Η επιδιδυμίδα ως θεραπευτικός στόχος της υπογονιμότητας

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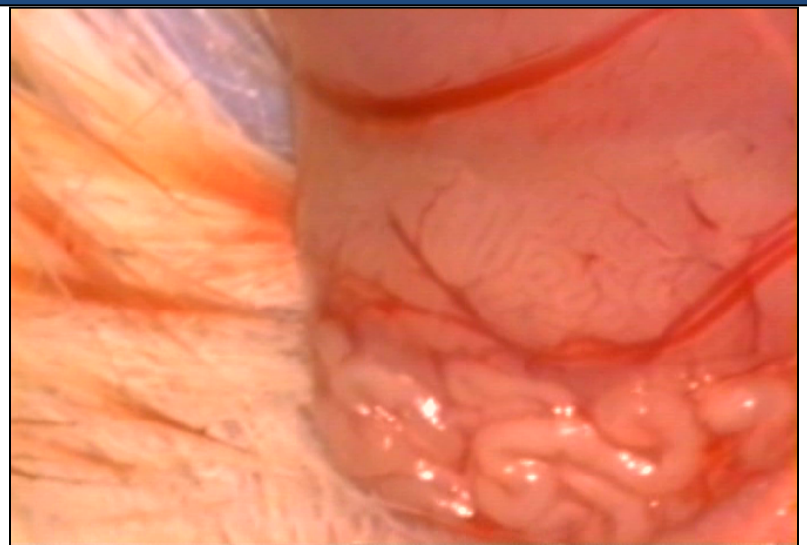
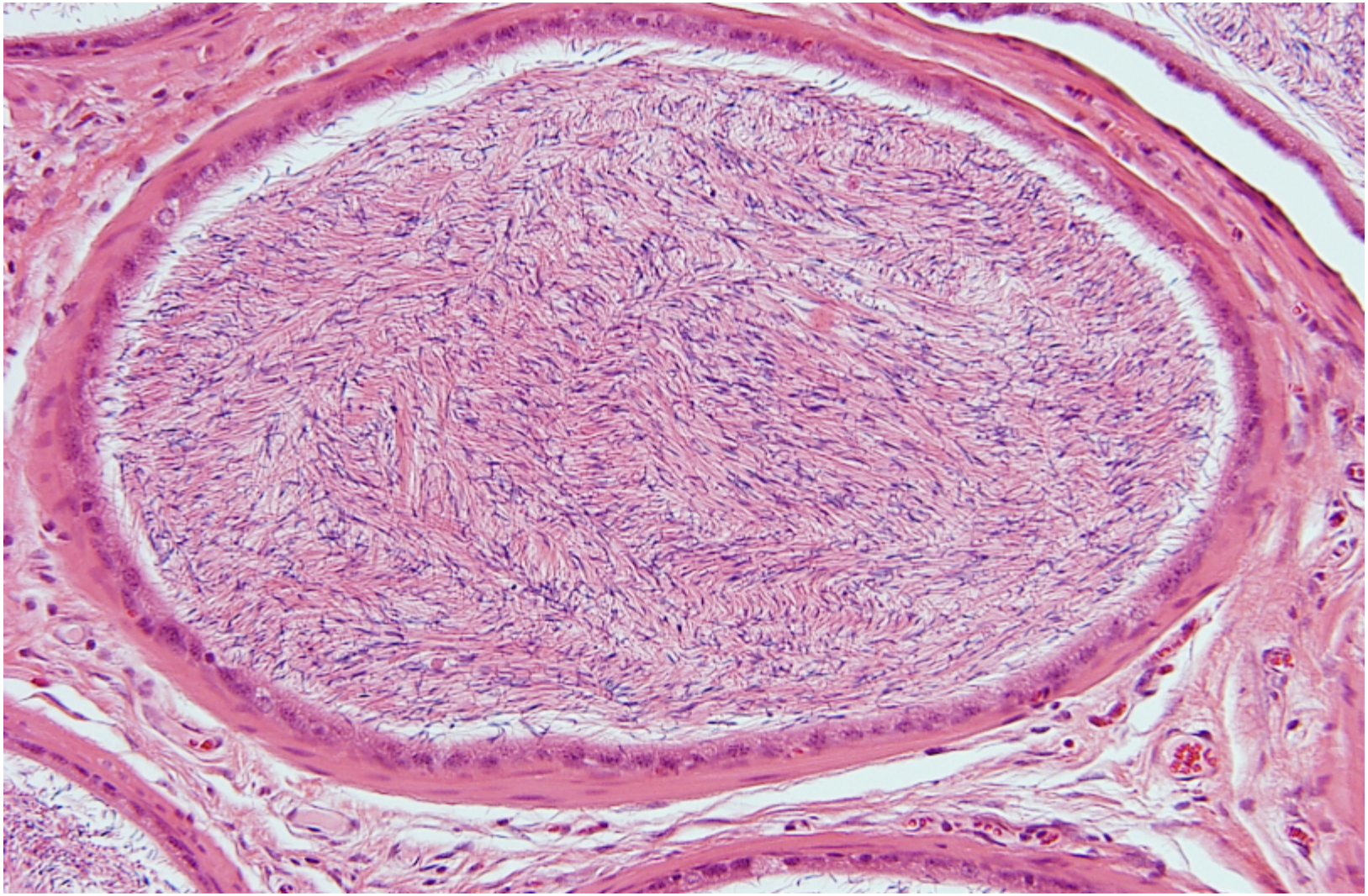
EPIDIDYMIS IS NOT THE BLADDER OF THE TESTIS

