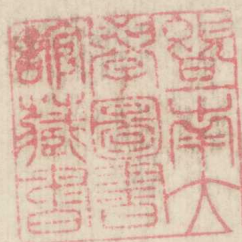


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Research of Contraceptive
Agents for Male

男 用 避 孕 药 研 究

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Selected Papers on Planned Parenthood

Vol. 6

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3665

**Research of
Contraceptive Agents
for Male**



October 1975

中 文 摘 要

综 述

The Male Reproductive System

3

男性生殖系统生理机能文献综述

本文阐述了近年来关于男性生殖生理研究的几方面进展:

- (一) 睾丸中液体产生的动力学: 包括睾丸血流的测定, 影响血流的因素, 逆流换热机制, 曲精细管内液体产生及其影响因素。
- (二) 睾丸中的酶: 酸性磷酸酶, 氨基酐酶, 己糖激酶, 乳酸脱氢酶, 山梨醇脱氢酶等。
- (三) 曲精细管中的激素: 雄激素的产生, 对 FSH 水平的调节。

Control of Fertility in the Male

27

雄性生育控制

本文介绍了男性避孕的三种可能途径: (1) 精子发生过程, 包括精子排放与运转的干扰; (2) 干扰精子在副睾中的成熟过程; (3) 干扰副性腺的正常生理活动。然后分别阐述干扰下丘脑——垂体——性腺轴药物、直接抗精子发生药物以及作用于副睾药物 (如 α -氯代甘油) 各自的作用机理及优缺点, 并指出今后研究的方向和途径。

精 子 发 生

Kinetics of Spermatogenesis in Mammals: Seminiferous Epithelium Cycle and Spermatogonial Renewal

42

哺乳类精子发生动力学: 生精上皮周期及精原细胞更新

本文全面而详尽地综述了哺乳动物的生精过程以及精原细胞的更新模式。

文中首先介绍了哺乳动物睾丸中曲精细管内的各类细胞的特点, 然后叙述整个生精过程。在叙述生精过程中, 提出了生精周期和生精细胞组合的概念。最后综述了大鼠、小鼠、田鼠、豚鼠、羊、牛、猴及人类精原细胞更新的模式。

Kinetics of the Human Seminiferous Epithelium

81

人类生精上皮的动力学

本文首先讨论了哺乳动物精子发生的一般过程, 说明精子发生是一个严格而有序的动态过程。

然后将人睾丸曲精细管的组织结构与一般实验动物加以比较, 发现人类的精子发生的严格有序性不及其他动物, 指出了人类精子发生动力学上的几个特点。

本文最后介绍了用氚标记的胸腺嘧啶作为示踪物来测定人的整个生精周期的持续时间, 发现每个细胞周期延续 16 天, 整个生精过程占据 3.8 个周期, 故为 61 天左右。

男性生殖器官的超微结构

Human Sperm Head Ultrastructure: A Freeze-Etching Study

84

人类精子头部的超微结构

本文用冰冻状态下表面复制以超薄切片方法研究人类的精子。介绍用此法观察人类精子头部微细结构的结果,主要观察了核后区、顶体及核内容物,並与其他动物精子作了比较。

Fine Structural Observations on the Development of the Sperm Head in the Mouse

105

小鼠精子头部发育过程的超微结构观察

本文介绍了运用电子显微镜研究了小鼠精子形成过程的结果,主要描述了小鼠精子头部的形态发生过程。作者认为染色体先附于核膜上,然后开始有染色质的浓集,並描述了染色质的浓集过程。

Comparative Histochemical Localization of Lysosomal Enzymes in Mammalian Epididymides

129

哺乳类副睾中溶酶体酶类比较组织化学定位研究

本文用组织化学及电子显微镜的方法研究了公羊、家兔、大鼠和地鼠副睾中的溶酶体及溶酶体酶。(包括酸性磷酸酶, β -葡萄糖醛酸苷酶与非特异性酯酶)这些酶的活性一般在副睾体部的上皮细胞中最强。本文最后简要地讨论了这些溶酶体酶与副睾机能的关系。

