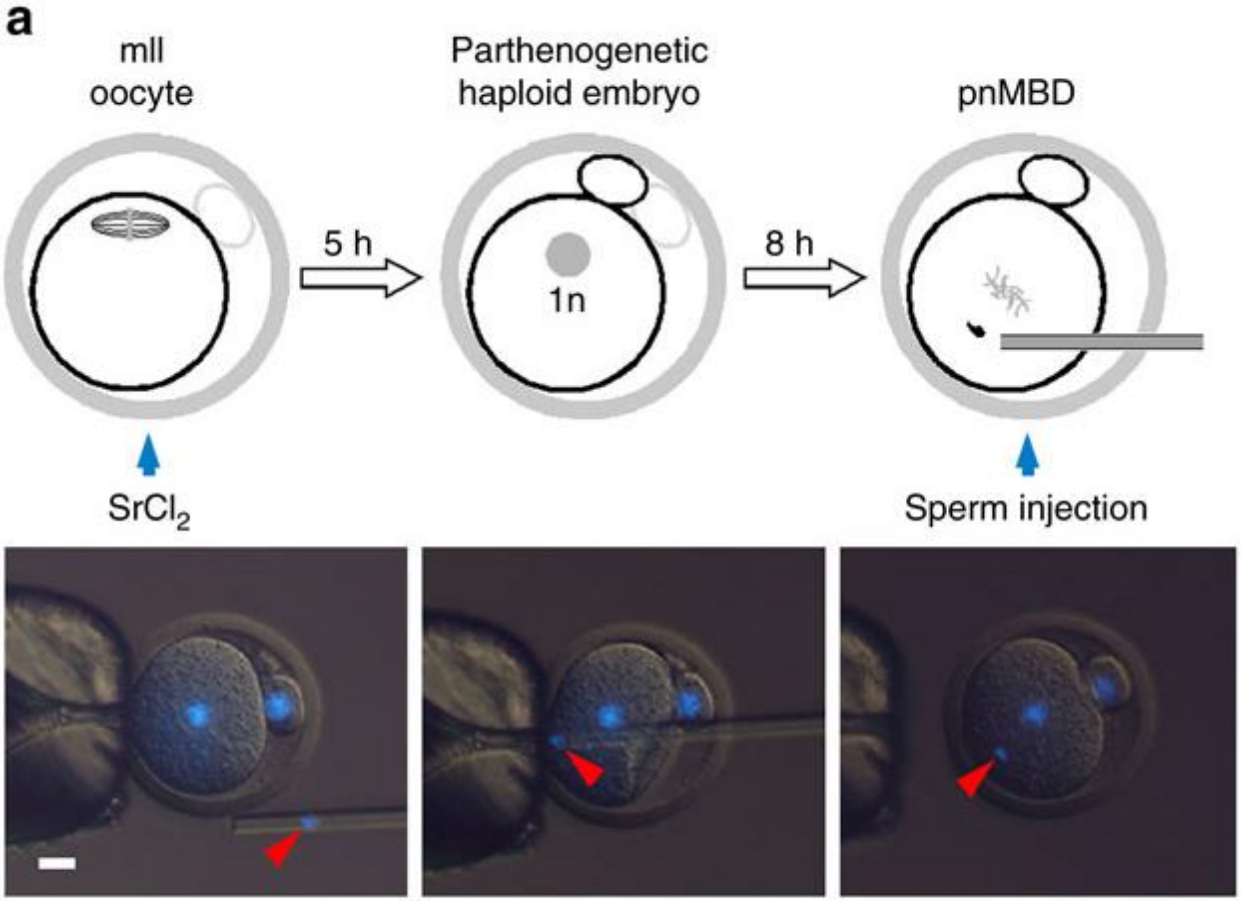
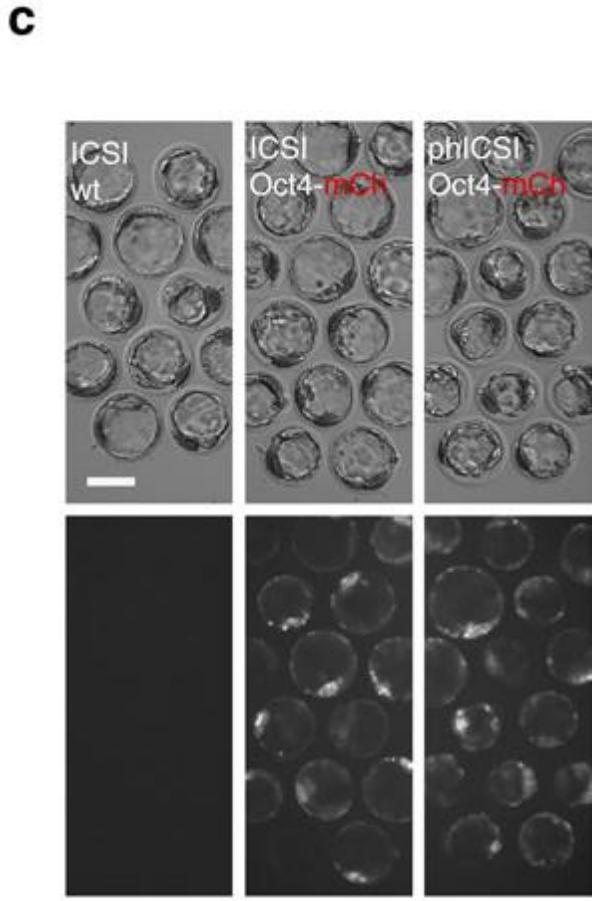
Professor Gerald Schatten
University of Pittsburgh School of Medicine

Why can't a woman be more like a man?*

***From A HYMN TO HIM in**
MY FAIR LADY
music by Frederick Loewe; lyrics by Alan Jay Lerner

Disclosure information: Nothing to declare





WEDNESDAY, SEP 14, 2016 **A masculine conception: Women may not be needed in the future of baby-making**

BBC News **Making babies without eggs may be possible, say scientists**

Gay Men Could Have Babies Together with Both Men's DNA According to Breakthrough Skin Cell Research

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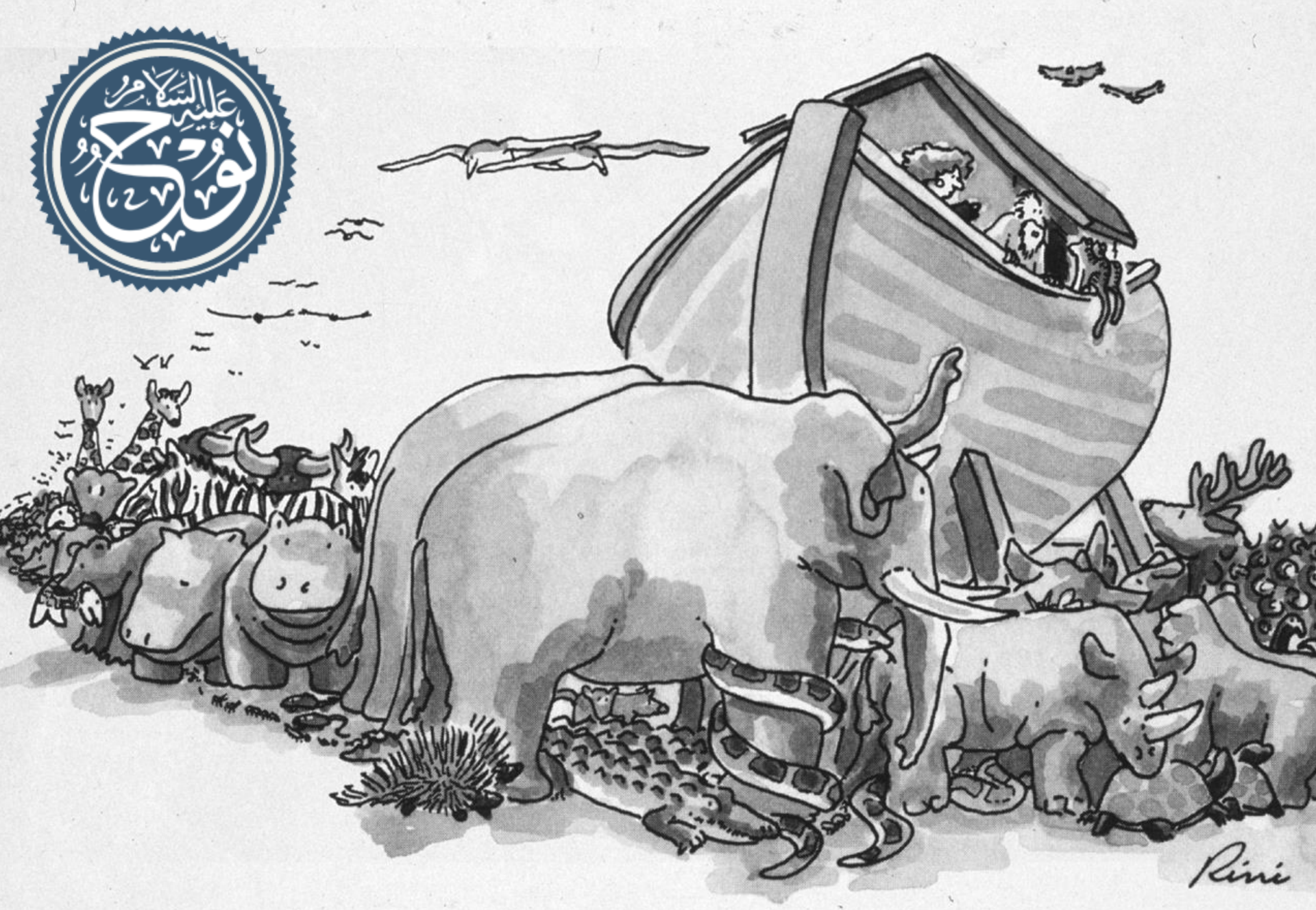


"Actually, we're only taking tissue samples."

Designer Babies?

doi:10.1038/nature20556

Zika virus infection damages the testes in mice

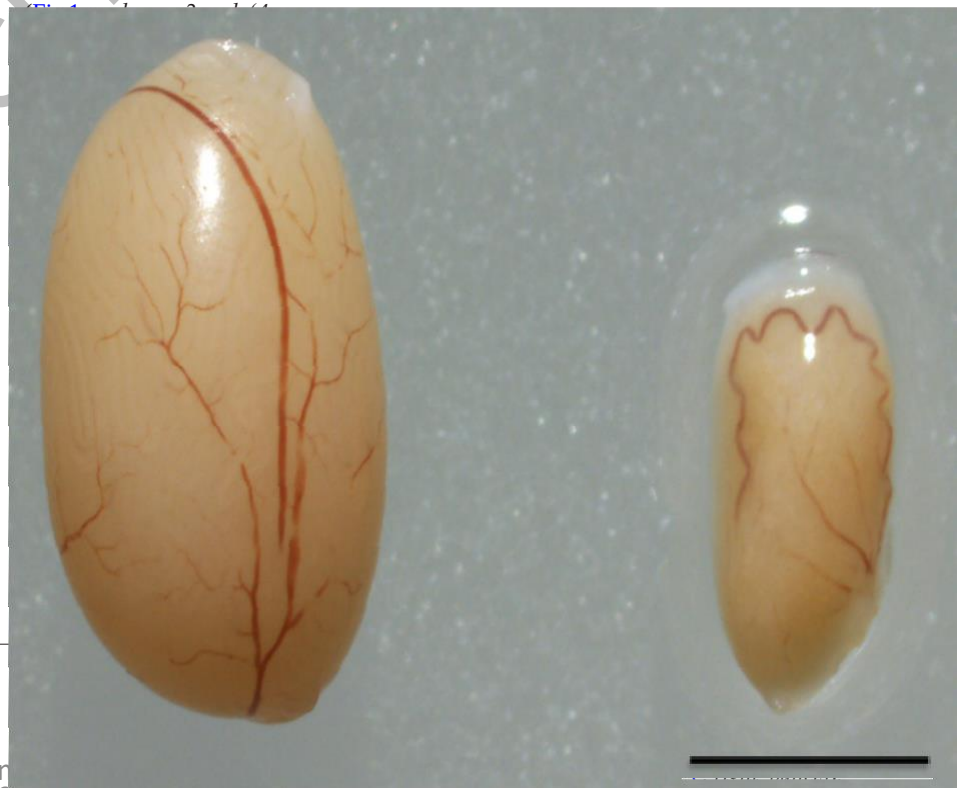
Jennifer Govero[1]*, Prabagaran Esakky[2]*, Suzanne M. Scheaffer[2], Estefania Fernandez[3], Andrea Drury[2], Derek J. Platt[4], Matthew J. Gorman[3], Justin M. Richner[1], Elizabeth A. Caine[1], Vanessa Salazar[1], Kelle H. Moley[2,5] & Michael S. Diamond[1,3,4,6]

Zika virus (ZIKV) infection of pregnant women can cause congenital malformations including microcephaly, which has focused global attention on this emerging pathogen[1]. In addition to transmission by mosquitoes, ZIKV can be detected in the seminal fluid of affected males for extended periods of time and transmitted sexually[2]. Here, using a mouse-adapted African ZIKV strain (Dakar 41519), we evaluated the consequences of infection in the male reproductive tract of mice. We observed persistence of ZIKV, but not the closely related Dengue virus (DENV), in the testis and epididymis of male mice, and this was associated with tissue injury that caused diminished testosterone and inhibin B levels, and oligospermia. ZIKV preferentially infected spermatogonia, primary spermatocytes, and Sertoli cells in the testis, resulting in cell death and destruction of the seminiferous tubules. Less damage was observed with a contemporary Asian ZIKV strain (H/PF/2013), in part because this virus replicates less efficiently in mice. The extent to which these observations in mice translate to humans remains unclear, but longitudinal studies of sperm function and viability in ZIKV-infected humans seem warranted.