Cold storage hypothesis
Bedford, 1977

Testicular descent secondary to the epididymal descent
Structural support in some species

However, in few ascrotal taxa the epididymis is located subcutaneously or intra-abdominally
(hyraxes, elephant shrew)





Epididymis is a Unique Organ

- Epididymal Lumen Testosterone
- Epididymal Lumen Androgen-Binding Protein
- Epididymal Maturation Process is not a Species Dependent

S288 Rat epididymis can induce hamster sperm maturation

S. Skouros, S. Stavrou, I. Giannakis, D. Baltogiannis, C. Papaioannou, F. Dimitriadis, A. Takenaka, N. Sofikitis (Ioannina,Greece; Yonago, Japan)

Presented in 10th SEEM, Belgrade, Serbia 24-26 October 2014.

The Epididymis as a Target for

- Surgical Approaches

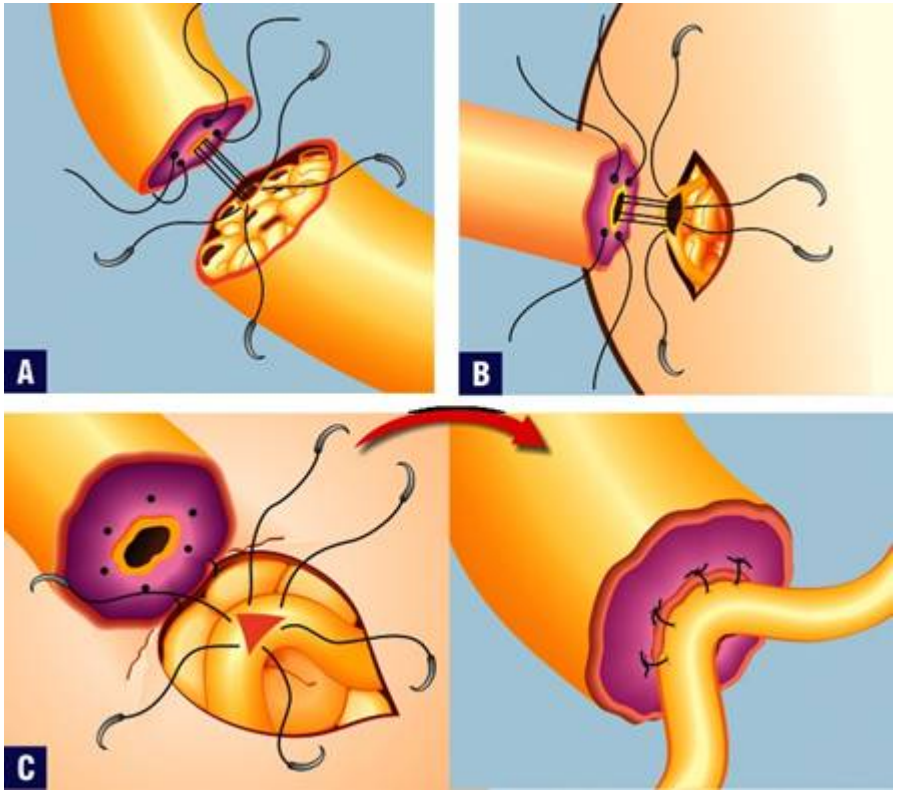
A. Etiological Surgical Treatment
B. Symptomatic Surgical Treatment

- Pharmaceutical Approaches

A. Direct Approaches (Antibiotics and Antioxidants)
B. Indirect Approaches (Mediated through Alterations in Testicular Function)