The Ultrastructure of Accessory Sex Organs of the Male Rat I: Normal Structure

145

雄性大鼠副性腺的正常超微结构

本文系统地研究了正常大鼠前列腺及精囊的超微结构。根据细胞的结构可将大鼠的副性腺细胞分为三型:前列腺侧叶与精囊属第一型;凝固腺及前列腺后叶属第二型;前列腺腹叶属第三型。少量的生物化学研究也支持这种分型。这三型可以作为研究与人类同类动物结构的参考。

雄性内分泌研究

Sites of Hormone Production in the Mammalian Testis, & Their Significance in the Control of Male Fertility

163

哺乳动物睾丸中激素产生的部位及其在雄性生育控制中的意义

本文主要介绍了睾丸中曲精细管内支持细胞(又称为 Sertoli 细胞)的结构与机能。作者认为动物的正常生精机能依赖于 Sertoli 细胞所产生的雄激素。并认为干扰此细胞产生雄激素的机能也可能作为男性避孕的方法。

Evidence for a Specific Seminiferous Tubular Factor Affecting FSH Secretion in Man

173

人类曲精细管中一种影响 FSH 分泌的特殊因子

本文介绍了十五例淋巴瘤患者在作化疗过程中,睾丸活检以及体内性激素和促性腺激素水平。15例中有 10 例,由于化疗而造成完全性生精障碍。此 10 人血浆中的 FSH 比正常人高四倍,而 LH 水平正常,睾丸酮水平也正常。这表明曲精细管内(很可能是 Sertoli 细胞)可以产生一种抑制 FSH 分泌的因子。

The Effect of Castration & Testosterone Replacement on Sperm Maturation in the Hamster 阉割及睾丸酮对田鼠精子成熟的影响

185

正常田鼠经结扎或阉割后每日给 100 微克睾丸酮于田鼠的副睾体部, 20 天后, 可使副睾尾部精子的受精能力下降。结扎输精管或作输精管切除, 则在副睾尾部有新的精子积聚, 20 天后仍可维持受精能力。阉割后用睾丸酮处理可使精子受精能力恢复, 但与睾丸酮的用量有关。总之, 在田鼠中, 血液睾丸酮的水平对精子成熟起重要作用。

Effect of Low Doses of Synthetic Progesterone on Testicular Function

191

低剂量合成孕激素对睾丸机能的影响

给正常男性口服合成孕激素(氯地孕酮 500 mg/天; 炔诺酮 100 mg/天), 给药 7—15 周。给药前与给药后分别测定下列指标: 精子计数, 精液中果糖、涎酸、酸性磷酸酶、碱性磷酸酶与核酮酶水平。这些指标均未见与药物有关的规律性变化。故认为低剂量孕激素对睾丸机能无显著影响。服药以后也未见精子穿透宫颈粘液的能力有明显改变。

Evaluation of Relationship between Plasma Testosterone and Human Seminal Citric Acid

对人的血浆睾丸酮水平和精液柠檬酸含量之间相互关系的评价

198

测定 56 个男子(20 个正常, 26 个少精子, 和 10 个无精子)血浆中睾丸酮和精液中柠檬酸的含量, 得到有意义的关系, 即柠檬酸的含量可以作为表示睾丸分泌雄激素的指标, 这一方法即称为柠檬酸试验。

探索性男用避孕药研究

Comparative Effects of Some Antispermatic Chemicals

205

一些抗生精化合物效果的比较

本文叙述硝唑咪, 乙二醇二甲磺酸酯, 磷酸三甲酯和氯丙二醇对实验动物的生育力的影响, 以及它们的化学结构和生物活性间的关系, 并对遗传的危害作出粗浅的估价。

The Action of the Isomers of Dimethylmyleran on Spermatogenesis

220

具有烷化作用的酯类 VIII 2,5-已二醇二甲磺酸酯异构体对生精作用的影响

2,5-已二醇二甲磺酸酯的内消旋体和外消旋体对小白鼠均具有抑制精原细胞发育的作用, 前者作用较大, 后者毒性较低, 两者抑制雄性大白鼠的生精作用均较差。但是它们的 50% 混合物一次腹腔内注射 4 毫克/公斤时, 具有显著的作用。右旋异构体和左旋异构体与外消旋体一样, 具有同样的抗生育效应, 和内消旋体起协同作用。