We and others have observed that ZIKV infection of male adult mice results in infection of the testes[3,4], which is consistent with observed male-to-female[5,6] and male-to-male[7] sexual transmission in humans. To address the consequences of infection on the male reproductive tract, we performed a longitudinal study in wild-type (WT) C57BL/6 mice infected with ZIKV (strains H/PF/2013 (French Polynesia 2013) or mouse-adapted Dakar 41519 (Senegal 1984)) or DENV serotype 2, strain D2S20). Because ZIKV and DENV do not efficiently antago- nize type I IFN signaling in mice compared to humans[8], animals were treated with a single dose of anti-Ifnar1 blocking monoclonal antibody to facilitate infection and dissemination. When WT mice were treated instead with an isotype control antibody and then infected, ZIKV RNA did not accumulate in the testes (Fig 1a.(

In the presence of anti-Ifnar1 antibody, high levels of viral RNA (10^5 to 10^8 focus-forming unit (FFU) equivalents/g or ml) and infectious virus (up to 10^8 plaque forming units (PFU)/g or ml) were detected in the testis, epididymis, and the fluid collected from the epididymis within seven days of infection with either of the two ZIKV strains but not DENV (Fig 1a–c). ZIKV-Dakar replicated to higher levels com- pared to ZIKV-French Polynesia, which is consistent with its enhanced virulence in WT mice[3]. Remarkably, ZIKV RNA and infectious virus also were detected in mature sperm harvested from the epididymis (Fig 1b–c, and Extended Data Fig 1). At day 7 after inoculation, ZIKV- infected testes appeared similar in size to uninfected testes from age- matched mice and had equivalent weights (Fig

column 1). The blood-testis-barrier (BTB) remained intact at day 7 after infection, as judged by equivalent staining of the ETV5 transcription factor (which mediates BTB function and testicular immune privilege[9]) in Sertoli and germ cells in sections from uninfected and ZIKV-infected mice (Fig 1g, *column 2*). Furthermore, there was no CD45 staining on the seminiferous tubular side of the BTB, near the TRA98$^+$ germ cells or spermatogonia (Fig 1g, *column 1*). A similar pattern of CD45 staining in the testicular interstitium and epididymal epithelium was described in patients infected with HIV[10]; indeed, we also observed scattered CD45$^+$ cells in the epididymal epithelium of ZIKV-infected mice (Fig 1g, *column 5*). However, at day 7, F4/80$^+$ macrophages were not apparent in the testicular interstitium or the lumenal epithelium of the epididymis of ZIKV-infected mice



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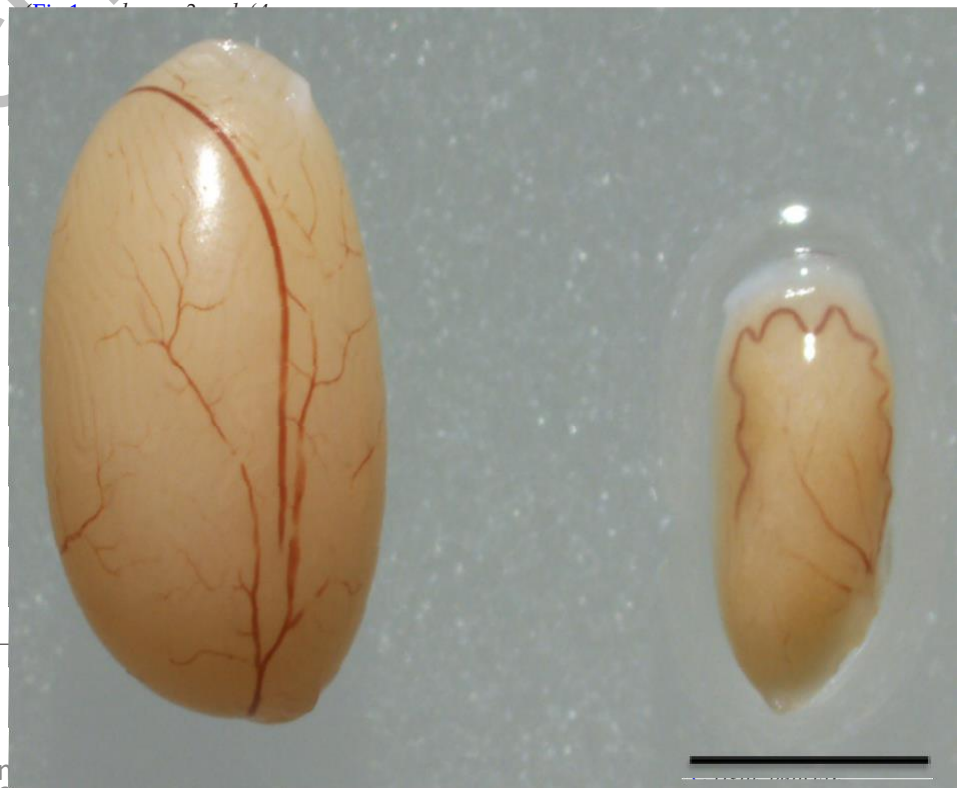


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FUNDAMENTAL SCIENCE QUESTIONS: WHYS, HOWS & IMPLICATIONS

♀ ≠ ♂: Sperm ≠ Eggs; Ovary ≠ Testis

Gestation: ♀ vs ♂

Natural vs Elective Sex Reversal

♀ vs ♂ Meiosis; Organs

Implications for ART & Society

J Assist Reprod Genet
DOI 10.1007/s10815-016-0814-1

REVIEW

Ovarian tissue cryopreservation and transplantation: scientific implications

Sherman Silber

Going beyond this, why should the oocyte begin meiosis and then be locked for a lifetime, while sperm are constantly produced by spermatogenic stem cells?
What is the benefit to the species of such a dichotomy?

The benefit of this dichotomy between spermatogenesis and oogenesis is that most of the mutations that occur in a species over many years occur during spermatogenesis in the testis, **as *xeroxing* errors**. The oocyte is spared that risk by not having to undergo recurrent mitosis. But of course the oocyte unfortunately ages, causing infertility.

These two mechanisms are wedded to each other evolutionarily. Without the mutations caused by spermatogenesis and thus constant germ cell error-prone duplication, there would be no evolution. However, without the locking of the oocyte and avoidance of constant duplication errors as what occurs in the sperm, the species would have no stability.

and recruitment of follicles in the adult ovary. As advancing our understanding of the mechanisms underlying primordial follicle recruitment and fetal oocyte meiotic arrest.

* Sherman Silber
silber@infertile.com

1 Infertility Center of St. Louis, 224 South Woods Mill Road, Suite 730, Saint Louis, MO 63017, USA

2 Sun Yat-Sen Medical School, Guangzhou, China

Published online: 08 October 2016

The developed world is in the midst of a widespread infertility epidemic. Economies in Japan, the USA, southern Europe, and even China are threatened by a decreasing population of young people having to support an increasing population of elderly and retirees [1]. Infertility clinics are popping up throughout the world in huge numbers because of a world-wide decline in fertility as women age and become less fertile [2]. In her teen years, a woman has a 0.2 % chance of being

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GLOBAL AGING

DAVOS SPECIAL REPORT It's not just Europe—China and other emerging-market economies are aging fast, too. There are solutions, but it's time to act. BY PETE ENGARDIO AND CAROL MATLACK (P. 40)

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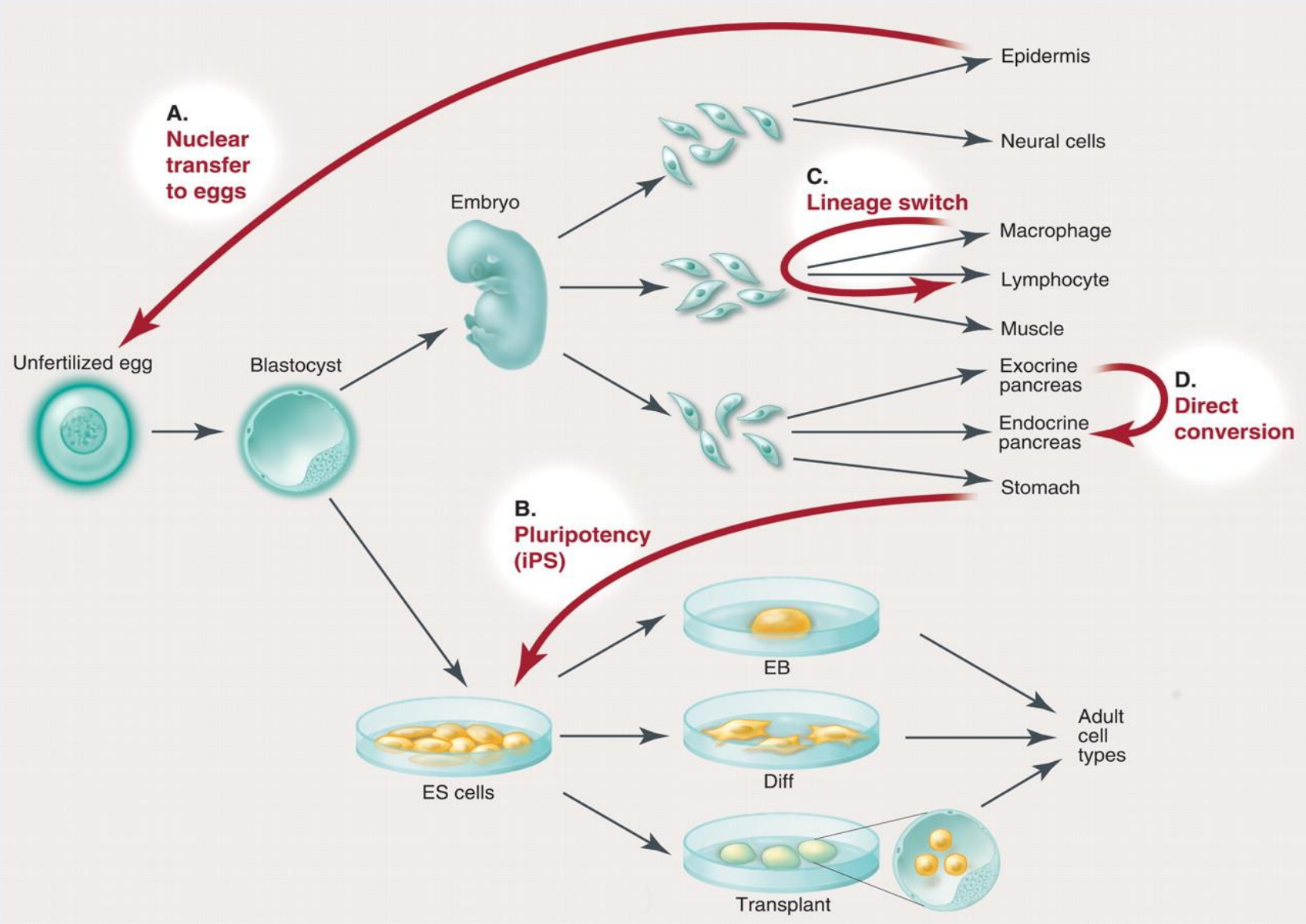
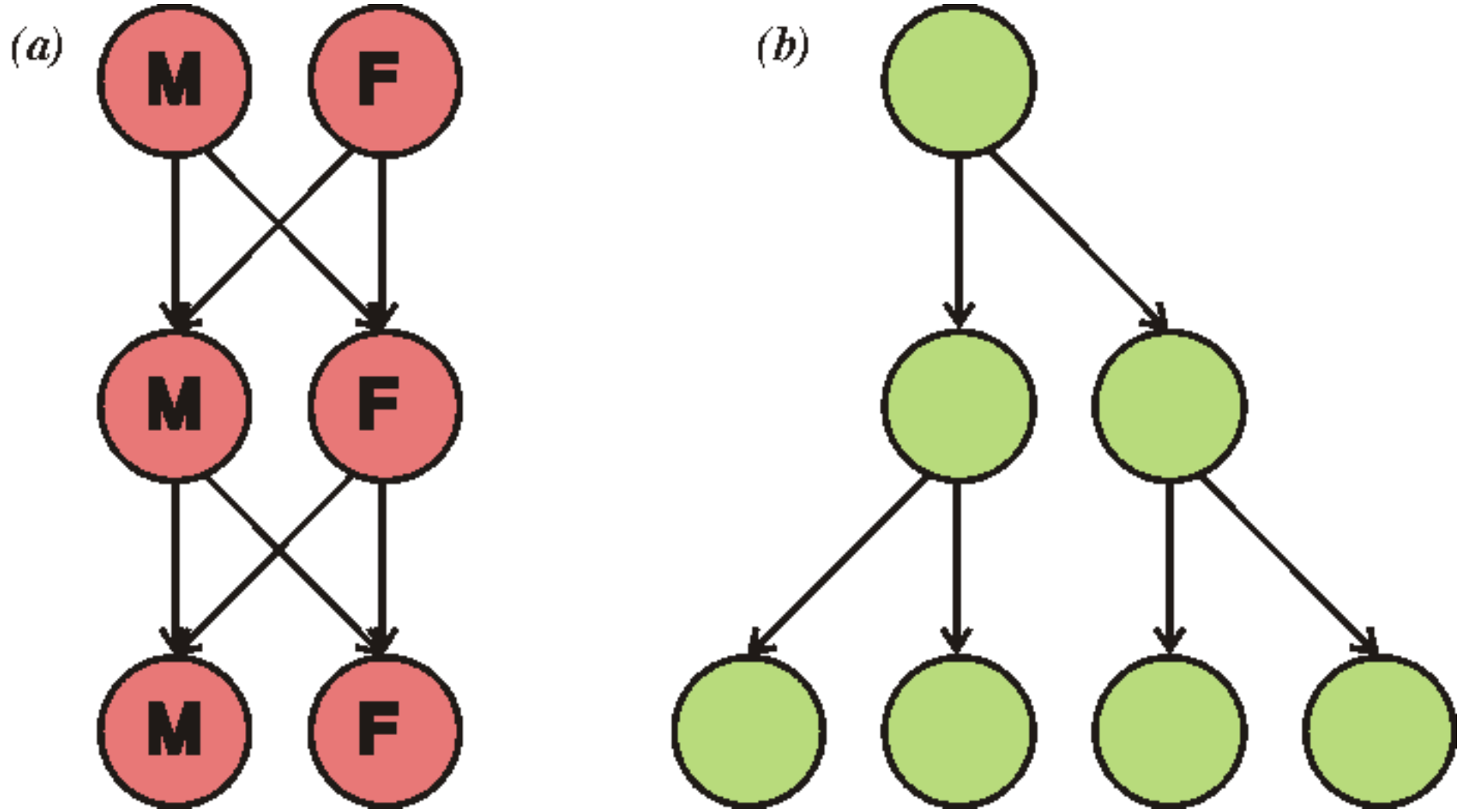