Etiological Surgical Treatment

Berger End to Side Vasoepididymostomy Technique

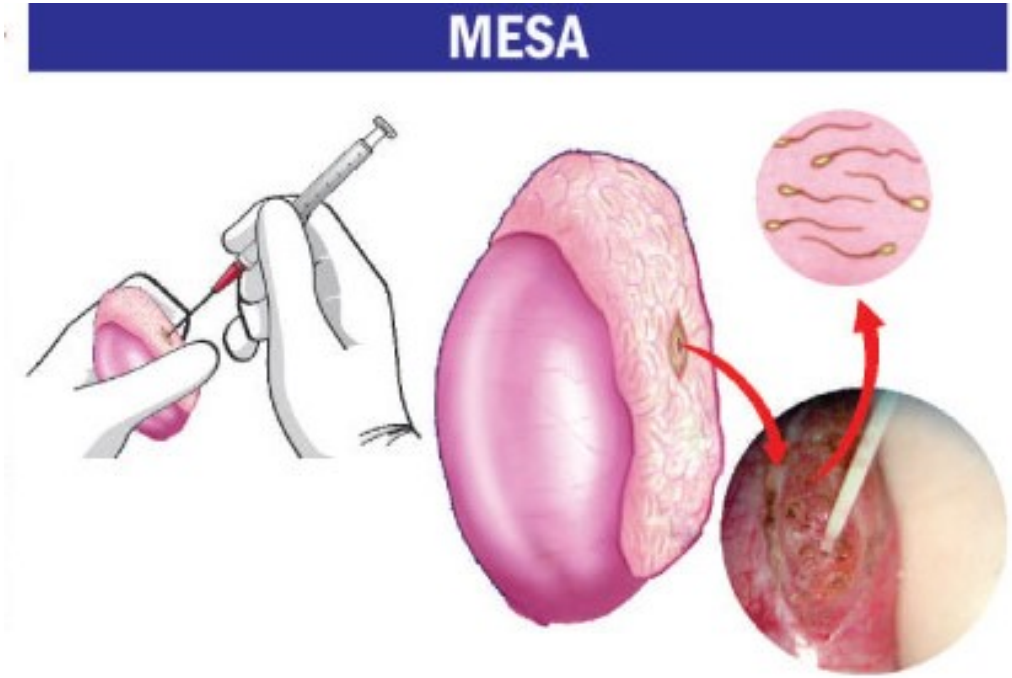


Factors Affecting the Outcome of V-E-stomy

- Time interval after the occurrence of the obstruction
- Experience of the surgeon
- Female Age

Symptomatic Surgical Treatment

- Microsurgical Sperm Aspiration



Direct Pharmaceutical Approaches
Antibiotics and Epididymitis

Epidemiological Data

- In 2002, epididymitis or orchitis accounted for 1 in 144 outpatient visits (0.69 percent) in men 18 to 50 years of age.1 There are approximately 600,000 cases of epididymitis per year in the United States, most of which occur in men between 18 and 35 years of age.

Trojian et al., Am Fam Physician 2009

Epidemiological Data

Permanent impairment of semen quality after unilateral epididymitis

	No. of patients	Follow-up (month)	Oligozoospermia (<20 Mio/ml)	Azoospermia
Tozzo	16	1–18	6	1
Osegbe	30	24	10	8
Weidner et al.	37	3	8	3
Ludwig and Haselberger	46	6	14	0
Dietz	82	3–8	No data	11
Total	211		38 (29.5%)	23 (10.9%)

Rusz et al., World J Urol 2012

Epidemiological Data

- 70 % of semen samples are contaminated with bacteria, and most of them are not pathogenic and are without significance for sperm function

(Weidner et al., Hum Reprod Update 1999)

Predominant pathogens:

- Neisseria gonorrhoeae

(*Manavi et al., 2005;* Redfern et al., 1984)

- Chlamydia trachomatis

(Manavi et al., 2005; Redfern et al., 1984)

- E. coli strains (65-80%)
- Klebsiela, Proteus mirabilis, Pseudomonas, Serratia, and Enterobacter aerogenes (10-15%)

(Meares, 1987; Weidner, 1991)

Other pathogens:

- Mycobacterium tuberculosis

(Manavi et al., 2005; Redfern et al., 1984)

- Staphylococci

(Weidner, 1991)

- Mycoplasma hominis

(Weidner, 1991)

- Ureaplasma urealyticum

(Weidner, 1980)

- Viruses

(Benson, 1992)

Additional Causes

- **The heart medication amiodarone (Pacerone).** In some cases, this anti-arrhythmic medication causes inflammation of the epididymis. Epididymitis caused by amiodarone is treated by temporarily discontinuing the drug or reducing the dose.

- **Urine in the epididymis.** Known as chemical epididymitis, this occurs when urine flows backward into the epididymis. It may occur with heavy lifting or straining.

By Mayo Clinic staff

Epididymo-orchitis

- Patients with epididymitis usually present with gradual onset of pain that is localized posterior to the testis and that occasionally radiates to the lower abdomen.
- Although patients often have unilateral pain that begins in the epididymis, the pain can spread to the adjacent testis.
- Symptoms of lower urinary tract infection, such as fever, frequency, urgency, hematuria, and dysuria, may be present.
- These symptoms are common with epididymitis and orchitis but are rare with testicular torsion. Recurrent pain is rare with epididymitis and torsion of the appendix testis (upper pole of testis), but can occur with testicular torsion (caused by intermittent torsion with spontaneous resolution).

Chronic epididymo-orchitis

- Is not life threatening
- Is difficult to eradicate, and may have or may have not serious sequelae
- Male infertility may be one of the more serious consequences of both bacterial and nonbacterial CEO, resulting from a number of potential mechanisms

Complications

Epididymitis may eventually cause:
1.Scrotal abscess, when infected tissue fills with pus
2.Chronic epididymitis, which can occur when untreated acute epididymitis leads to recurrent episodes
3.Shrinkage of the affected testicle (atrophy)
4.Reduced fertility

If the condition spreads from your epididymis to your testicle, the resulting condition is known as epididymo-orchitis. Signs, symptoms and treatment options are basically the same as they are for epididymitis.

