的测定都具有微细、但是有意义的影响。

Contraceptive Use—Efficacy Study Utilizing Medroxyprogesterone Acetate Administered As An Intramuscular Injection Once Every 90 Days

247

每三月肌注一次醋酸甲孕酮避孕药的效果

本文介绍了从 1965 年 2 月到 1971 年 10 月,注射合成制剂醋酸甲孕酮避孕药的研究方法、效果和付作用。志愿参加者有 8,857 名健康育龄妇女,共观察了 72,215 个月经周期,平均观察时间为 12 个月(1—70 个月)。药物失效率为 0.25%/百妇年,这种制剂虽有阴道流血和闭经等付作用,但仍受到一些妇女的欢迎。其效能与口服避孕药及宫内节育器相似。

Contraception by An Injectable Long-acting Oestrogen-Progestogen Agent. II: Evaluation of Cycles, Menstrual Flows & Side Effects

257

长效雌孕激素避孕针对妇女的月经周期、经量的影响和付作用的评价

本文报导了 22 名能生育的妇女注射 Deladroxate 雌孕激素长效避孕针 341 周期的结果。注射是在每个月经周期第 8 天(7—9 天)进行的。在注射前连续观察了 2 个月的月经周期;经期;经量。她们在用药前的平均月经周期为 28.4 天,用药后为 25.3 天,缩短了 3.1 天;在可统计的 320 周期中,有 71.6% 的经期为 4—8 天,平均周期为 7.8 天;60% 的经量是正常的,其余大多数的经量比用药前减少。

关于付作用方面,22 名用药妇女中有 17 人观察 1—2 周期中有轻微和短暂的付反应:如乳房胀痛,浮肿,和不规则出血。未发现妊娠。

停药后 11 人的不规则出血自然缓解。

Post-"pill" Amenorrhea

273

服药后的闭经

文献报导服用避孕药者,在停药后发生闭经 6 个月以上的发生率达 2.2% 到 3.8%。本文对 89 例进行了临床分析,50% 的患者在服药前曾有不规则月经史,应用复方避孕药后的

发病率高于序贯用药者。17.9%的闭经者合并乳溢 (Galatorrhoea), 这些患者中脑垂体肿瘤的发病率在上升。内腔镜检查, 如果卵巢已呈现为硬化囊性状态, 治疗效果较正常卵巢或多囊卵巢为差。

在治疗及预后上, 黄体酮撤退性试验是个重要步骤, 注射黄体酮后出现撤退性流血者, 可以应用 Clomid 治疗, 每月剂量可由 50 毫克/日 \times 5 天增加到 200 毫克/日 \times 5 天, 直到出现排卵。如无撤退性流血, 则首先进行 1~2 个月雌激素-黄体酮的周期性治疗, 而后应用 Clomid, 并可考虑应用皮质激素、绒毛促性腺激素。本组 24 例希望生育者经过治疗, 12 例受孕。

Effect of Pyridoxine Hydrochloride (Vitamin B₆) upon Depression Associated with Oral Contraception

281

维生素 B₆ 对口服避孕药所引起的精神抑郁症的治疗效果

口服合并式单一孕激素避孕药与色氨酸和维生素 B₆ 代谢异常之间的关系, 前已有所报导。本文对 22 例精神抑郁妇女 (估计其发病原因系由于服用避孕药所引起) 进行了研究。生化测定结果发现维生素 B₆ 完全缺乏者有 11 例。本组妇女在双盲交叉试验中对应用维生素 B₆ 的临床反应良好。另外 11 例则无如此反应。服用安慰剂者并无作用。作者讨论了有关口服避孕药产生精神抑郁症的可能机制及维生素 B₆ 的治疗问题。

Early Incidence Rates of Precancerous Cervical Lesions in Women Using Contraceptives

290

用避孕药具的妇女中癌前期宫颈损伤的早期发生率

本文是纽约计划生育联合门诊对妇女中子宫颈癌前期发生与不同避孕药具关系的进一步研究。在初步研究中曾报导了应用甾体药物避孕妇女的癌前期发病率稍高于应用阴道隔膜妇女。进一步研究目的在于观察延长使用各种避孕器具后子宫颈癌前期的发病情况。