Birthdays are good for you - the more you have the longer you live.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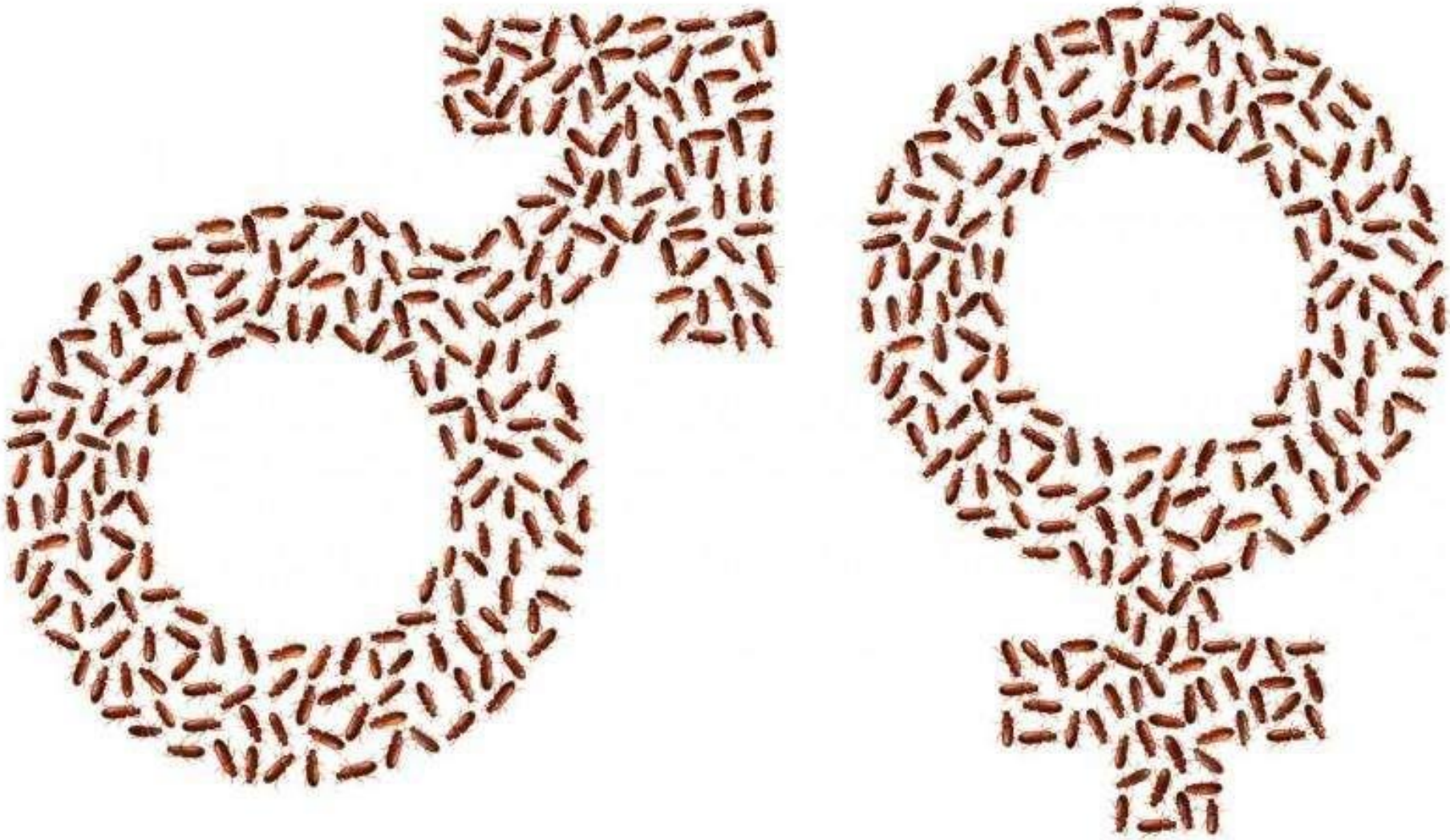

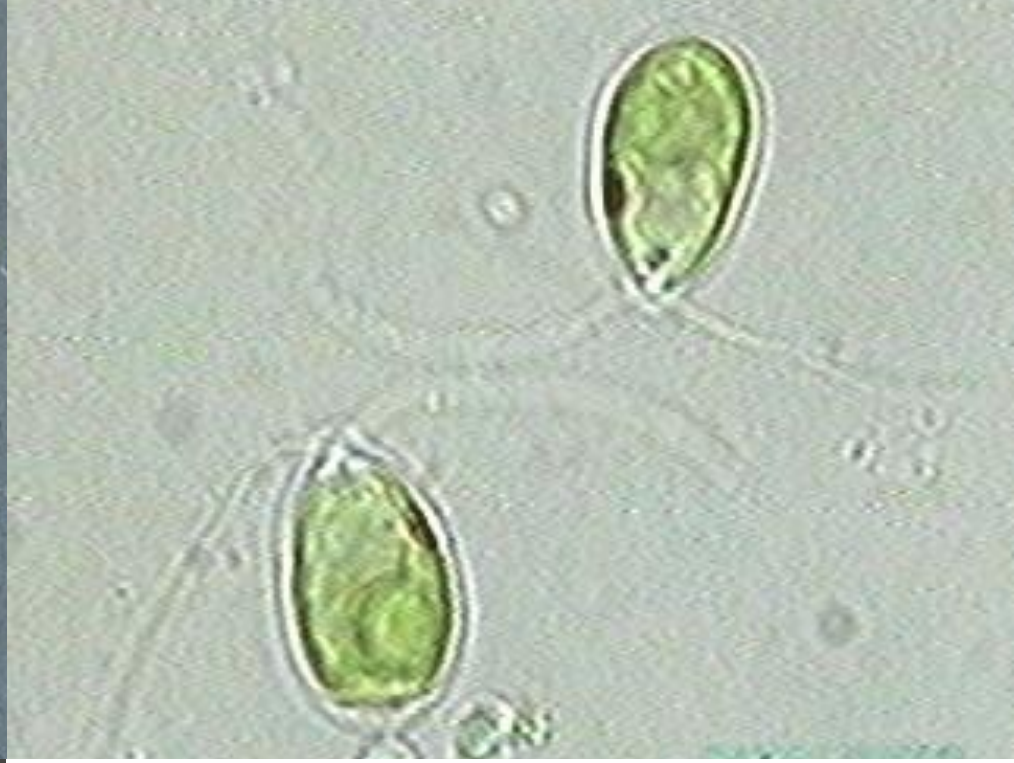

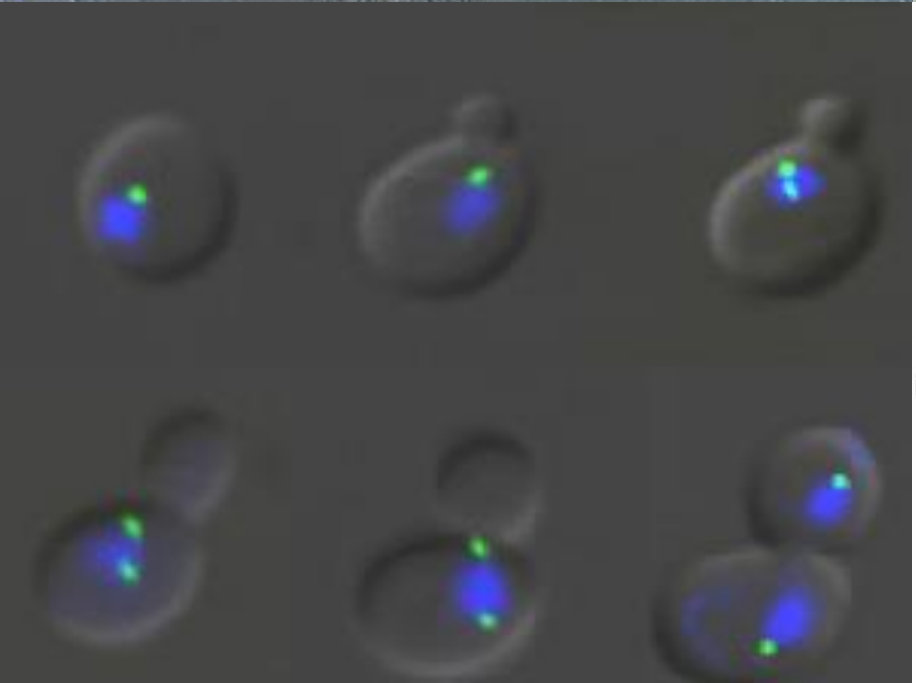

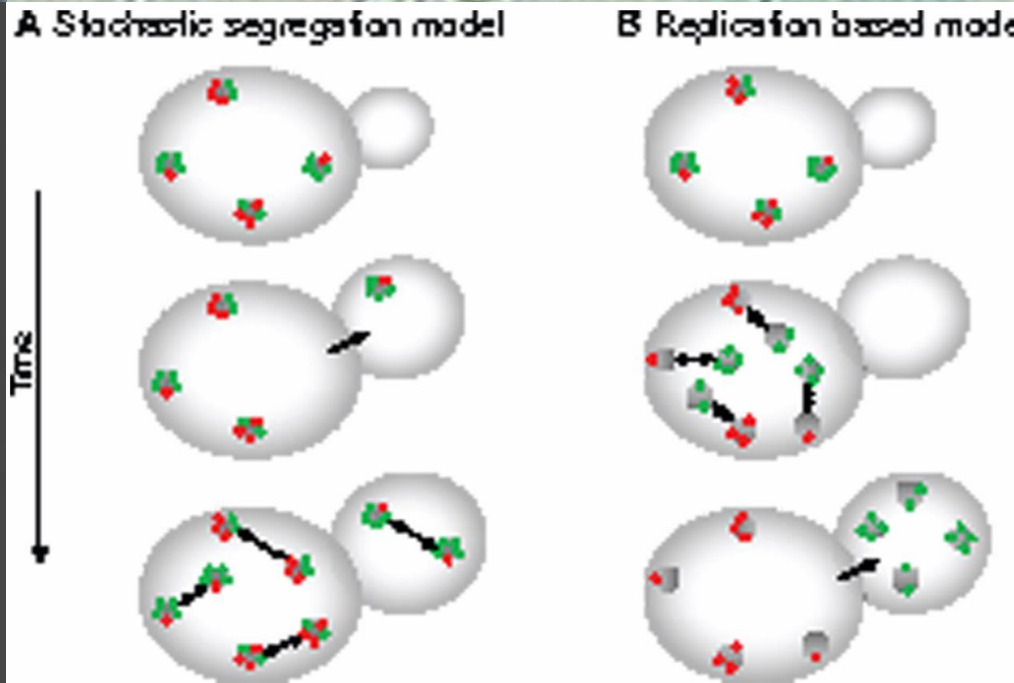
A Stochastic segregation model
B Replication based mode
Time