By Mayo Clinic staff

The following factors may contribute to the subfertility secondary to chronic epididymo-orchitis.

1. Secretory dysfunction of the epididymis.
2. Secretory dysfunction of the prostate（？）.
3. Secretory dysfunction of the seminal vesicles in those patients in whom seminal vesiculitis follows epididymo-orchitis（？）.
4. Stricture or obstruction of the excretory ducts acquired following infections of those, structures as a complication of epididymo-orchitis.
5. Testicular atrophy following long-standing proximal obstruction.
6. Direct effect of bacteria on semen quality by utilization of important substances. Recruitment of neutrophils and generation of ROS.
7. Abnormal number and motility of spermatozoa in seminal fluid positive for specific microorganisms; or a direct effect of the microorganisms on the spermatozoa.
8. A disturbance of sperm penetration related to the production of diffusible, relatively heat-labile factors in the semen of infected men.
9. High incidence of antibodies reactive with the spermatozoa.
10. Presence of pelvic inflammatory disease in the female partner.

Initial therapy of acute unilateral epididymitis using ofloxacin. II. Andrological findings

In most patients, initially decreased sperm counts increased significantly and global motility improved, while the numbers of abnormal spermatozoa decreased. Only in a few cases were azoospermia, kryptozoospermia, consistently reduced motility, and constant or even increasing numbers of deformed spermatozoa observed.

Weidner et al., Urologe A. 1990

Acute nongonococcal epididymitis--pharmacological and therapeutic aspects of levofloxacin

The concentration of LVFX in semen were 1.19 micrograms/ml (7th day) and 1.32 micrograms/ml (13th day). Semen/serum ratios were 1.12 and 1.26, respectively. No affection of LVFX on the sperm was observed. Antimicrobial activity of LVFX to C. trachomatis showed good MICs of 0.25-1.0 micrograms/ml. LVFX was administered in a dose of 100 mg two or three times daily for 14 days to 23 patients with acute epididymitis. The overall efficacy rate based on a criteria for acute epididymitis showed 100% (excellent: 16, good: 4, 20/20). A better efficacy rate was obtained on the 14th day than 7th day. No subjective or objective adverse reactions were observed.

Saito et al., Hinyokika Kiyo. 1992

Effect of early antibiotic treatment on the formation of sperm antibodies in experimentally induced epididymitis

It is concluded that epididymitis consequent to infection with E. coli can induce cytotoxic antibody formation in Lewis rats. Treatment with appropriate antibiotics may suppress the antibody response either through a direct immunosuppressive effect of the antibiotic or through a decrease in the antigenic load of killed sperm secondary to eradication of the infection.

Greskovich et al., Arch Androl.1993

Mono or bilateral inflammatory postmicrobial prostato-vesciculo-epididymitis (PVE): differences in semen parameters and reactive oxygen species production.

Although sperm abnormalities (including seminal leukocyte concentration, number of spermiophages, and ROS production) can distinguish patients with PVE from those with prostatitis alone, the abnormalities did not discriminate between unilateral and bilateral PVE. In diagnostic suspicion of PVE, didymo-epididymal and prostato-vescicular ultrasonography can help discriminate monolateral from bilateral forms of PVE, and is a useful aid in the follow-up of these patients.

La Vignera et al., Minerva Endocrinol. 2006

Chronic epididymitis: impact on semen parameters and therapeutic options

Positive effects of antiphlogistic/antibiotic treatment on semen quality have been reported; however, controlled prospective studies are still lacking.

Table 1 Alteration of semen parameters in chronic epididymal inflammation

Sperm count (↓)
Sperm motility (↓)
Sperm morphology (±)
Atypical staining of flagella (↑)
Disturbed DNA integrity and increased apoptosis of spermatozoa, pathological acrosome reaction
Number of leukocytes (↑)
Granulocyte elastase (↑)
Pro-inflammatory cytokines (e.g. IL-6, IL-8) (↑)
α-Glucosidase (↓)
Pathogenic microorganisms (+)

Haidl et al., Andrologia 2008

Direct Pharmaceutical Approaches Antioxidants and Epididymitis

Generation of ROS

- The first evidence that spermatozoa lose their motility more rapidly when incubated with oxygen was provided in 1943 by MacLeod

(MacLeod, Am J Physiol, 1943)

- Excessive generation of ROS in semen could be a cause for infertility, since both the outcome of the hamster sperm-oocyte penetration assay and fertility in vivo are inversely correlated.

(Aitken et al, Am J Obstet Gynecol 1991)

ROS and DNA Integrity

According to the current literature one can state the following:

- Sperm nuclear DNA damage is a cause of fertilization failure and pregnancy loss.
- A major cause for sperm DNA damage is ROS, which can be derived from male genital tract infections/inflammations.
- If looking at sperm DNA damage, one has to consider nuclear and mtDNA.