Side Effects of Medicaments and Toxins on Seminal Quality

223

药物和毒素对精液品质的副反应

本文介绍了许多药物和毒物影响精液的组成和精子的品质, 又影响生精上皮、生精作用, 副性腺体以及射精过程。例如金属离子, 抗癌药物, 杀菌剂、激素, 镇静剂和抗高血压药物等。

抗生育化合物在雄性大白鼠体内的协同作用

雄性大白鼠腹腔内同时注射三乙撑三聚氰胺 (TEM, 0.01 毫克/公斤/日), 乙二醇二甲磺酸酯 (EDS, 10 毫克/公斤/日) 和氯丙二醇 (1.5 毫克/公斤/日) 后, 产生了抑制生育作用, 毁坏了生精过程至减数分裂各期, 使副睾的许多细管中找不到精子。停止用药后, 生育力迅速恢复至正常水平。但如按上述剂量单用一种或任二种合并应用, 都无降低生育力的效果。

Effects of Protease Inhibitors on the Fertilizing Capacity of Hamster Spermatozoa

233

蛋白酶抑制剂对田鼠受精能力的影响

用人工合成的蛋白酶抑制剂处理田鼠副睾精子, 可以抑制其受精能力, 而天然的胰蛋白酶抑制剂无此效应。用 0.003—0.005% 人工合成抑制剂处理后, 存活的仔胎数显著下降 ($P < 0.05$), 但仔胎外观及重量未受影响。

Prevention of Fertilization in Vitro by an Acrosim Inhibitor from Rete Testis Fluid of the Ram

239

公羊辜网液中顶体素抑制剂在体外抑制受精作用

公羊及公牛的辜网液中, 有浓度的胰蛋白酶抑制剂。此抑制剂在体外培养精子时可与精子的顶体形成复合物, 以达到防止受精的目的。

Purification of Aspermatogenic Substance in Bull Seminal Vesicle Fluid

243

公牛精囊中抗精子发生物质的提纯

将公牛精囊液给许多动物作肌肉或皮下注射, 可引起生精功能障碍, 本文介绍了这种引起生精障碍物质的提纯。每只小鼠每日注射一次, 总剂量达 2.5—3 毫克时就能引起生精障碍。此物质还能引起孕鼠体内的胚胎死亡。

Structure-Activity Studies with Chlorohydrins as Orally Active Male Antifertility Agents

245

口服有效的雄性抗生育剂——氯代醇类的化学结构和生物活性间关系的研究

作者制备了一系列氯丙二醇的结构类似物, 并用雄性大白鼠进行了抗生育试验, 其中有些化合物有效, 只有 1-氨基-3-氯代-丙-2-醇盐酸盐有显著的活性, 其他有效的衍生物被认为是在体内水解为上述化合物或氯丙二醇的缘故。将消旋-1-氨基-3-氯代-丙-2-醇拆分为旋光异构体, 可将生物活性和急性毒性分开, 即左旋异构体盐酸盐具有毒性低而有抗生育作用, 右旋异构体有毒而无抗生育作用。

Mechanism of Antifertility Action of Low Doses of α -Chlorohydrin in the Male Rat

253

低剂量氯代甘油对雄性大鼠抗生育作用的机制

对 Sprague-Dawley 大鼠, α -氯代甘油的最小有效剂量为 2.5 毫克/公斤/天。当剂量增加时, 出现抗生育效果快, 停药后恢复慢。剂量达 10 毫克/公斤/天时, 大鼠性腺及副性腺虽量变化不大, 但在交配后雌鼠生殖道中取出精子, 发现精子数目不变而活力极差, 很少精子能到达输卵管。若交配后 3—4 小时, 将精子直接取出注入卵巢, 则可以受精。未服药的大鼠精液可以使卵运转加速, 而服药大鼠的精液则不能。因此 α -氯代甘油抗生育作用最主要的机制可能是抑制精子的运转, 同时其精液中类似前列腺素等平滑肌刺激剂可能也受影响, 而间接抑制了卵的运转。