Volume 25
Number 10

May 18, 2015

Current Biology

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Gestational Surrogate
by Ben Kunz
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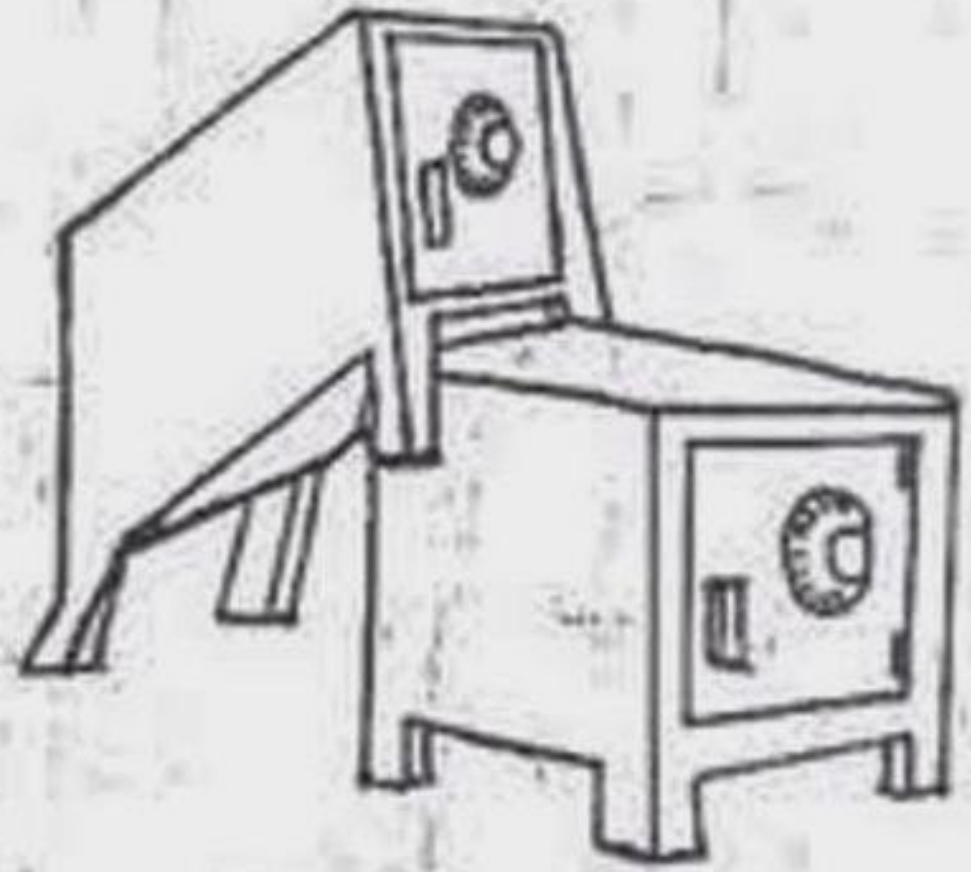
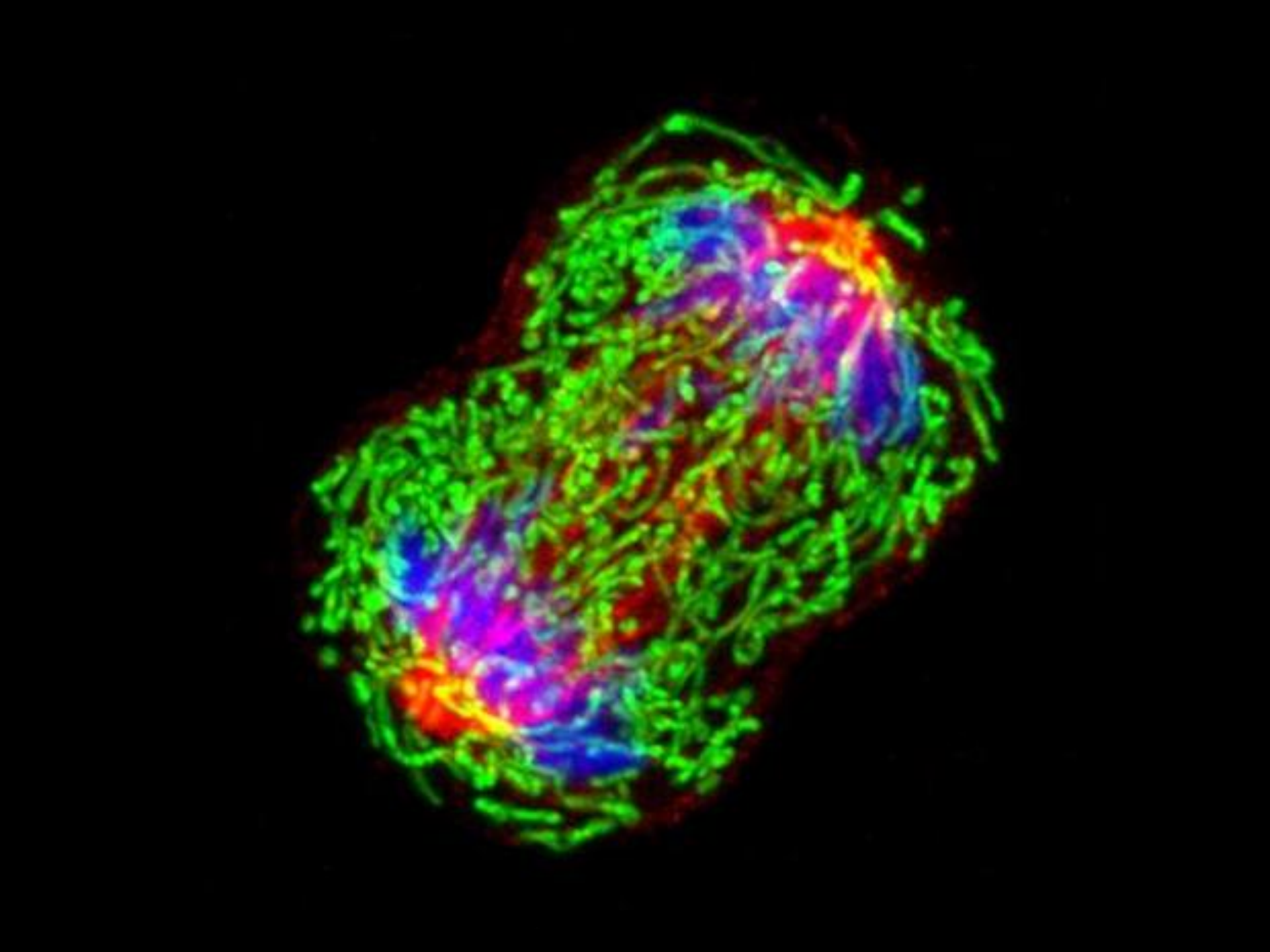
@benkunz
I'm really
digging
this phrase:
gestational
surrogate
GONNA