在研究中该联合门诊对每一个节育妇女详细询问病史; 包括年龄, 种族, 初产年龄, 生育次数、家庭经济等项目; 并作全身和阴道细胞学检查。在 78098 节育妇女中选择了 13018 人应用甾体避孕药, 阴道隔膜或宫内节育器者, 其中有 7704 人连续 2 年阴道细胞学阴性定为配对统计分析对象: 甾体药物 3045 人和阴道隔膜 1015 人配对, 比例为 3:1。甾体药物 2733 人和宫内节育器 911 人配对, 比例为 3:1。

统计结果表明应用甾体药物避孕的原位癌和癌前期的发病率和应用阴道隔膜或宫内节育器的原位癌和癌前期的发病率无统计学上有意义数的区别。同时在这次研究中, 也未发现由于应用避孕药具导致癌前期和癌的发病率的增加。

CONTENTS

Physiology of Reproduction

生殖生理

Physiology of Menstruation	2
月经生理	
(<i>Clinical Obstetrics & Gynecology</i> , V. 13, N. 2, p. 365-385, 1970)	
Regulation of the Human Menstrual Cycle	22
人体月经周期调节	
(<i>American Journal of Obstetrics & Gynecology</i> , V. 109, N. 2, p. 234-247, 1974)	
The Hypothalamus & Control of Ovulation	37
丘脑与排卵控制	
(<i>British Medical Bulletin</i> , V. 26, N. 1, p. 3-9, 1970)	
Pituitary & Gonadal Hormones in Women During Spontaneous & Induced Ovulatory Cycles.....	47
在妇女自发与诱导排卵周期中的脑下垂体与性激素	
(<i>Recent Progress in Hormon Research</i> , Vol. 26, Part 1—Proceedings of the 1969 Laurentian Hormone Conference, 1-62, 1970)	
Hormonal Regulation of Sperm Capacitation	109
精子获能的激素调节	
(<i>Advances in the Biosciences</i> 4—Schering Symposium on Mechanisms Involved in Conception, p. 13-33, 1969)	
Hormonal Requirments for Egg-Implantation	131
卵着床的激素需要	
(<i>Advances in the Biosciences</i> 4—Schering Symposium on Mechanism Involved in Conception, p. 275-290, 1969)	
The Steroidal Hormonal Contraceptive Agents & Thier Pharmacology	
甾体激素避孕药物与药理	
Developments in Steroidal Hormonal Contraception.....	149
甾体激素避孕药的发展	
(<i>British Medical Bulletin</i> , V. 26, N. 1, p. 39-44, 1970)	

New Developments in Anti- Fertility Drugs: Clinical Perspectives.....	155
抗生育药物的新进展：临床观察	

(*Biochemical Society Transactions*, V. 1, N. 2, p. 539-542, 1973)

Endocrine Properties & Mechanism of Action of Oral Contraceptives	159
---	-----

口服避孕药的内分泌性质与作用机制

(*Federation Proceedings*, V. 29, N. 3, p. 1211-1219, 1970)

The Effect of Drugs on Egg Transport	169
--	-----

药物对卵子运行的影响

(*Advances in the Biosciences 4—Schering Symposium on Mechanisms Involved in Conception*, p. 165-180, 1969)

Oral Contraceptive Activity of Danazol in the Rhesus Monkey	185
---	-----

口服新药 Danazol 对恒河猴的避孕作用

(*Fertility & Sterility*, V. 25, N. 4, p. 363-366, 1974)

Pituitary Gonadotropin Inhibitory Activity of Danazol	189
---	-----

Danazol 对垂体促性腺的抑制作用

(*Fertility & Sterility*, V. 25, N. 4, p. 367-372, 1974)

Side Effects & Thier Therapeutics

避孕药付作用及其治疗

Oral Contraceptives: Therapeutics <i>versus</i> Adverse Reactions, with an Outlook for the Future I	197
---	-----

口服避孕药：疗效与毒性(附展望)，第一部份

(*Journal of Pharmaceutical Sciences*, V. 62, N. 2, p. 179-200, 1973)