单次高剂量氯代甘油对大鼠副睾作用的超微结构病理学研究

本文用电子显微镜研究单次高剂量氯代甘油作用后大鼠副睾的变化。当剂量大于 30 mg/kg 时,可在副睾头部产生一个特异的病灶,有上皮的剥落,肉芽肿形成,最终副睾管完全阻塞。若剂量达 140 mg/kg 时,用药 2 小时后就有变化,达 48 小时时大部分管腔已闭塞。本文也讨论了氯代甘油抗生育作用的可能机理。

A New Orally Active Male Antifertility Agent 291

一种新的口服有效的雄性抗生育剂

左旋 1-氨基-3-氯代-丙-2-醇盐酸盐 (CL 88236) 是雄性化学不育剂,对大白鼠、小白鼠、田鼠及猴子均有效。最低有效剂量是:大白鼠 5—10 毫克/公斤/日;小白鼠、田鼠均为 100—300 毫克/公斤/日、猴子 15—100 毫克/公斤/日。大白鼠在处理的第 6 日出现不育,停药后能维持一周有效,一周后则恢复正常生育力,若用药一周,停药一周循环用药,可以维持不育。在有效剂量下,此药无激素、抗激素或抗生精作用的性质。它的抗生育作用显然是由于影响了副睾和输精管中的精子,它的毒性比氯丙二醇小,其对映体毒性大而无活性。作用机理、尚待阐明。

Antitesticular and Antifertility Activity of a Pipecolinomethyl-hydroxyindane in Rats 303

一种甲基哌啶基-甲基-羟基茚满对大白鼠的抗睾丸和抗生育的活性

雄性大白鼠用 DL-6-(N- α -甲基哌啶基-甲基)-5-羟基-茚满马来酸盐 (PMHI) 处理后,它的睾丸重量减少,生精作用和生育能力受到干扰,在 50 毫克/公斤/日的剂量时,使大白鼠睾丸重量减少的程度,比 WIN 18446, 硝基糠胺, Methallibure, 已烯雌酚等来得强,对使精囊,前列腺的重量减少的程度,比 Methallibure, 已烯雌酚等弱。同等剂量下,对雌性大白鼠的动情周期或生育力没有影响。

DL-6-(N- α -甲基哌啶基-甲基)-5-羟基-茚满马来酸盐 (PMHI) 使未成熟大白鼠、小白鼠、田鼠和豚鼠的睾丸重量减少,对于大白兔、狗和两种猴子也有相似的作用。它对未成熟大白鼠睾丸的作用,没有受到睾丸酮、促生殖激素、消旋-生育酚乙酸酯和蛋氨酸等药物的拮抗。大白鼠切除垂体时,它对睾丸重量的影响更为显著,表示它直接作用于睾丸,而且口服和皮下注射都有这种作用。

Effect of Aspirin upon Male Mouse Fertility 319

阿斯匹林对雄性小鼠生育力的影响

阿斯匹林是一种前列腺素合成的抑制剂。给原先次不育雄性小鼠口服阿斯匹林可以提高这些小鼠的生育能力。本文作者认为前列腺素可调节雄性动物的生育能力。在雄性小鼠中,前列腺素对生育力有一种负性的调节作用。

Seminal Fluid and Plasma Prostaglandin Responses to Aspirin in Normal Subjects 325

正常人精液和血浆中的前列腺素对阿斯匹林的反应

阿斯匹林和消炎痛在体内和体外都是前列腺素生物合成抑制剂,用放射免疫法证实阿斯匹林使正常男性精液中前列腺素 (E 和 F) 的含量明显降低,血浆中前列腺素也降低,前一效应可能是男性不育的因素。

本文介绍六组病人使用睾丸酮及黄体酮复剂以后对生精过程和血浆睾丸酮的影响。单纯用睾丸酮作皮下埋藏不足以引起生精抑制。在睾丸酮皮下埋藏的同时,口服炔诺酮或甲地孕酮,可在6—12周内,使精子计数下降达零。停药以后生精功能可以恢复。十六个病人在生精抑制时未发现血浆睾丸酮水平增加。

Successful Inhibition of Spermatogenesis in Man without Loss of Libido: A Potential New Approach to Male Contraception