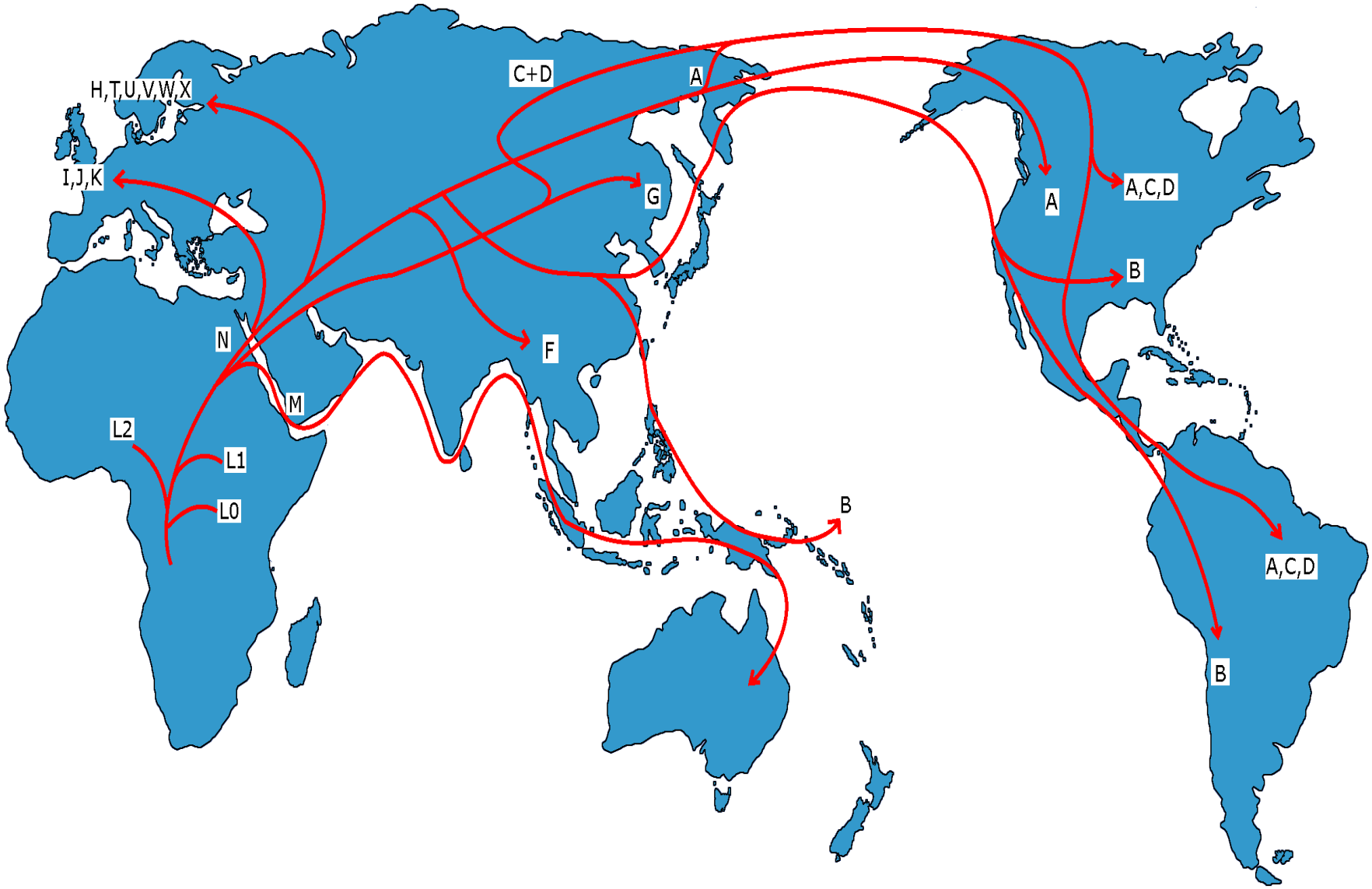
SAFE SEX

INFERTILITY & INDEPENDENCE

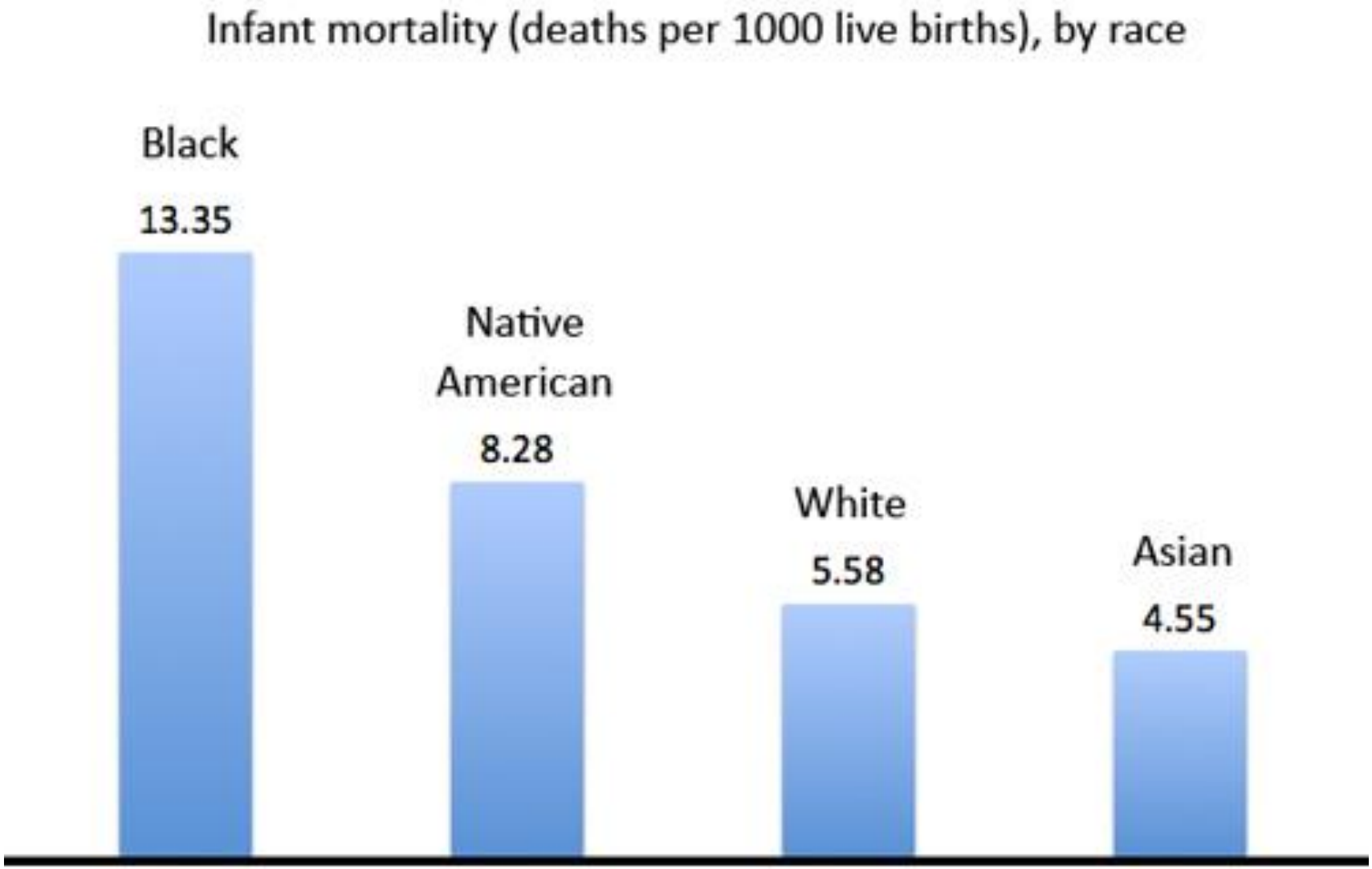
National Fathers, not Biological One…



mtDNA haplotypes



St. John & Tsai, 2016: http://www.ivf-worldwide.com/vaoeh/chapters/the-role-of-mitochondria-and-mitochondrial-dna-in-fertilisation-and-development-outcome.html


Infant mortality (deaths per 1000 live births), by race
Black
13.35
Native American
8.28
White
5.58
Asian
4.55

Infant birth-weights of African-born black women and U.S.-born white women are more closely related to one another than to the birth weights of infants of **U.S.-born black women**.

Brief Report

PATERNAL INHERITANCE OF MITOCHONDRIAL DNA

MARIANNE SCHWARTZ, PH.D,.
AND JOHN VISSING, M.D., PH.D.

MAMMALIAN mitochondrial DNA (mtDNA) is thought to be strictly maternally inherited.[1,2] Sperm mitochondria disappear in early embryogenesis by selective destruction, inactivation, or simple dilution by the vast surplus of oocyte mitochondria.[3]

Very small amounts of paternally inherited mtDNA have been detected by the polymerase chain reaction (PCR) in mice after several generations of interspecific backcrosses.[4] Studies of such hybrids and of mouse oocytes microinjected with sperm support the hypothesis that sperm mitochondria are targeted for destruction by nuclear-encoded proteins.[5-7] We report the case of a 28-year-old man with mitochondrial myopathy due to a novel 2-bp mtDNA deletion in the *ND2* gene (also known as *MTND2*), which encodes a subunit of the enzyme complex I of the mitochondrial respiratory chain. We determined that the mtDNA harboring the mutation was paternal in origin and accounted for 90 percent of the patient's muscle mtDNA.

CASE REPORT

The patient was a 28-year-old man with severe, lifelong exercise intolerance. He had never been able to run more than a few steps. His cardiac and pulmonary functions were normal, and he was otherwise well. Both parents and a 23-year-old sister were healthy and had normal exercise tolerance.

The myopathic symptoms were associated with severe lactic acidosis induced by minor physical exertion. His plasma lactate level after walking 100 m at a slow pace was 6 to 8 mmol per liter (the normal level is below 2.5 mmol per liter). His creatine kinase levels were marginally elevated in periods of no physical exertion. Biopsies of the right and left quadriceps muscle revealed that 15 percent of the fibers were of the ragged-red type, a result consistent with the accumulation of abnormal mitochondria with impaired respiratory function. Biochemical analysis demonstrated an isolated deficiency of the mitochondrial enzyme complex I of the respiratory chain in muscle. There were no signs of muscular atrophy or weakness. The abnormal findings in muscle-biopsy specimens from both thighs and the finding of severely impaired oxygen extraction when the forearm muscles were repeatedly contracted[8] suggested generalized muscular involvement.

METHODS

DNA was isolated from the patient's blood, muscle, hair roots, and fibroblasts (derived from a skin biopsy) by standard methods. DNA was also isolated from the blood of the patient's parents and paternal uncle, and from the blood and the quadriceps muscle of the patient's sister. The mtDNA was amplified into two products with the primers OLA (5756–5781) + D1B (282–255) and D1A (336–363) + OLB (5745–5721),[9] and the products were purified. We sequenced most of the mtDNA, including all transfer RNA (tRNA) genes, *CYTB,* and all seven genes encoding subunits of enzyme complex I, using a genetic analyzer (ABI PRISM 310, Applied Biosystems) and a terminator cycle-sequencing ready-reaction kit (ABI PRISM BigDye, Applied Biosystems). The sequences obtained were compared with the revised Cambridge reference sequence[10,11] (AC J01415) with use of the DNAsis program (Hitachi Software Engineering Europe.(

Two different mtDNA haplotypes were found in the patient; presumably, one came from the father and the other from the mother. Solid-phase minisequencing[12] was performed to establish the ratios of the mtDNA haplotypes in blood and muscle. The target was nucleotide position 3197, which, among others, distinguished the maternal haplotype (3197T) from the paternal one (3197C). PCR products spanning the position in question were generated by the 5'-biotinylated forward primer (3014–3034) and the reverse primer (3376–3356). PCR products were immobilized on a streptavidin-coated solid support (96-well plate) and denatured by sodium hydroxide. A sequencing primer (3220–3198) was designed to anneal adjacent to (upstream from) nucleotide .3197

The nucleotide at position 3197 was analyzed by the primer extension reaction, in which a tritium-labeled deoxynucleoside triphosphate corresponding to either the maternal nucleotide (deoxyadenosine triphosphate) or the paternal nucleotide (deoxyguanosine triphosphate) was added to two parallel reactions. After washing, the elongated primers were eluted by sodium hydroxide, and the amount of incorporated [^{3}H]deoxynucleoside monophosphate was determined with a liquid scintillation counter. The ratios of adenine to guanine incorporated into each sequencing primer were determined and compared with the values on a standard curve constructed on the basis of known proportions of cloned segments of mtDNA harboring 3197T and 3197C, respectively.

The ratio of the 2-bp deletion to wild-type mtDNA in tissues (the level of heteroplasmy) was determined by PCR fragment analysis. The mtDNA was amplified by the 5'-fluorochrome–labeled forward primer (5041–5060) and the reverse primer (5196–5177). The PCR products were analyzed on a genetic analyzer with a GeneScan standard (PE Applied Biosystems) as a size marker. The areas of the mutant (2-bp deletion) and wild-type peaks were used to calculate the percentage of mutant (paternal) mtDNA in the patient's muscle.

The nuclear genotypes of the patient, his parents, and his sister were determined for the highly polymorphic markers (microsatellites) D7S2212, D7S817, D19S219, D19S559, and TNFB. PCR products were analyzed on a genetic analyzer with GeneScan software (Applied Biosystems) and GeneScan standard as a size marker. The patient and his family

 DOI: 10.1534/genetics.103.025049

Paternal Mitochondrial DNA Transmission During Nonhuman Primate Nuclear Transfer

Justin C. St. John* and Gerald Schatten[†,1]

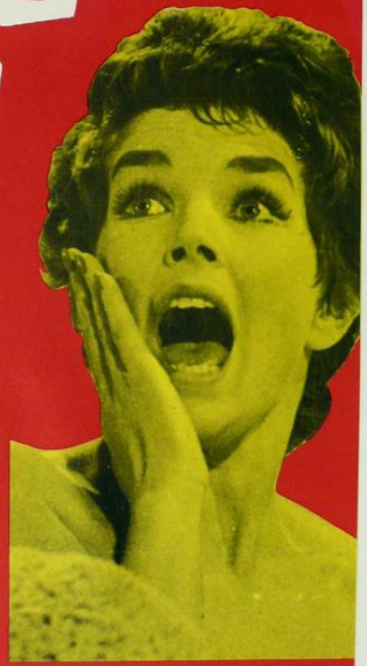
**Mitochondrial and Reproductive Genetics Group, Division of Medical Sciences, University of Birmingham, Birmingham B15 2TH, United Kingdom and [†]Pittsburgh Development Center, Magee-Women's Research Institute, Departments of Obstetrics-Gynecology-Reproductive Sciences and Cell Biology-Physiology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213*

ABSTRACT

Offspring produced by nuclear transfer (NT) have identical nuclear DNA (nDNA). However, mitochondrial DNA (mtDNA) inheritance could vary considerably. In sheep, homoplasmy is maintained since mtDNA is transmitted from the oocyte (recipient) only. In contrast, cattle are heteroplasmic, harboring a predominance of recipient mtDNA along with varying levels of donor mtDNA. We show that the **two nonhuman primate *Macaca mulatta* offspring born by NT have mtDNA from three sources: (1) maternal mtDNA from the recipient egg, (2) maternal mtDNA from the egg contributing to the donor blastomere, and (3) paternal mtDNA from the sperm that fertilized the egg from which the donor blastomere was isolated**. The introduction of foreign mtDNA into reconstructed recipient eggs has also been demonstrated in mice through pronuclear injection and in humans through cytoplasmic transfer. The mitochondrial triplasmy following *M. mulatta* NT reported here forces concerns regarding the parental origins of mtDNA in clinically reconstructed eggs. In addition, mtDNA heteroplasmy might result in the embryonic stem cell lines generated for experimental and therapeutic purposes ("therapeutic cloning.("