Oral Contraceptives: Therapeutics <i>Versus</i> Adverse Reactions, with an Outlook for the Future II	219
--	-----

口服避孕药：疗效与毒性(附展望)，第二部份

(*Journal of Pharmaceutical Sciences*, V. 62, N. 3, p. 349-392, 1973)

Coordinated Studies of the Effects of Oral Contraceptives	233
---	-----

口服避孕药作用的综合研究

(*Contraception*, V. 9, N. 2, p. 109- 122, 1974)

Contraceptive Use—Efficacy Study Utilizing Medroxyprogesterone Acetate Administered As an Intramuscular Injection Once Every 90 Days	247
--	-----

每三月一次肌注的醋酸甲孕酮避孕针的效果

(*Fertility & Sterility*, V. 24, N. 5, p. 331-339, 1973)

Contraception by an Injectable Long-Acting Oestrogen-Progestogen Agent II: Evaluation of Cycles, Menstrual Flows & Side Effects	257
---	-----

长效单一孕激素避孕针剂对妇女月经周期、经量的影响及副作用的评价

(*Acta Endocrinologica*, V. 65, N. 4, p. 683-697, 1970)

Post "pill" Amenorrhea 273

服药后的闭经

(*International Journal of Fertility*, V. 19, N. 1, p. 37-44, 1974)

Effect of Pyridoxine Hydrochloride (Vitamin B₆) Upon Depression Associated
with Oral Contraception 281

维生素 B₆ 对口服药引起的抑郁症的治疗效果

(*The Lancet*, V. 1, N. 7809, p. 897-904, 28 April 1973)

Early Incidence Rates of Precancerous Cervical Lesions in Women Using
Contraceptives 290

用避孕药具的妇女中癌前期宫颈损伤的早期发生率

(*Gynecologic Oncology*, V. 1, N. 1, p. 290-298, 1973)

Physiology of Reproduction

PHYSIOLOGY OF MENSTRUATION

EDWARD E. WALLACH, M.D.

*From the Department of Obstetrics and Gynecology,
University of Pennsylvania School of Medicine, Phila-
delphia, Pennsylvania*

THE MENSTRUAL CYCLE AND ITS ASSOCIATED features profoundly affect many facets of female behavior. Besides the overt signs and symptoms of menstruation, subtle influences may relate female reproductive aspirations and apprehensions to the menstrual cycle. These interactions serve to emphasize the pervasive authority exercised by the reproductive cycle and by menstrual function.

Menstruation follows the withdrawal of hormonal support from the uterine endometrium with consequent bleeding. The state of the endometrium thus reflects the controlling influence of ovarian hormones. Although a relationship between ovarian function and menstruation was speculated upon in 1793 (10), it was not until the mid-nineteenth century that investigations of the reproductive cycles in lower animals were undertaken. Discovery of the mammalian ovum in 1827 by von Baer, the prominent zoologist, started an enthusiastic exploration of reproductive physiology (19), but the basic concepts of menstruation in the human and subhuman primate were not unraveled for another hundred years. The framework of our current understanding of cyclic endometrial changes was built by the pioneering work of such investigators as Allen, Bartelmez, Corner, Hartman, and Markee (2,3,4,5,7,9,10,13,20,21).

In this article we will: 1. Review the changes in the uterine endometrium leading to menstruation; 2. Discuss endocrine factors which govern the process of menstruation; and 3. Outline hormonal changes occurring during the normal menstrual cycle and their physiologic significance, to provide a background for succeeding discussions on *dysfunctional uterine bleeding* which is characterized by its deviation from the norm.

BACKGROUND

For many years concepts of menstruation in the human were based on extensive work carried out in lower animals. Formulation of present knowledge of menstrual physiology, therefore, was delayed because

PHYSIOLOGY OF MENSTRUATION

species differences are extensive, not only in morphology of the reproductive tract, but also in physiologic patterns of reproduction. For example, the domestic hen ovulates daily, while ovulation in the dog occurs only approximately twice per year during periods of "heat." The rabbit ovulates on response to coitus; ovulation in other species is confined to intervals of increased sexual receptivity during which copulation occurs.