343

一种不影响性欲而能抑制精子发生的男子节育新方法

八个有生育力的男性皮下埋藏睾丸酮及下列三种药物中的一种。(① Norgestrienone ② R 2323 ③ Norethindrone)。发现前二者可以使精子数目显著下降,但病人性欲性功能正常。因此,此二药物有可能成为男用避孕药。

一些实验技术及方法

Preparation of Spermatozoa for Electron and Light Microscopy

357

用于电子显微镜及光学显微镜研究的精子制备法

本文介绍了一种新的可供光学显微镜及电子显微镜研究的精子制备方法,根据此方法制备的标本十分利于观察与保存。

In Vivo Sperm Penetration and in Vitro Sperm Migration Tests

364

精子的体内穿透与精子体外移动测定

本文介绍了体内精子穿透及体外精子移动能力测定的二种标准方法。

体内精子穿透测定是在性交后测定宫颈管中下列指标:(1)精子总数;(2)活动精子数;(3)前向运动精子数。

体外精子移动测定是用毛细管法测定下列指标:(1)穿透距离;(2)穿透密度;(3)活动能力;(4)生存时间。

CONTENTS

Review

综述

The Male Reproductive System.....3	
男性生殖系统生理机能的文献综述	

(*Annual Review of Physiology*, V. 36, p. 307-330, 1974)

Control of Fertility in the Male27	
雄性生育控制	

(*Pharmacology & the Future of Man—Proceedings of the 5th International Congress on Pharmacology*, San Francisco 1972, p. 208-220, 1973)

Spermatogenesis

精子发生

Kinetics of Spermatogenesis in Mammals: Seminiferous Epithelium Cycle and Spermatogonial Renewal42	
----------------------------------------------------------------------------------------------------------	--

哺乳类精子发生动力学：生精上皮周期及精原细胞更新

(*Physiological Review*, V. 52, N. 1, p. 198-236, 1972)

Kinetics of the Human Seminiferous Epithelium81	
人类生精上皮的动力学	

(*Research in Reproduction*, V. 4, N. 1, p. 3-4, 1972)

Ultrastructure of Male Reproductive Organs

男性生殖器官的超微结构

Human Sperm Head Ultrastructure: a Freeze-Etching Study84	
人类精子头部的超微结构	

(*Journal of Ultrastructure Research*, V. 39, No. 5-6, p. 520-539, 1972)

Fine Structural Observations on the Development of the Sperm Head in the Mouse105	
-----------------------------------------------------------------------------------------	--

小鼠精子头部发育过程的超微结构观察

(*The American Journal of Anatomy*, V. 136, N. 3, p. 339-362, 1973)

Comparative Histochemical Localization of Lysosomal Enzymes in Mammalian Epididymide.....	129
-------------------------------------------------------------------------------------------	-----

哺乳类附睾中溶酶体酶类比较组织化学定位研究

(*Journal of Anatomy*, V. 111, Part. 3, p. 437-452, 1972)

The Ultrastructure of Accessory Sex Organs of the Male Rat I: Normal Structure	145
--------------------------------------------------------------------------------------	-----

雄性大鼠附性腺的正常超微结构

(*Zeitschrift für Zellforschung und Mikroskopische Anatomie-Cell & Tissue Research*, V. 137, N. 3, p. 345-359, 1973)

Male Hormone Research

雄性内分泌研究

Sites of Hormone Production in the Mammlian Testis, & Their Significance in the Control of Male Fertility	163
-----------------------------------------------------------------------------------------------------------------	-----

哺乳动物睾丸中激素产生的部位及其在雄性生育控制中的意义

(*British Medical Bulletin*, V. 26, N. 1, p. 87-91, 1970)

Evidence for A Specific Seminiferous Tubular Factor Affecting Follicle-Stimulating Hormone Secretion in Man.....	173
------------------------------------------------------------------------------------------------------------------	-----

人类曲精细管中一种影响 FSH 分泌的特殊因子

(*Journal of Clinical Investigation*, V. 51, p. 1009-1019, 1972)

The Effect of Castration & Testosterone Replacement on Sperm Maturation in the Hamster	185
----------------------------------------------------------------------------------------------	-----