SOMETHING NEW SOMETHING EVIL
SOMETHING UNSPEAKABLY TERRIFYING

NIGHT OF THE LIVING DEAD



NO LOVE STORY, NO HERO,
NO HEROINE, NO MESSAGE,
NO QUESTIONS, NO ANSWERS

JUST TERROR

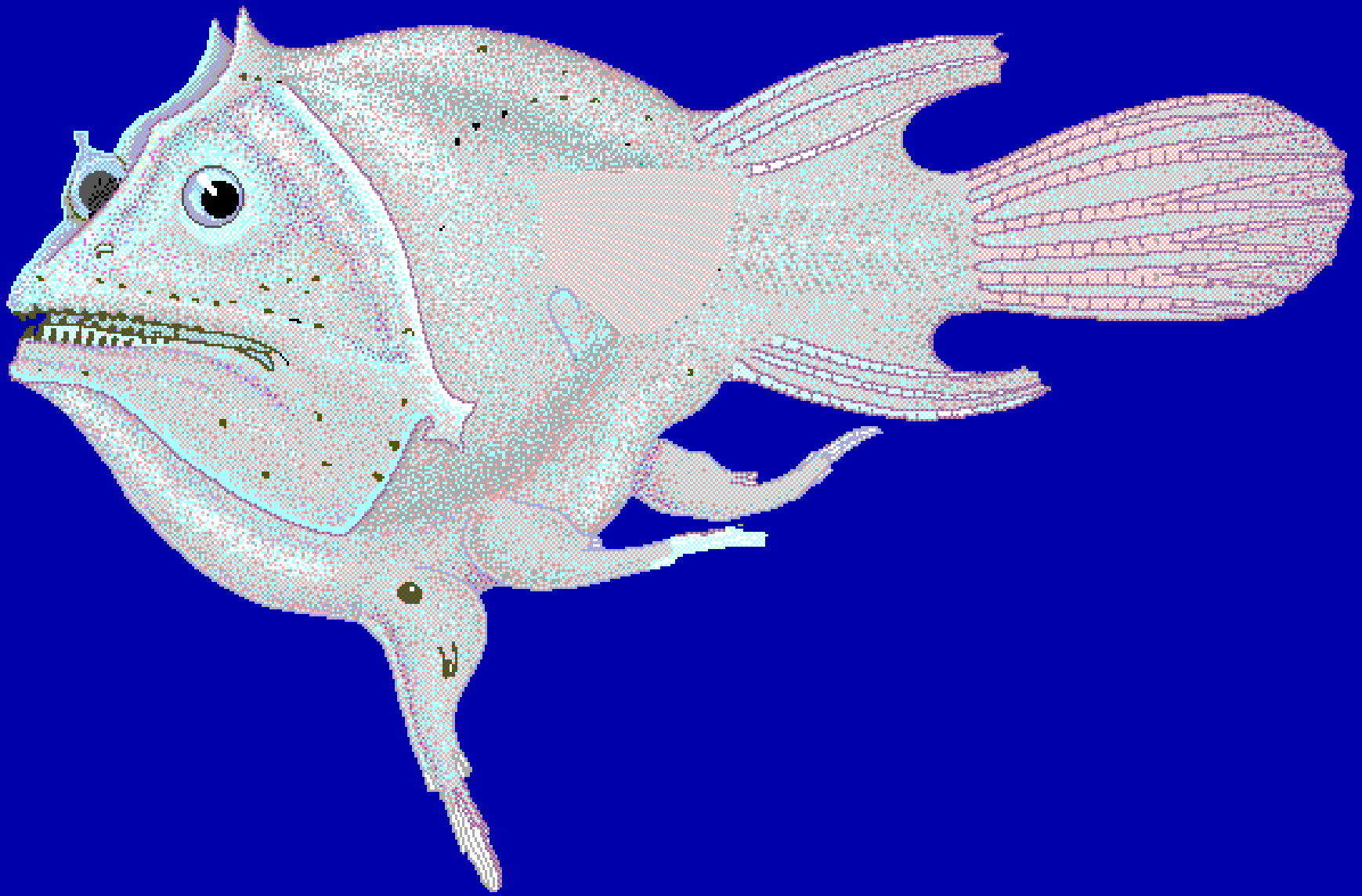
WHICH GNAWS AT YOUR VERY BEING

Starring JUDITH O'DEA · DUANE JONES · MARILYN EASTMAN · KARL HARDMAN · JUDITH RIDLEY · KEITH WAYNE

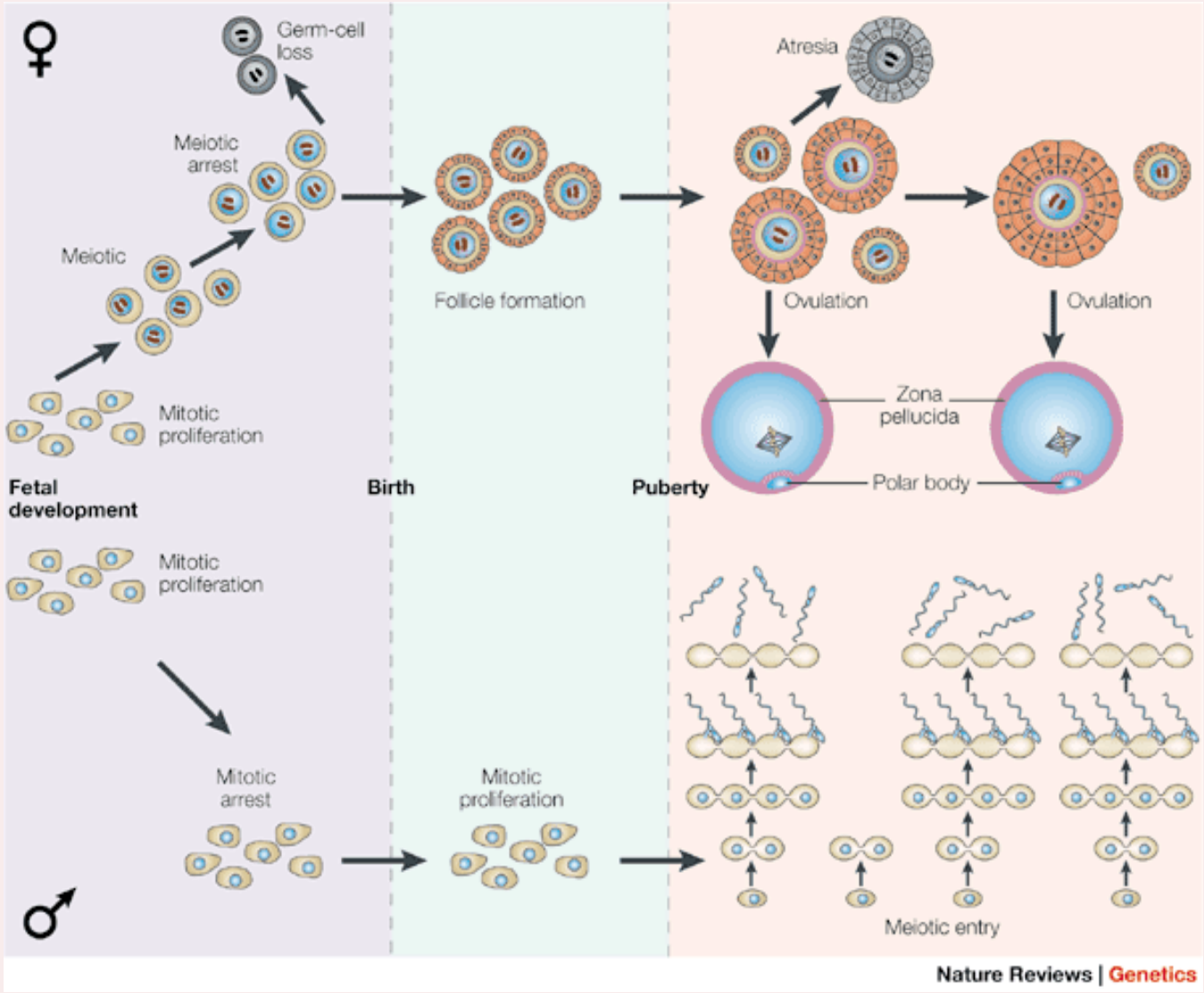
Produced by Russell W. Streiner and Karl Hardman · Directed by George A. Romero · Screenplay by John A. Russo

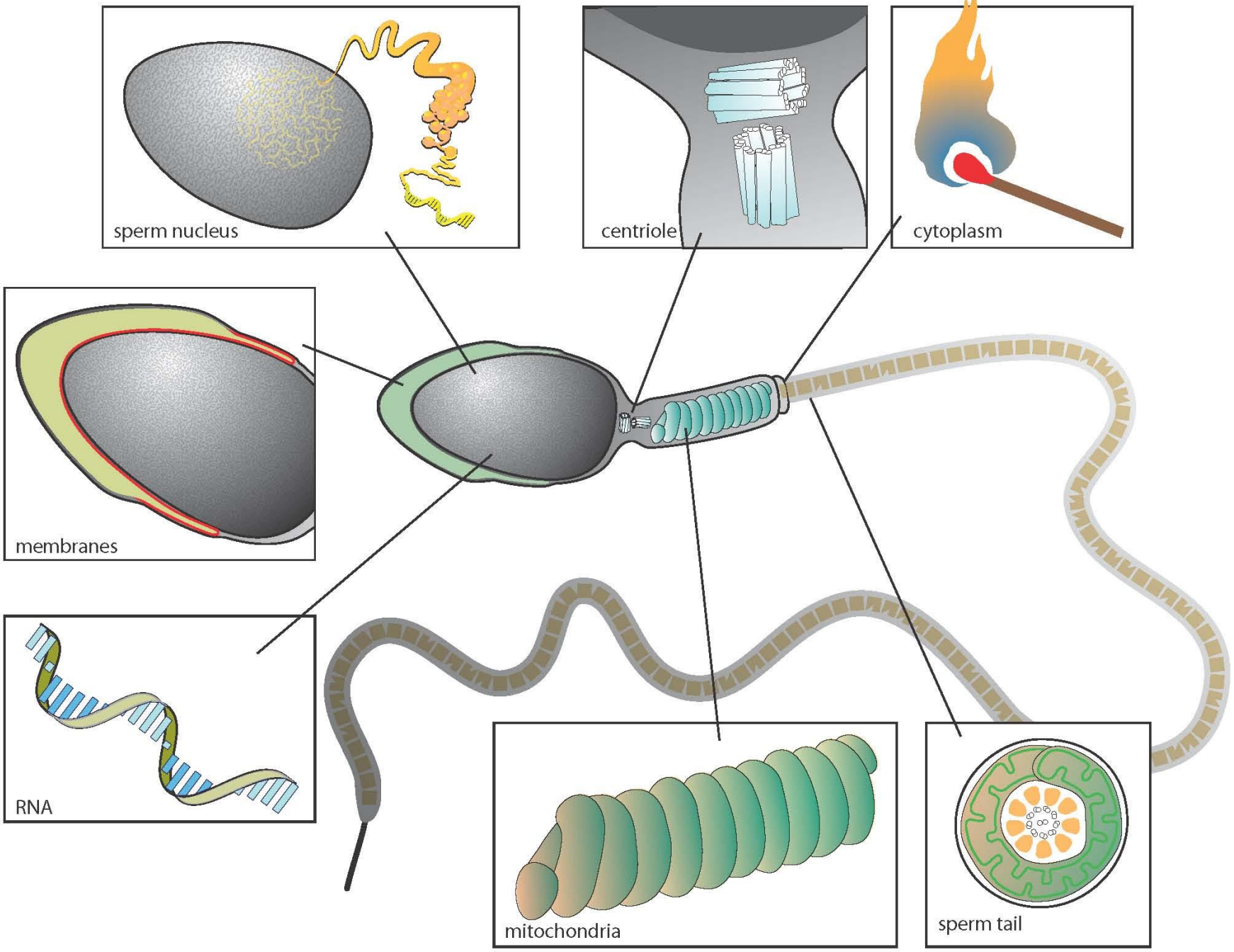
released by

M.A.P.S. LITHO PTY. LTD.



Human Female vs Male Meiotic Timelines




sperm nucleus
centriole
cytoplasm
membranes
RNA
mitochondria
sperm tail

Cell Divisions for Sperm

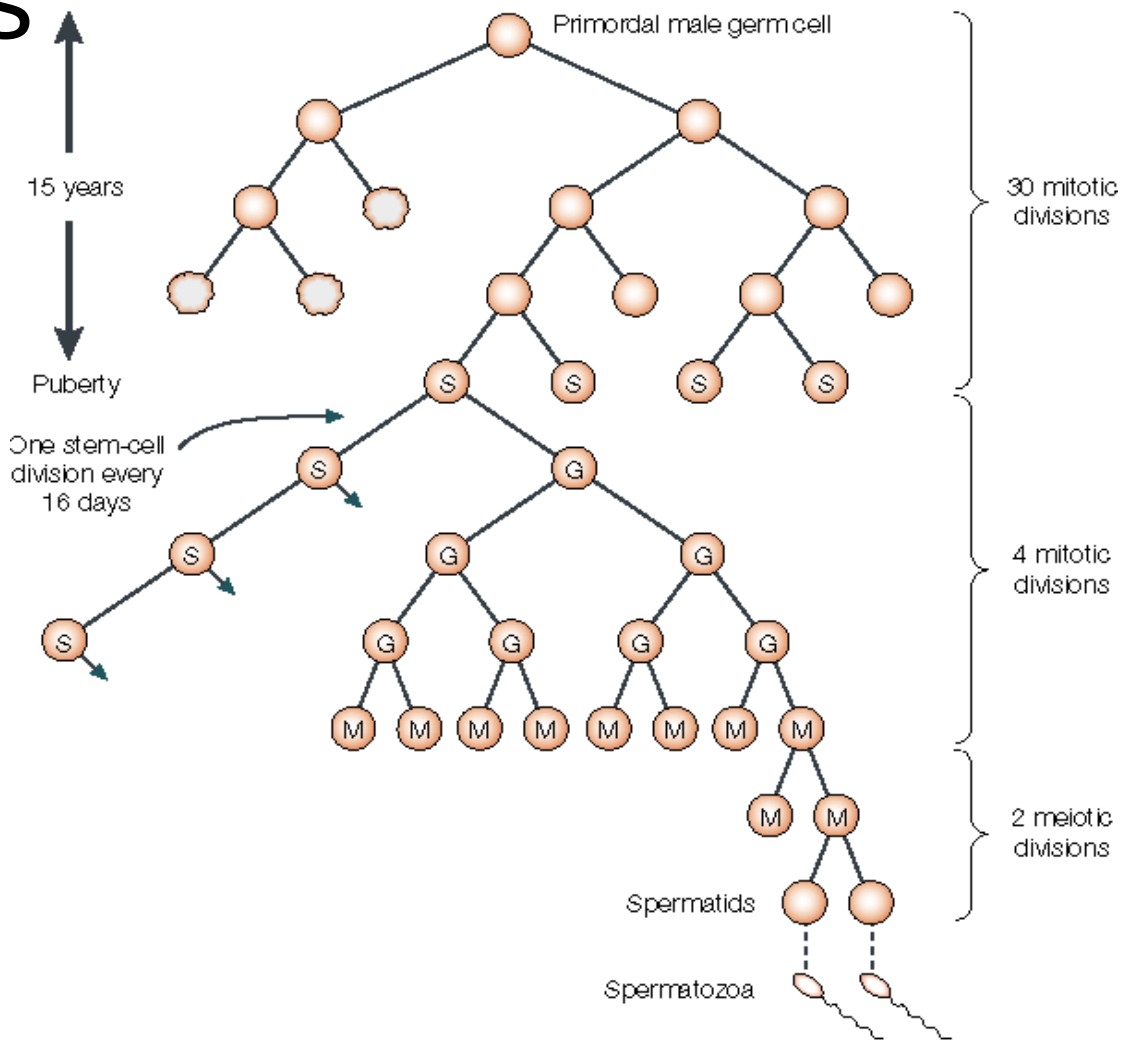
15 yr= 35

20 = 150

30 = 380

40 = 610

50 = 840



REVIEW ARTICLE

AMERICAN JOURNAL OF medical genetics PART B

Neuropsychiatric Genetics

Paternal Age and Psychiatric Disorders: A Review

Hilde de Kluiver,[1,2]* Jacobine E. Buizer-Voskamp,[3] Conor V. Dolan,[1,2] and Dorret I. Boomsma[1,2,4]