(Henkel Clinical Andrology 2010)

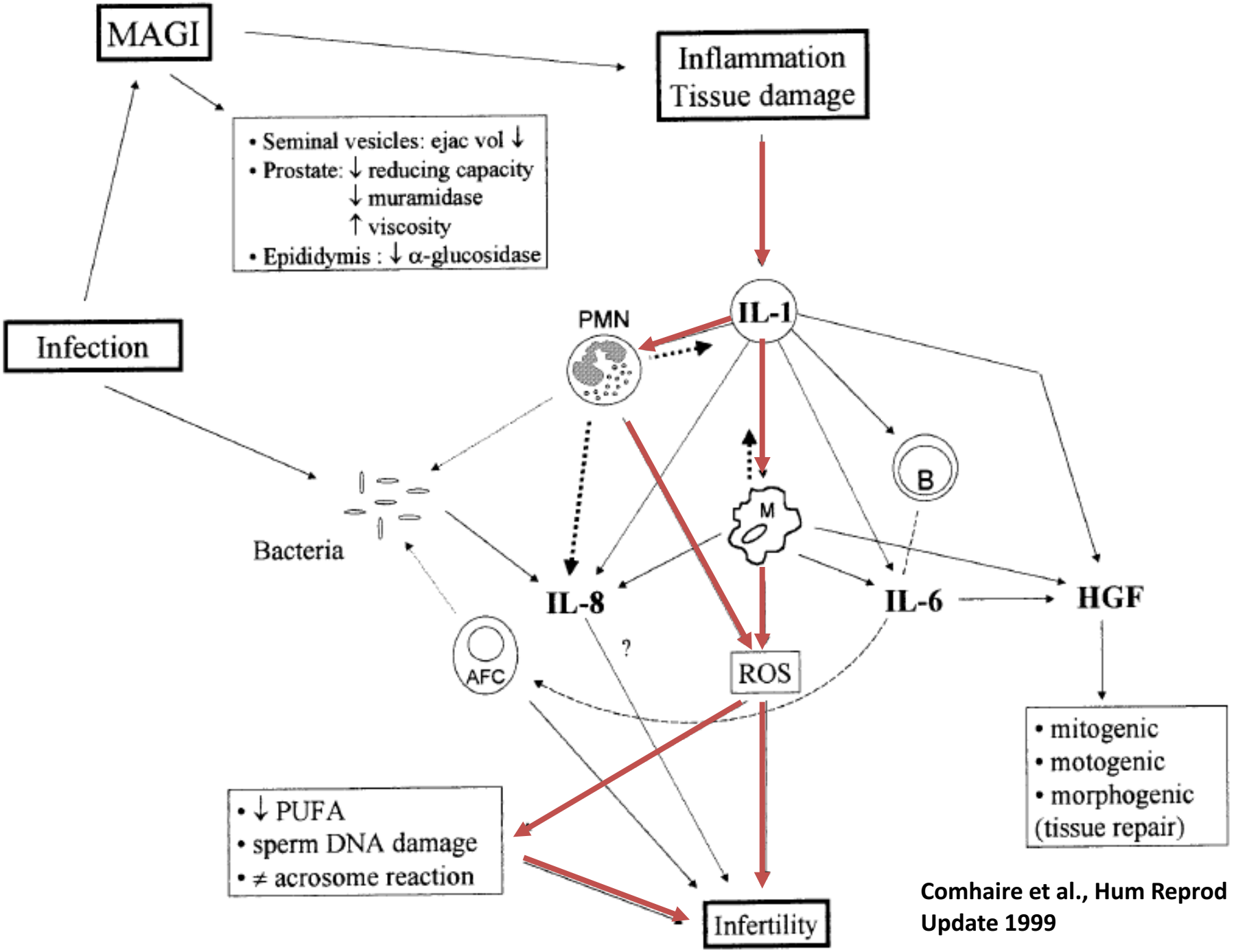
Inflammatory Cytokines

- Patients with epididymo-orchitis/ prostatitis present significantly elevated levels of TNF-α and IL-1 in seminal plasma and reduced semen quality potentially associated with infertility.

(Hu et al., Pros Can Pros Dis 2007)

- IL-8 concentration in seminal plasma was also positively correlated with symptom score and PSA levels in such patients.

(Penna et al., Eur Urol 2007)



Comhaire et al., Hum Reprod Update 1999

Treatment of Epididymitis or CBP or NBP; effect on male infertility

Modalities of therapy include

- antibiotics
- antiphlogistic drugs
- surgical procedures
- normalization of urine flow
- physical therapy
- changes in general and sexual behavior

(Weidner *et al.*, Andrologia 1998)

Treatment of Epididymitis or CBP or NBP; effect on male infertility

- Unfortunately, until now only the antibiotic therapy of epididymitis or chronic bacterial prostatitis has proved to be really efficacious in providing symptomatic relief, eradication of microorganisms and a decrease in cellular and humoral inflammatory parameters in urogenital secretions

(Weidner *et al.*, Andrologia 1998)

Treatment of Epididymitis or CBP or NBP; effect on male infertility

The improvement of male subfertility after conservative or surgical treatment of the complications of prostatic infections confirms a cause and effect relationship between CBP and male subfertility.