睾丸酮及阉割对田鼠精子成熟的影响

(*Journal of Reproduction & Fertility*, V. 37, N. 2, p. 251-255, 1974)

Effect of Low Doses of Synthetic Progestine on Testicular Function	191
--------------------------------------------------------------------------	-----

低剂量合成孕素对睾丸机能的影响

(*International Journal of Fertility*, V, 17, N. 3, p. 113-119, 1972)

Evaluation of Relationship between Plasma Testosterone & Human Seminal Citric Acid.....	198
-----------------------------------------------------------------------------------------	-----

对人的血浆睾丸酮水平和精液柠檬酸含量之间关系的分析

(*Fertility & Sterility*, V. 23, N. 3, p. 168-171, 1972)

Research of Discoveral Contraceptive Agents for Male

探索性的男用避孕药研究

Comparative Effects of Some Antispermatogetic Chemicals.....	205
一些抗生精化合物效果的比较 (<i>Regulation of Mammalian Reproduction</i> , p. 257-270, 1973)	
Alkylating Esters VIII. The Action of the Isomers of Dimethylmyleran on Spermatogenesis	220
具有烷化作用的酯类: 2,5-己二醇二甲酸磺酸酯异构体对生精作用的影响 (<i>Experientia</i> , V. 30, N. 2, p. 178-179, 1974)	
Side Effects of Medicaments and Toxims on Seminal Quality.....	223
药物和毒素对精液品质的付作用 (<i>Medical Gynaecology Andrology and Sociology</i> , V. 7, N. 5-6, p. 7-10, 1972)	
The Synergistic Action of Antifertility Compounds in the Male Rat.....	228
各种抗生育化合物对雄性大白鼠的协同作用 (<i>Biology of Reproduction</i> , V. 9, N. 5, p. 544-548, 1973)	
Effects of Protease Inhibitors on the Fertilizing Capacity of Hamster Spermatozoa	233
蛋白酶抑制剂对田鼠受精能力的影响 (<i>Biology of Reproduction</i> , V. 9, N. 5, p. 533-537, 1973)	
Prevention of Fertilization in Vitro by an Acrosin Inhibitor from Rete Testis Fluid of the Ram.....	239
公羊睾网液中顶体素抑制剂在体外抑制受精作用 (<i>Journal of Reproduction & Fertility</i> , V. 34, N. 2, p. 385-388, 1973)	
Purification of Aspermatogetic Substance in Bull Seminal Vesicle Fluid ...	243
公羊精囊液中抗精子发生物质的提纯 (<i>Journal of Reproduction & Fertility</i> , V. 31, N. 2, p. 273-274, 1972)	
Structure-Activity Stubies with Chlorohydrins as Orally Active Male Antifertility Agents.....	245
口服有效的雄性抗生育剂——氯代甘油的化学结构和生物活性间的关系研究 (<i>Contraception</i> , V. 9, N. 5, p. 451-457, 1974)	
Mechanism of Antifertility Action of Low Doses of α -Chlorohydrin in the Male Rat	253
低剂量氯代甘油对雄性大鼠抗生育作用的机制 (<i>Journal of Reproduction & Fertility</i> , V. 38, N. 1, p. 1-10, 1974)	