Analogy Between Menstruation and Estrus Cycles in Animals

Formulation of present concepts of menstrual physiology was also restrained by the persistent belief that menstruation in the human female is analogous to periods of estrus in lower forms. While it is true that estrus in certain species and menstruation in the human play a similarly prominent role in the reproductive cycle, menstruation and estrus are now recognized to be quite dissimilar. Periods of estrus or "heat" are intervals of heightened sexual activity with a propensity towards mating. Sexual activity in the human is not restricted to specific times in the cycle so that coitus does not carry the same risk of impregnation that accompanies mating in species with estrus cycles.

Ovulation, the focal point of the reproductive cycle, is common to all mammalian species. Ovum release may occur during estrus, in response to coitus or other stimulation, or, as in the human, periodically without an associated interval of estrus. The onset of estrus is accompanied by changes in the ovaries and follicular ripening. Some species with estrus cycles, such as the guinea pig, do not demonstrate behavioral signs of estrus; however, distinctive cytologic changes in vaginal epithelium can be correlated with particular phases of the ovarian cycle and with periods of estrus. In the rabbit, coitus initiates a series of changes which result in follicular maturation and culminate approximately 12 hours later in ovulation. In the human, however, ovulation does not come about during a period of heightened sexual activity, nor is it a consequence of each act of coitus. In the absence of pregnancy, however, ovulation in the human defines the time of the succeeding menstruation. Thus the prominent features in all mammalian reproduction are the development of the graafian follicle and its accompanying significant changes in the genital tract, ultimate release of the ovum with ensuing establishment of the corpus luteum, and further effects on the reproductive structures brought about by luteal secretions which essentially prepare the uterus for possible nidation.

The details and timing of these events in individual species are related to its particular reproductive mechanism. Care must be exercised in drawing conclusions about these physiologic processes in one species from information on another species. Obviously, the experimental animal lends itself more easily than the human to the extensive investigations required to understand reproductive processes. The experimental animal must be as similar as possible to the human in reproductive habit, and the possible importance of differences must be kept in mind when results are interpreted.

Observations on Menstruation in the Rhesus Monkey

At the turn of the century Walter Heape reported his observations on menstruation and ovulation in the *Macaca rhesus* to the Royal Society of London (15). The report was significant for several reasons: first, his work with the rhesus monkey led Heape to speculate on reproductive cycle similarities between monkey and human; second, at a time when it was generally felt that menstruation and ovulation occurred simultaneously, Heape suggested that this relationship need not hold true. Third, he pointed out that ovulation does not necessarily take place in each menstrual cycle in the monkey, especially during the nonbreeding season, and that anovulatory cycles may also occur in the human. Since further work has confirmed that reproductive cycles in the higher monkeys and the human are similar, the rhesus monkey has been used extensively for studies of menstrual physiology. Corner (8) recognized a temporal relationship between ovulation and subsequent menstruation, with menstruation occurring approximately 12-13 days after ovulation in this species. He also observed that menstruation may occur *without* a preceding ovulation, and suggested a correlation between the premenstrual phase of primates and the postestrus interval of other mammals. Allen's rhesus monkey investigations reported in 1927 form the basis today for the widely held estrogen deprivation theory of menstruation (2). Further work in the same species by Hisaw (16) demonstrated that withdrawal of corpus luteum extracts resulted in uterine bleeding. Hartman (13) subsequently recorded data on over 7000 menstrual cycles in the *Macaca rhesus*, with some animals followed for more than 50 cycles. Mastering the technique of bimanual ovarian palpation, he was able to record ovarian dimensions and diagnose the occurrence of ovulation on the basis of his findings. These observations also suggested that although regular alternation of ovulation from one ovary to another was the usual condition, it was not the rule. Similarities

PHYSIOLOGY OF MENSTRUATION

between the reproductive cycle of the human female and that of the subhuman primate have opened the way for additional basic studies in the monkey which could not have been carried out in the human, such as Markee's direct visualization of endometrial tissue transplanted to the anterior chamber of the eye (21) and Sturgis' studies on follicular atresia (31).