[1]Department of Biological Psychology, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

We review the hypotheses concerning the association between the paternal age at childbearing and childhood psychiatric disorders (**autism spectrum- and attention deficit/hyperactive disorder**) and adult disorders (**schizophrenia, bipolar-, obsessive–compulsive-, and major depressive disorder**) based on epidemiological studies. Several hypotheses have been proposed to explain the paternal age effect. We discuss the four main—not mutually exclusive—hypotheses. These are **the de novo mutation hypothesis, the hypothesis concerning epigenetic alterations, the selection into late fatherhood hypothesis, and the environmental resource hypothesis**. Advanced paternal age in relation to autism spectrum disorders and schizophrenia provided the most robust epidemiological evidence for an association, with some studies reporting a monotonic risk increase over age, and others reporting a marked increase at a given age threshold. **Although there is evidence for the de novo mutation hypothesis and the selection into late fatherhood hypothesis, the mechanism(s) underlying the association between advanced paternal age and psychiatric illness in offspring remains to be further clarified**.

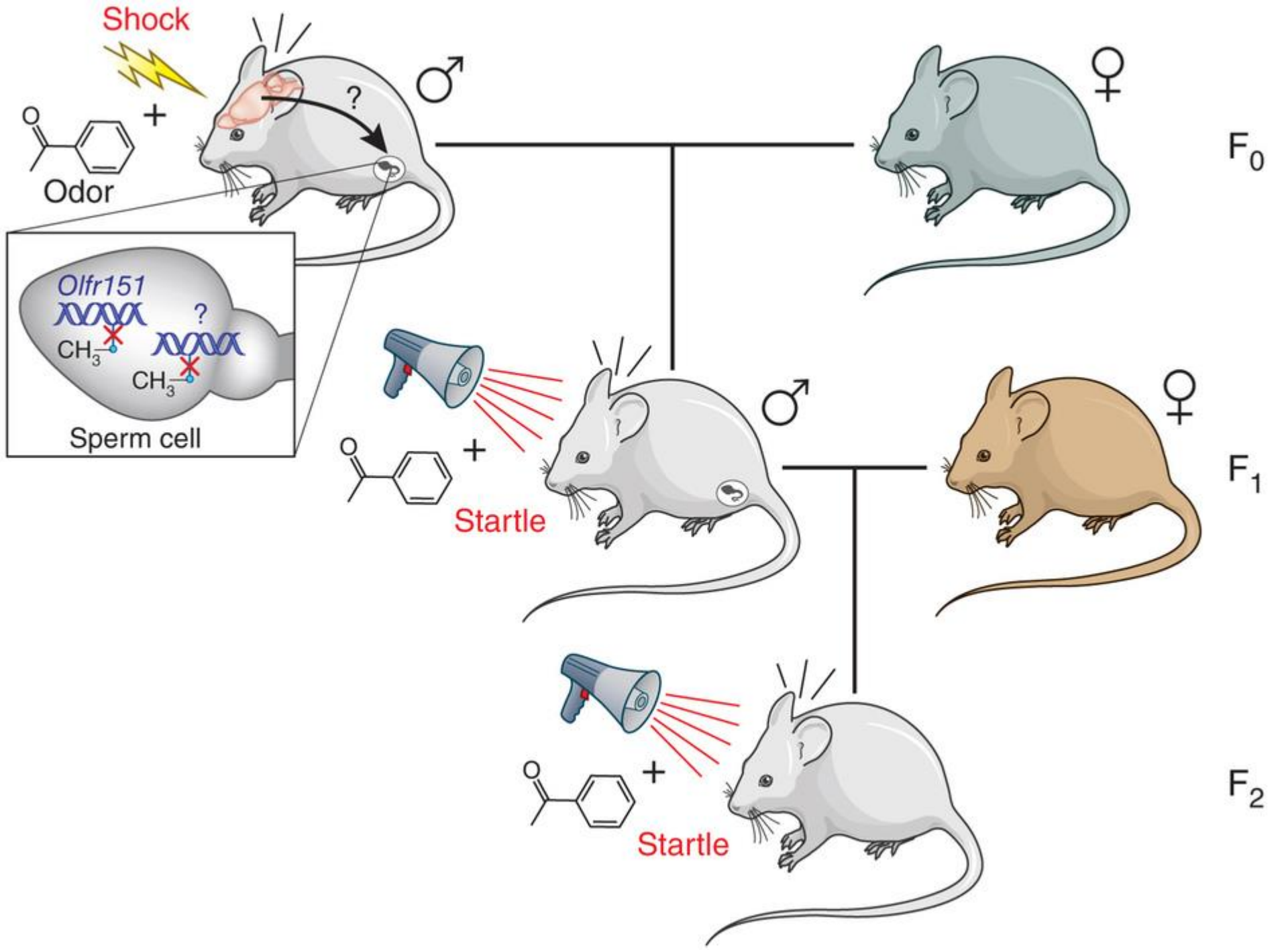
Manuscript Received: 25 March 2016; Manuscript Accepted: 3 October 2016

INTRODUCTION

The worldwide trend of postponing parenthood implies an increase in average parental age [Sobotka, 2010]. Notably maternal age increase is associated with heightened risks for theoffspring, for instance, it iswell established that increased maternal age at childbearing is a risk factor for errors of chromosome segregation [Penrose, 1933; Hassold and Hunt, 2009]. However, there is a growing realization that, independently of maternal age, advanced paternal age at childbearing is associated with offspring morbidity, including psychiatric disorders. The association between increased paternal age at childbearing and offspring morbidity is known as the "paternal age effect." There is no general consensus about the mechanism underlying this effect. The following four—not necessarily mutually exclusive—hypotheses have been proposed.

The first and leading hypothesis is the "de novo mutation hypothesis." De novo mutations occur spontaneously in the male germline during spermatogonial stem cell divisions and propagate insuccessive clones of spermatocytes [Penrose, 1955; Crow, 2000]. Such de novo mutations in the male germline occur more often with increasing paternal age and are hypothesized to increase offspring morbidity.

The second hypothesis concerns mechanisms related to epigenetic alterations, where impairments in epigenetic modifications result in altered chromatin structure and DNA-methylation patterns, which lead to altered gene expressions [Perrin et al., 2007]. A genome-wide DNA-methylation screen comparing sperm from young and old mice revealed a significant loss of methylation in the older mice in regions associated with transcriptional regulation.


Shock
Odor
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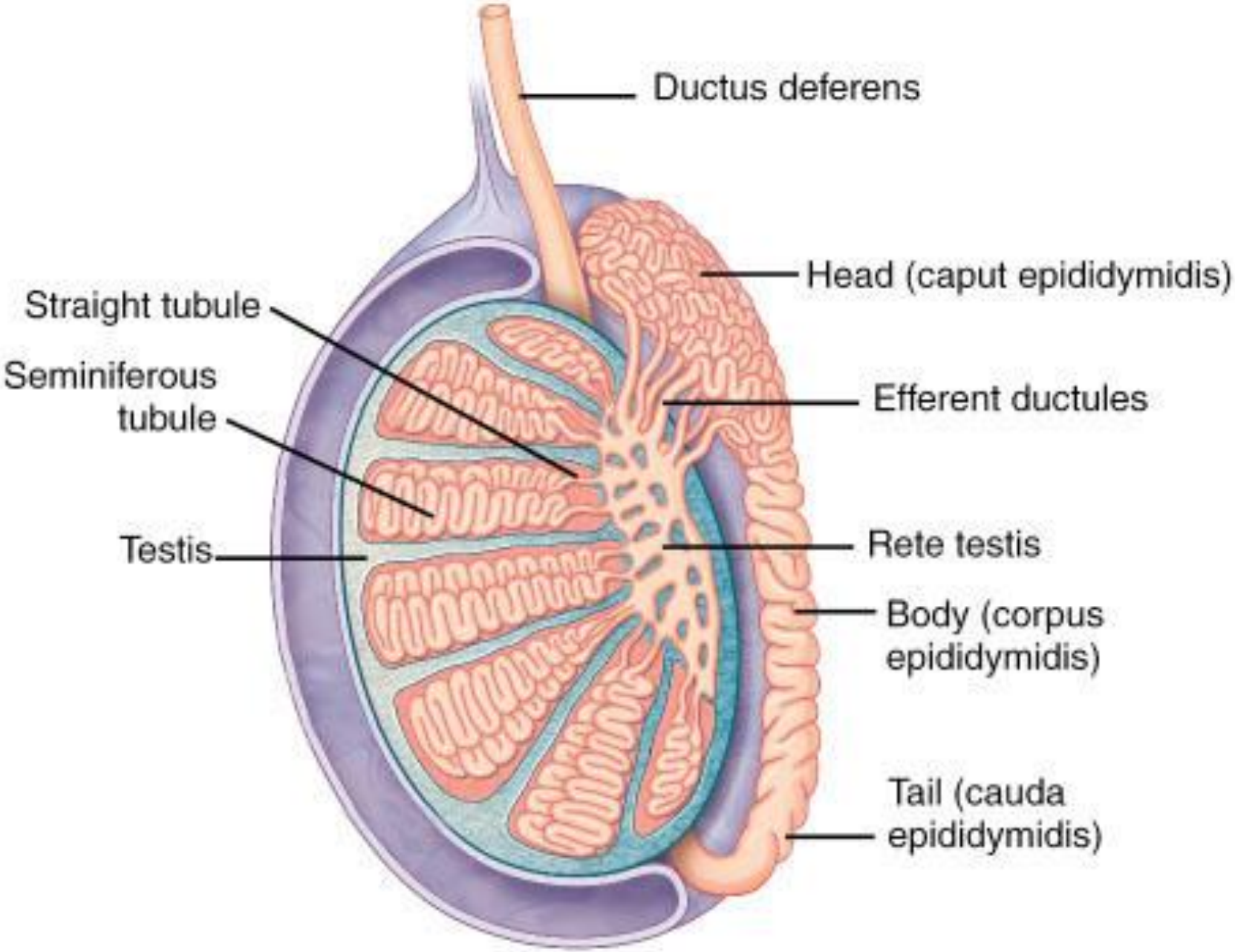
Ductus deferens
Head (caput epididymidis)
Straight tubule
Seminiferous tubule
Efferent ductules
Testis
Rete testis
Body (corpus epididymidis)
Tail (cauda epididymidis)

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Post-Testicular Sperm Maturation: Centriole Pairs, Found in Upper Epididymis, are Destroyed Prior to Sperm's Release at Ejaculation

C. Simerly[1,2], C. Castro[3], C. Hartnett[3], C. C. Lin[3], M. Sukhwani[3], K. Orwig[1,2] & G. Schatten[1,2,3,4]

The fertilizing sperm's lengthiest unchartered voyage is through the longest, least-investigated organ in a man's body – the Epididymis. Over six meters long in men, ~80 meters in stallions and over one-hundred times a mouse's body length, there are few functions known aside from sperm storage and nutrition. While spermatogenesis is completed in the testes, here we demonstrate sperm centriole reduction occurs within the epididymis. Investigations of GFP-CENTR mice and controls demonstrate both the presence of centriole pairs in the upper caput region of the epididymis and, the destruction, first, of the distal and, then, of the proximal centriole as the sperm transits to the cauda and vas deferens in preparation for its climactic release. These centrioles can neither recruit γ-tubulin nor nucleate microtubules when eggs are inseminated or microinjected, yet numerous maternally-nucleated cytasters are found. These sperm centrioles appear as vestigial basal bodies, destroyed in the mid-to-lower corpus. Post-testicular sperm maturation, in which sperm centrioles found in the caput are destroyed prior to ejaculation, is a newly discovered function for the epididymis.