Mol Cell Biochem
DOI 10.1007/s11010-012-1382-z

Antioxidant treatment with edaravone or taurine ameliorates diabetes-induced testicular dysfunction in the rat

Panagiota Tsounapi · Motoaki Saito · Fotios Dimitriadis · Sotirios Koukos · Shogo Shimizu · Keisuke Satoh · Atsushi Takenaka · Nikolaos Sofikitis

- The morphological damage, increased lipid peroxidation, and apoptosis in testicular tissue can be significantly relieved by edaravone or taurine treatment through suppressing the increased oxidative stress in the rat testis.

Tsounapi et al., 2012. Mol. Cell. Biochem.

Administration of Antioxidants in Men with OAT

- Did you quantify ROS generation?

ROS ARE IMPORTANT

- Human spermatozoa appear to use reactive oxygen species for a physiological purpose and have the difficult task of ensuring the balanced generation of these potentially harmful, but biologically important, modulators of cellular function.
- Bioessays. 1994 Apr;16(4):259-67.
- Aitken J, Fisher H.

- Spermatozoa of fertile men produce extremely low levels of ROS and yet, paradoxically, these molecules appear to be important mediators of normal sperm function.

Respect ROS

Do not administer large amounts of antioxidants

Direct Effects of PDE3i on Epididymal Function

- Epididymal spontaneous contraction – modulatory effect of the specific inhibitor of this cGMP-dependent PDE, milrinone has been observed

Mewe at al., Endocrinology, 2006, 147:2051-62.

The Epididymis as a Target for Indirect Pharmaceutical Approaches

Hormonal treatment
1. GnRH analogues 2. GnRH antagonists 3. Gonadotrophins 4. Testosterone 5. Testosterone rebound therapy 6. Antiestrogens (Clomiphene, Tamoxifen) 7. Testolactone-Anastrazole (aromatase inhibitors) 8. Bromocryptine
Non-hormonal treatment
1. PDE5 inhibitors 2. Kallikrein 3. Indomethacin 4. ACE inhibitors 5. Arginine 6. Pentoxyphyline 7. Antioxidants

Consequences in Epididymal Function after Testicular Surgery

EUROPEAN UROLOGY SUPPLEMENTS 13 (2014) 89–99

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Mysteries, Facts, and Fiction in Varicocele Pathophysiology and Treatment