Thus, our knowledge of menstrual physiology has developed largely through relatively recent studies, in the rhesus monkey. It must be re-emphasized, however, that any hypotheses concerning menstruation derived from monkey investigations and applied to the human, are conditional on the possibility of significant differences, despite strong interspecies similarities.

PHYSIOLOGY

Cellular regression and replacement are characteristic features of life cycles of most tissues, and the cyclic shedding of the uterine endometrium is one of the most dramatic examples. The human endometrium may undergo growth and proliferation followed by shedding of its superficial portion some 300-400 times during reproductive life! The accompanying bleeding is self-limited and restoration of endometrial integrity begins almost immediately after onset of desquamation. Perhaps the most outstanding contribution to our knowledge of events in the endometrial cycle was provided by Markee (21) in 1940. Transplanting fragments of endometrial tissue to the anterior chamber of the eye of the rhesus monkey, Markee was able to observe the endometrium directly, continuously, and at high magnification. His description of endometrial changes through many cycles is classic both for its ingenious technique and for its invaluable information.

Endometrial Growth Cycle

Four periods in the endometrial growth cycle were recognized, beginning with a resting phase of variable length from the end of the last bleeding phase to the onset of endometrial growth. An initial period of growth lasted 8-15 days, during which some of the ocular transplants increased up to threefold in size. Slight regression occurred at about ovulation time, followed by a second period of growth during which transplanted fragments again doubled or tripled in area. Finally a period of regression decreased transplants to their original size. Bleeding occurred on the second to seventh day of regression when the area occupied by each endometrial fragment had decreased 25-75

per cent. Onset of regression varied from one transplant to another even in the same animal. Although menstruation was always preceded by regressive changes in the endometrium, regression was not always followed by menstruation.

VASCULAR CHANGES AND BLOOD FLOW

Markee paid particular attention to the vasculature of the endometrium, having previously demonstrated rhythmic fluctuations in endometrial vascularity with blanching before menstruation (20). He observed that regression of the endometrium was preceded by decreased blood flow through endometrial vessels. Two types of arteries were recognized. The basal one-third of the endometrium receives its blood supply from straight, short arteries, while the superficial two-thirds derives its blood supply from coiled vessels. These two types of vessels can be recognized histologically, coiled arteries have thicker walls and a larger diameter. During endometrial growth coiled arteries lengthen, and their rate of linear growth exceeds that at which the endometrium thickens. Consequently, tips of the coiled vessels closely approach the epithelial surface. Similarly, as the phase of endometrial regression begins, thickness of the endometrium diminishes more rapidly than arterial length. Both of these processes result in an increased arterial coiling and a closer proximity of vessels to the endometrial surface.

As a consequence of increased vascular coiling and subsequent compression, the blood flow through coiled vessels is slowed during the phase of endometrial regression. Stasis of flow is accompanied by vasodilatation, varying in incidence, duration and degree. Menstruation usually begins within 4 days of vascular compression. No extravasation of blood occurs during vasodilatation; prior to the onset of menstruation, vasodilatation gives way to a period of vasoconstriction. Coiled vessels which supply blood to the superficial two-thirds of the endometrium contract 4-24 hours prior to bleeding producing ischemia of the superficial portion of endometrium. The straight arteries do not constrict, leaving blood supply to the basal endometrium uncompromised.

During the period of stasis, leukocytes migrate through capillary walls, first into stroma immediately adjacent to the capillary and ultimately into surrounding stroma. Bartelmez (3) considered leukocytic infiltration a constant criterion for histologic diagnosis of "impending menstruation," and even speculated that leukocytes may function to accelerate tissue destruction.

PHYSIOLOGY OF MENSTRUATION

After coiled arteries have been constricted for several hours, blood escapes from their branches. In Markee's ocular transplants 5 types of menstrual bleeding were found: 1. Hemorrhage from hematomata formed after breakage in a capillary or arteriole wall; 2. Direct bleeding from capillaries or arterioles through epithelium without hematoma formation; 3. Diapedesis of blood cells through capillary walls; 4. Venous bleeding from vessels opened by shed tissue; and 5. Secondary bleeding from defects in arteriolar walls.