The Ultrastructural Pathology of the Rat Epididymis after Administration of α -Chlorhydrin (U-5897) I: Effects of a Single High Dose	263
单次高剂量氯代甘油对大鼠附睾作用的超微结构病理学研究 (<i>The Anatomical Record</i> , V. 175, N. 2, p. 203-230, 1973)	
A New Orally Active Male Antifertility Agent.....	291
一种新的口服有效的雄性抗生育剂 (<i>Contraception</i> , V. 9, N. 5, p. 459-470, 1974)	
Antitesticular and Antifertility Activity of a Pipecolinomethyl-hydroxyindane in Rats	303
一种甲基哌啶基甲基羟基茛满对大白鼠抗睾丸和抗生育活性 (<i>Journal of Reproduction & Fertility</i> , V. 38, N. 2, p. 387-400, 1974)	
Effect of Aspirin upon Male Mouse Fertility.....	319
阿斯匹林对雄性小鼠生育力的影响 (<i>Prostaglandins</i> , N. 4, p. 285-290, 1973)	
Seminal Fluid & Plasma Prostaglandin Responses to Aspirin in Normal Subjects	325
正常人精液与血浆中的前列腺素对阿斯匹林的反应 (<i>Fertility & Sterility</i> , V. 24, N. 12, p. 977-978 1973)	
Control of Spermatogenesis in Men by Combined Administration of Progesterin & Androgen.....	327
合并使用孕素及雄酮对男子精子发生的控制 (<i>Contraception</i> , V. 8, N. 3, p. 191-206, 1973)	
Successful Inhibition of Spermatogenesis in Man without Loss of Libido: a Potential New Approach to Male Contraception	343
一种不影响性欲而能抑制精子发生的男子节育新方法 (<i>Contraception</i> , V. 8, N. 3, p. 207-217, 1973)	

Some Experimental Methods & Technic

一些实验方法与技术

Preparation of Spermatozoa for Electron and Light Microscopy	357
用于电子显微镜及光学显微镜研究的精子制备方法 (<i>Journal of Reproduction & Fertility</i> , V. 33, N. 1, p. 145-149, 1973)	
In Vivo Sperm Penetration and in Vitro Sperm Migration Test	364
精子的体内穿透与精子体外移动测定 (<i>Fertility & Sterility</i> , V. 24, N. 8, p. 584-591, 1973)	

Review

Review

THE MALE REPRODUCTIVE SYSTEM ♦1114

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INTRODUCTION

This paper marks the first appearance in the *Annual Review of Physiology* of a review devoted exclusively to male reproductive phenomena. Obviously space limitations make it impossible, under the circumstances, to comment on all articles published since the previous review on reproduction. Therefore, specific aspects of male reproduction have been selected for review in an attempt to update areas which appear of current interest in several laboratories. Even within these areas, the bulk of recent literature and space limitations force the use of secondary references for most earlier work, and citation of one or two papers in other cases where three or four would be preferable.

A number of recent reviews are available detailing many aspects of the male reproductive system which could not be covered here. The interested reader is referred to these for coverage of many facets of testicular (121) and epididymal (59) function, sperm transport (8) and testicular morphology (23), endocrinology (31), and pharmacology (64). Pre-1970 literature has been extensively summarized in recent treatises on male reproduction (68, 103, 107).

FLUID DYNAMICS IN THE TESTIS

In the last 10 to 15 years great strides have been made in understanding the dynamics of the fluids flowing into and out of the testes as a result of the development of adequate micro-methods of measuring blood, lymph, and testicular fluid flow. Since these fluids are responsible for supplying nutrients, hormones, and gases, and removing waste products and secretory products of the testes, it is clearly important that the processes involving these fluids be understood.

Earlier reviews have presented or referred to detailed methods for the measurement of blood flow (113, 142, 143) and have considered factors affecting blood flow and metabolism within the testis, epididymis, and scrotum, and discussed the blood

supply to the testis, testicular lymph, and lymphatics, and testicular fluid in the rete testis. Waites (140) has discussed the vascular role in countercurrent heat exchange in his review of temperature regulation in the testis.

Measurement of Blood Flow

As Setchell (113) has pointed out and documented with several references, one of the striking features of the vascular anatomy of the scrotal testis is the presence of a large number of convolutions in the internal spermatic artery in many species. This coiling of the artery occurs in the pampiniform plexus, just after the artery leaves the inguinal canal, with the convolutions forming a vascular cone. In primates there is only moderate coiling and in man the artery is nearly straight as it approaches the testis.

In the scrotal testis the veins usually arise within the substance of the testis and run either directly to the surface or to a central vein near the mediastinum. The veins then join the pampiniform plexus where they break up into many fine veins (numbering as many as 300 in a ram), which lie closely applied to the coils of the spermatic artery (141).

Within the testis the arteries follow different patterns of coiling on the surface and then descend into the interior portion of the testis, where they break down into arterioles and capillaries. In some cases there are arteriovenous anastomoses as well as capillaries (113).