The purpose of the epididymis[1–5] remains mysterious and the reasons for the sperm's extensive journey is perplexing. If a sperm were human-sized, its week or two trek through the epididymis would be ~2,750 kilometers[6]. Testicular sperm, and those collected from the upper epididymal regions from both mice and men are competent for reproduction when injected using intracytoplasmic sperm injection (ICSI), demonstrating their reproductive competence[7,8]. With advances in assisted reproductive technologies (ART), men without any sperm in their ejaculates are able to conceive through the application of sophisticated sperm-retrieval protocols[9] and ICSI[10] from epididymal sources. ART success rates are higher with epididymal sperm than with testicular ones, suggesting post-testicular maturation[11]. Noteworthy investigations using primarily bull or mouse epididymal isolates have found important regional differences in gene expression patterns[12], proteins[13,14], and post-translational modifications[15], as well as epididymosomes[4], important ves- icles found in the epididymal lumen. Here we show sperm maturation occurring within the epididymis involves a pre- viously unappreciated event. The sperm centriole-pair persist with the sperm after release into the lumen of testicular tubules and as they travel into the epididymis head. Nearly all sperm have centrioles in the caput, and first the distal and then the proximal centrioles are destroyed as they pass through the corpus to reach the cauda epididymis on their transit to the vas deferens. The destruction of these centrioles is neither accelerated in young males nor slowed in older ones, though individual variabilities are found. Further, caput sperm with intact centriole pairs are unable to nucleate microtubules when introduced into metaphase-II oocytes. The term 'Zombie centrioles' recently introduced by Khire *et al.*[16], seems apt to describe these non-functional centrioles awaiting their disassembly in the male reproductive tract. The sperm is thought to contribute primarily the imprinted haploid genome and the sperm centrosome to the offspring. The sperm tail[17] and the sperm mitochondria[18,19] are destroyed as the zygote develops, though the fate of the

to G.S. (email: gschatten@ohsu.edu)

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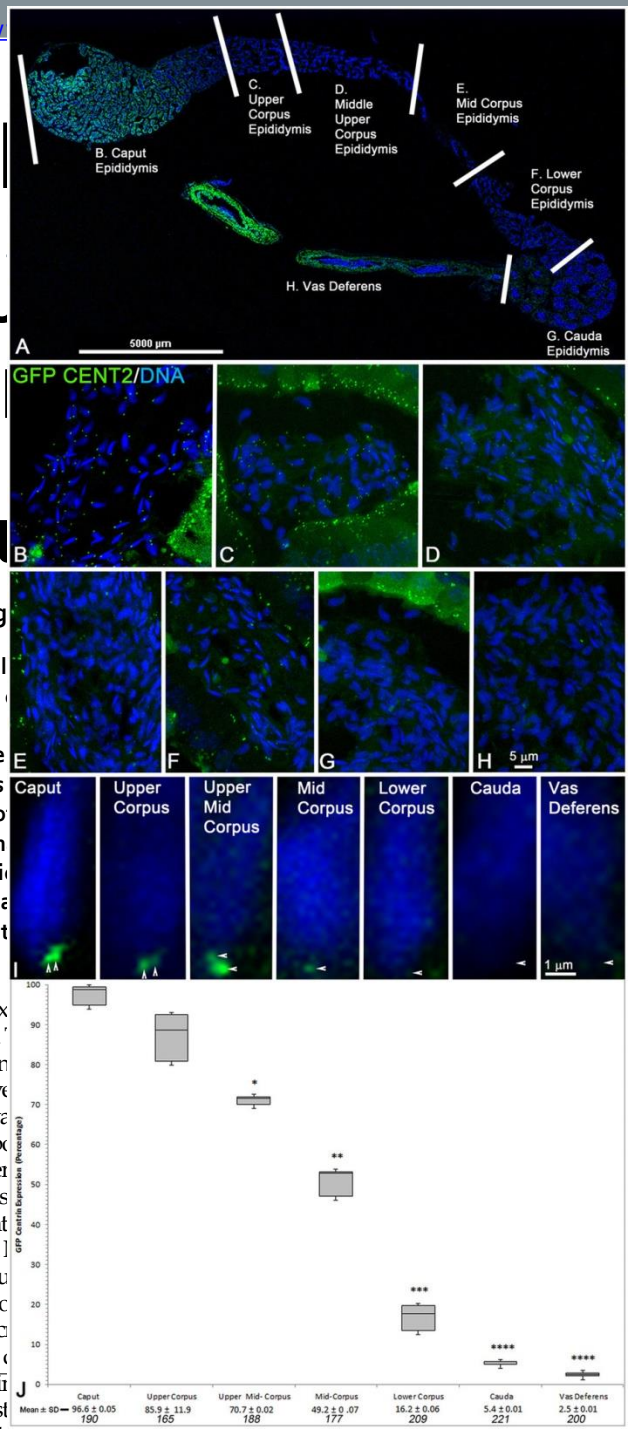
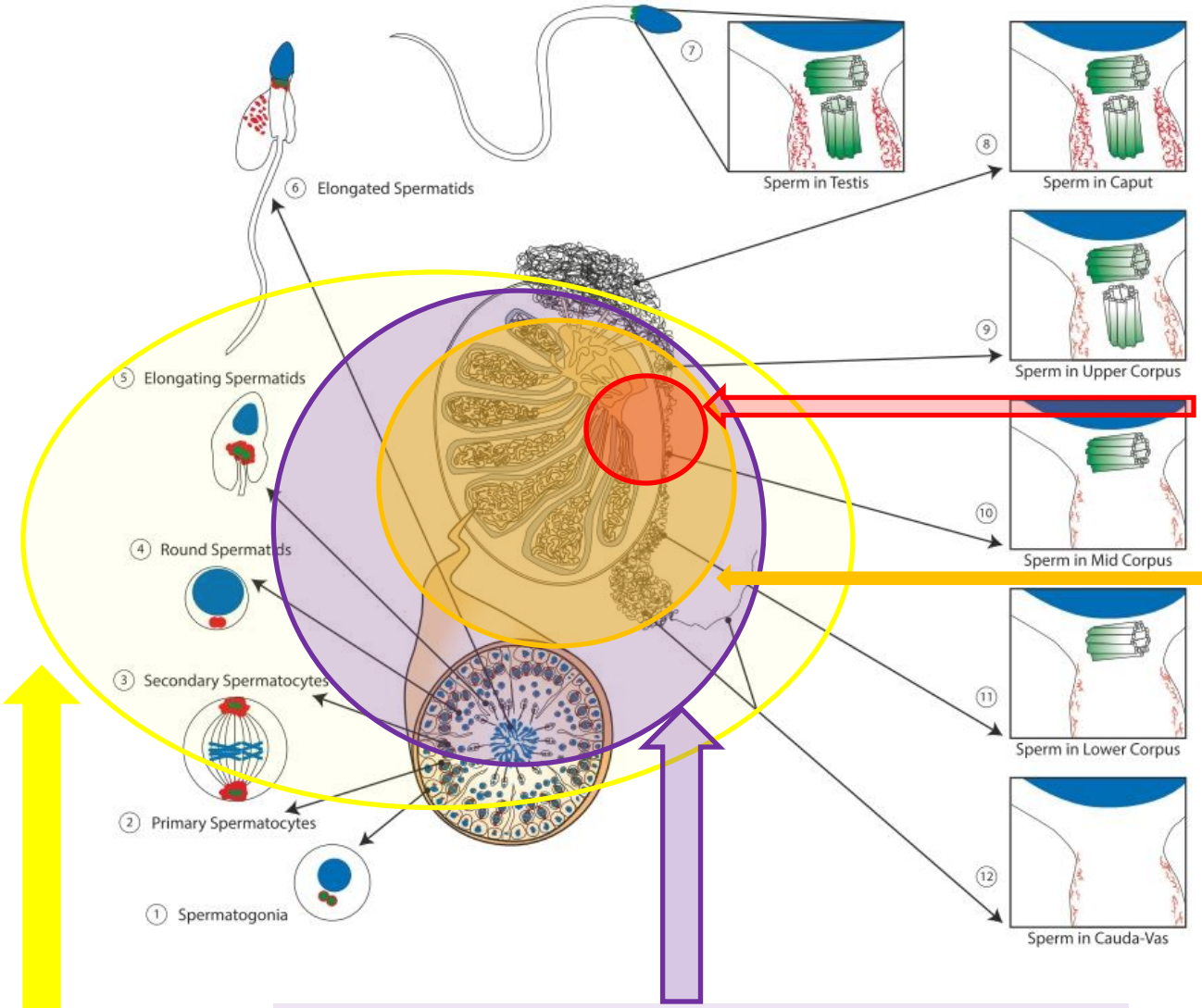


IS THE EPIDIDYMUS THE EPICENTER OF MALE EPIGENESIS?

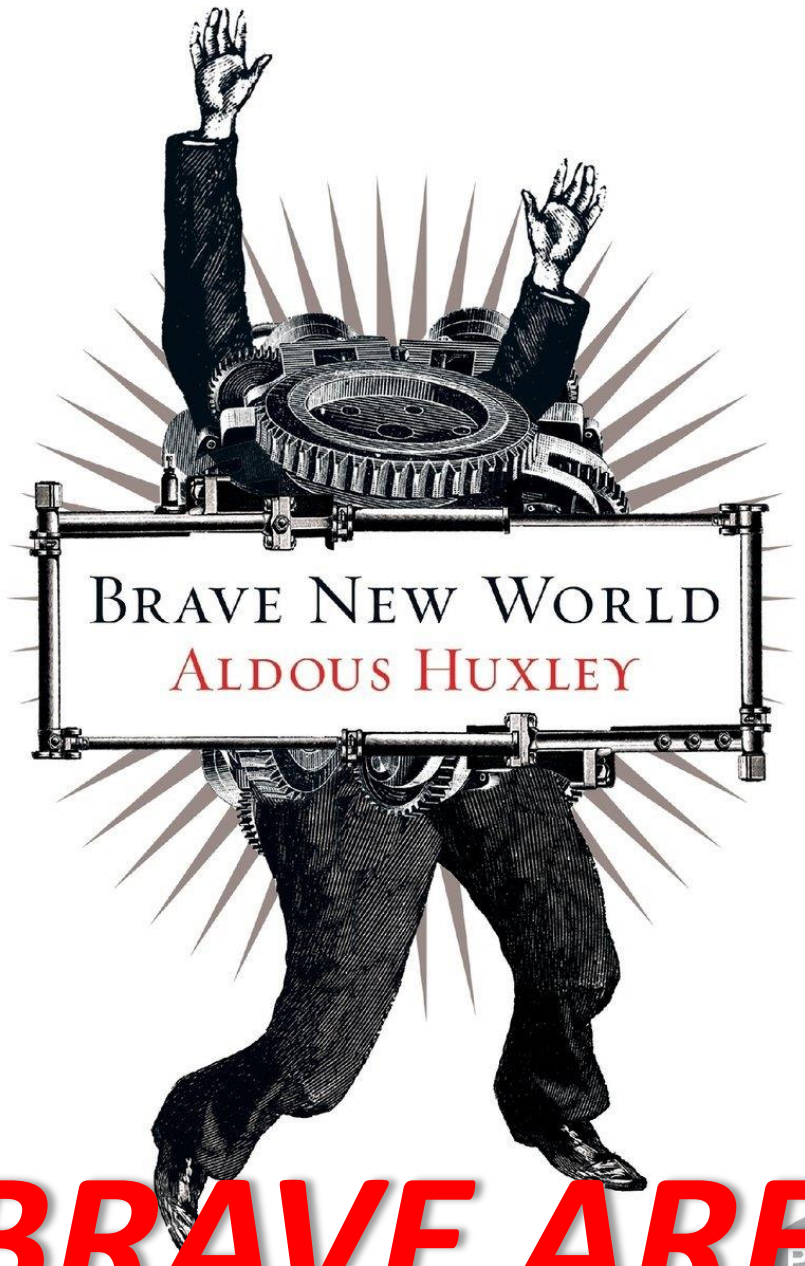


RNAs, e.g. tRNA frags; miRNAs (miR-34c, miR-98, miR-144, miR-190b), ncRNAs

Centriole and Centrosome Reduction

Histone Post-translational Modifications

DNA Imprints, e.g. 5'-methycytosines,5'-hydroxymethylcytosines, N^6-methyladenine



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