Little tissue is lost in the first 12 hours, but thereafter tissue fragments become detached and are shed. The amount of tissue lost seems to correlate with the degree of coiling in superficial arteries: the more highly developed the coiled arteries, the more tissue is lost.

CHANGES IN ENDOMETRIAL LAYERS

During an ovulatory menstrual cycle, endometrium may increase in thickness from 0.5–5 mm. or more (4). Loss of thickness during regression and menstruation can be accounted for by dehydration of tissue as well as by tissue loss. A number of investigators have postulated that during menstruation the superficial compact layer of endometrium and the intermediate stratum spongiosum are both completely sheared off, and that regeneration occurs from the basal layer. Bartelmez (4), however, has indicated that some of the spongiosum remains in place and dedifferentiates to reorganize into new epithelium. The persistence of residual tissue superficial to the basal layer is supported by McClennan and Rydell who feel that, in the human, newly regenerated endometrial surface is usually derived from active endometrium which has already participated in secretory activity. Even as late as cycle days 3 and 4, portions of the spongiosum are retained, but McClennan has been unable to find remnants of the stratum compactum during menstruation. Considerable variation, however, can be seen from one uterus to another, as well as in different regions of the same uterus.

In Markee's studies, regeneration of the vascular system is initiated shortly after rupture sites in the coiled arteries are plugged. With relaxation of the basal portions of coiled arteries, blood flow is restored, and new capillaries sprout from the functional zone. The restoration of an adequate circulation may be correlated with termination of menstrual flow.

Cyclic growth and regression associated with periodic menstruation normally persists throughout reproductive life in higher primates, interrupted physiologically only by pregnancy and lactation. As early

as 1897, Heape observed that corpora lutea were *not* present during every menstrual period in the rhesus monkey, and commented that ovulation was *not* a consistent event in every cycle. Corner later confirmed these observations (8) and also found a greater cycle regularity in late winter and spring, with cycles of excessive lengths occurring between June and January. Such observations probably delayed recognition of the now well-recognized temporal relationship between ovulation and menstruation. They may also have provoked Corner's statement that the "occurrence of regular menstruation without corresponding cyclic maturation of follicles and corpora lutea in the ovary is a phenomenon beyond the scope of current theories of ovarian physiology, and offers new complications and difficulties in the way of continued investigation of the primate reproductive cycle." (8) Thus the enigmatic phenomenon of anovulatory cycles was recognized. Markee was able to distinguish only a small number of subtle dissimilarities in the behavior of intraocular implants in ovulatory and in anovulatory cycles. In the ovulatory cycle he noted greater development of coiled arteries, more prominent vasodilatation, closer approximation of coiled arteries to the surface, increased blood loss, more endometrial desquamation and larger shed fragments.

HISTOLOGICAL FEATURES OF ENDOMETRIAL RESTORATION

In the ovulatory cycle, once menstrual flow has started, restoration of endometrium begins. These progressive changes in the human have been described in detail by Noyes, Hertig, and Rock. Proliferative changes characterize the endometrial response to estrogen in the pre-ovulatory phase of the cycle. Initially the surface epithelium is thin, but glands begin to become more tortuous and lining epithelium becomes composed of tall columnar cells. Mitoses can soon be seen in the glandular epithelium; pseudostratification is apparent (Fig. 1A); nuclei of stromal cells seem isolated and stromal mitoses can be recognized. Later in the proliferative phase stroma becomes dense (Fig. 1B) and degree of pseudostratification increases. Following ovulation, endometrial glandular secretory changes begin. Glandular tortuosity increases further, and subnuclear vacuoles can be recognized in the glandular epithelium. The gland nuclei seem pushed to the center of the epithelial cells (Fig. 1C); pseudostratification decreases; and by the third to fourth postovulatory day secretion can be seen in the gland lumina. The vacuoles become displaced to the supranuclear portion of the epithelium. Secretion reaches a maximum approximately 6 days after ovulation (Fig. 1D). By the eighth postovulatory