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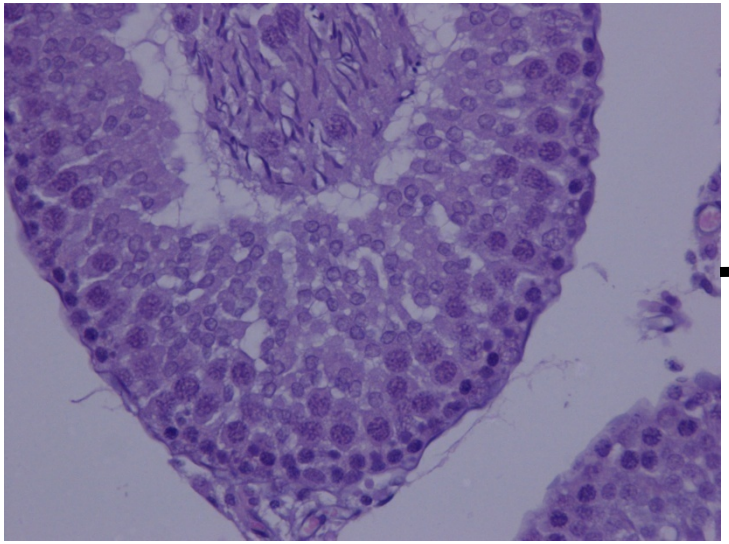
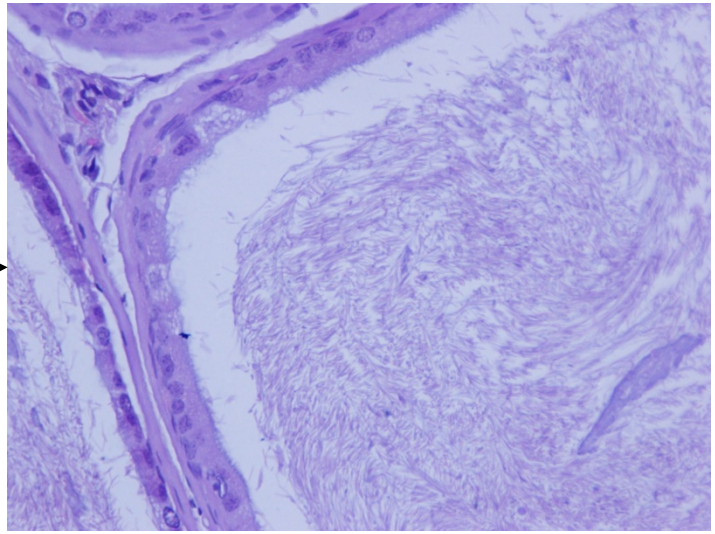
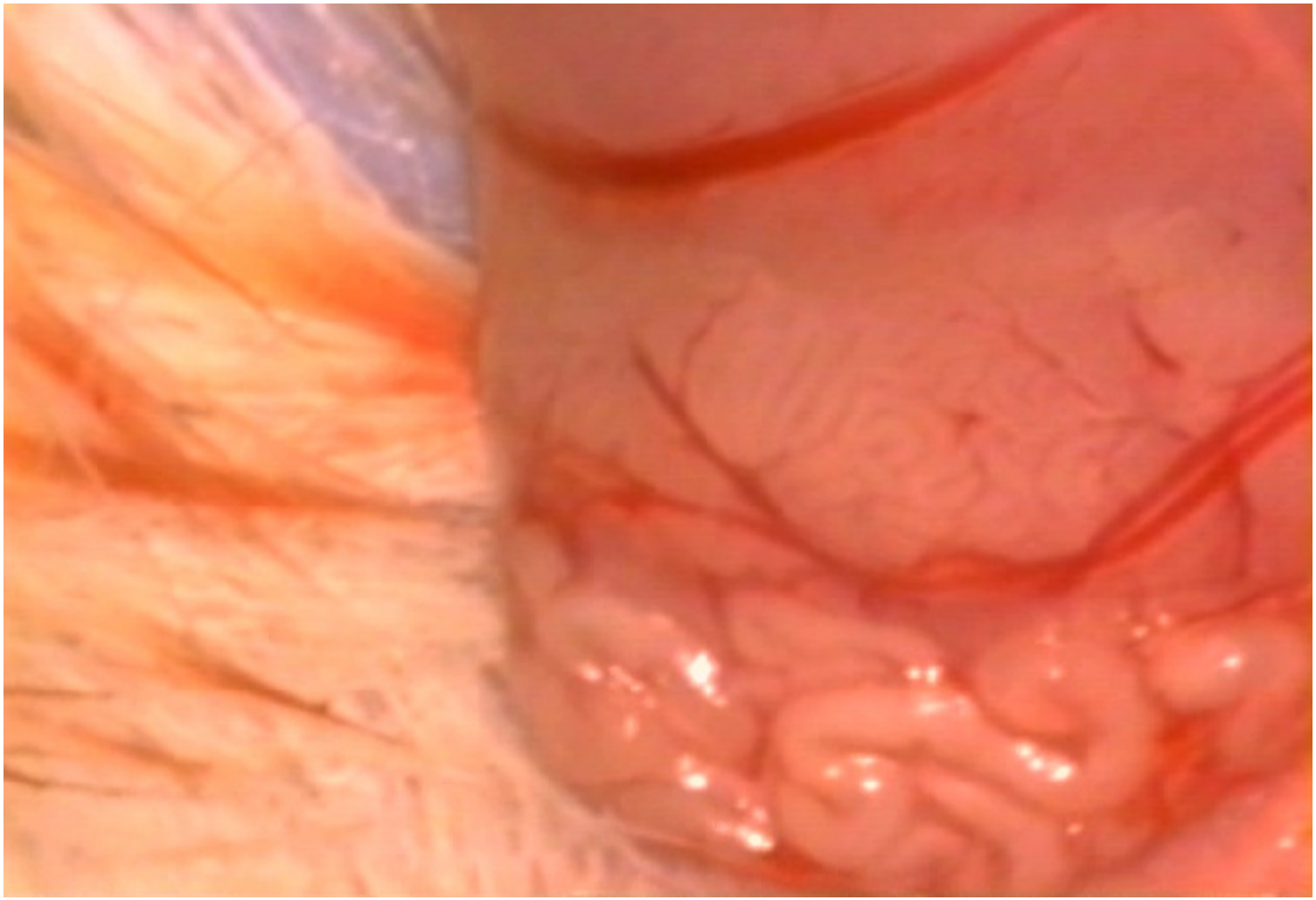
The Epididymis as a Target for