Many of the techniques available for measuring blood flow cannot be used on reproductive organs because of the small size and slow flow rates of these organs in most species (113). Flowmeters employing electromagnetic or ultrasonic principles can be used for larger animals, but their application is limited. Use of the Fick principle, inert gas clearance rates, and indicator fractionation techniques have greatly enhanced our understanding of blood flow and its control.

Setchell (113) has also described methods of measuring the total venous outflow and of measuring capillary flow. Flowmeters—electromagnetic and ultrasonic devices that can be attached to arteries to measure inflow—present problems because the veins in the pampiniform plexus, if molested in exposing the internal spermatic artery, interfere with normal flow. Local thermal dilution methods also present difficulties because of the complex anatomy of the internal spermatic artery and veins. A diffusion method is described (113) which employs 4-aminoantipyrine as an indicator substance. This compound was originally used to measure uterine blood flow (62). This method also has been used with tritiated water as an indicator. The method is time consuming and there is no way of determining the proportion of the blood which is contributed by the testis itself and that which is contributed by the epididymis. Thus, while total metabolic change and total endocrine change can be determined, appropriate apportionment of these changes to segments of the testis and epididymis cannot be made. Capillary blood flow methods using ^{85}Kr and an indicator fractionation technique have also been reviewed in detail by Setchell. Other radioactive substance such as ^{86}Rb and 4-(^{131}I)-iodoantipyrine have been used as isotopes in blood flow techniques in the testis.

Jaffe & Free (65) recently developed a method of measuring blood flow in the

THE MALE REPRODUCTIVE SYSTEM

testis with a miniature friction flowmeter which operates at flowrates below the range of electronic flow sensors and can be used in arteries of the testis as small as 0.6 mm inside diameter.

The method relies on the measurement of the pressure drop across a small resistance. Using this technique, these investigators found very close agreement with methods using tritiated water and the Ludwig-type stromuhr procedure. The miniature friction flowmeter has been used successfully in monitoring the blood flow in the testis of a conscious rat up to 8 hr during treatment with various vasoactive substances. The method also permits the sampling of arterial-venous blood for analysis.

Factors Affecting Blood Flow

Using the method just described, Free & Jaffe (41) have reported large increases in testis tissue pressure caused by contractions in the testicular capsule which cause a concomitant increase in testis vein pressure and a small transient decrease in testis blood flow. When the testicular capsule was opened in the anesthetized rat, testis vein and artery pressure and blood flow were unaffected.

Infusion of epinephrine or norepinephrine into the spermatic artery of rats (65) or rams (142) led to a rapid vasoconstriction with a marked decrease in blood flow. The relationship of this finding to physiological events, however, remains obscure, as extensive treatment with large doses of epinephrine was necessary to cause significant changes in testes of rabbits and rats (50). On the other hand, definite relationships have been shown between testis function and crowding, social interaction, or other stresses (50), and adrenal contribution would likely play a role. Related to this is the recent report (136) that ACTH did not affect blood flow through the testis. Unfortunately, these workers (136) employed ^{86}Rb in an indicator fractionation technique, and the testis is one of three tissues known that partially excludes rubidium (113).

Other agents which can affect blood flow appear to be serotonin and prostaglandins (43), but the role of these compounds in normal *in vivo* function of the testis remains obscure.

Setchell (113) has reviewed several articles which indicate that the vascular bed of the testis is relatively unresponsive to heat changes, unlike most other organs where similar temperature changes bring increases in blood flow with increased temperatures and decreases with decreased temperatures. He also points out that blood flow to the testis increases following periods of vascular occlusion. Blood flow through the testis is also affected by the posture of the animal. This was found to be true when the scrotum the the ram was raised to the level of the heart, causing a doubling of the blood flow through the testis. Setchell (113) and Gunn & Gould (54) have reviewed, in some detail, the evidence for vascular disruption in the testis as a result of the effects of cadmium salts, which cause an immediate and profound fall in testicular blood flow. Other organs respond with only a slight reduction in blood flow as a result of the effects of cadmium salts.

Johnson & Turner (69) have confirmed the effects of cadmium on blood flow in the testis of the rat showing an increase 1 hr following the administration of