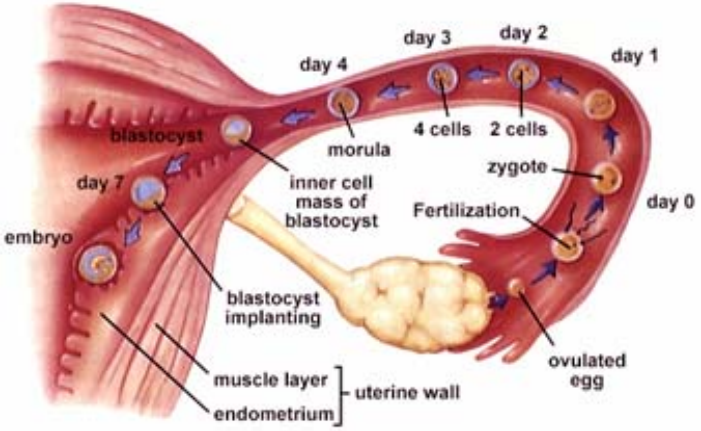
- Male Contraception

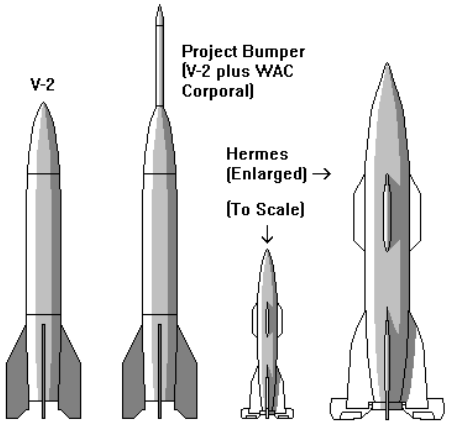
Ας αλλάξουμε τον στόχο

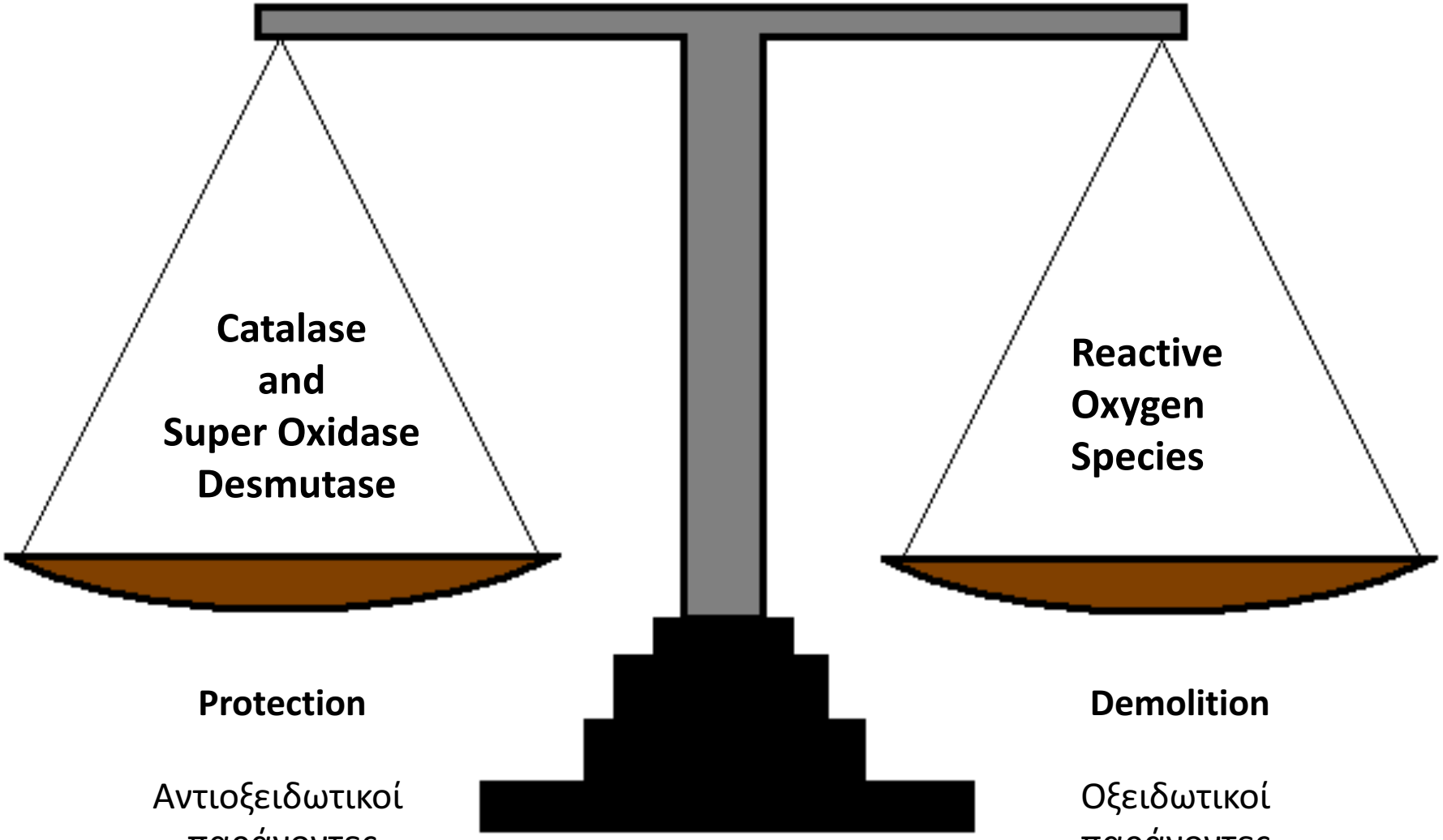




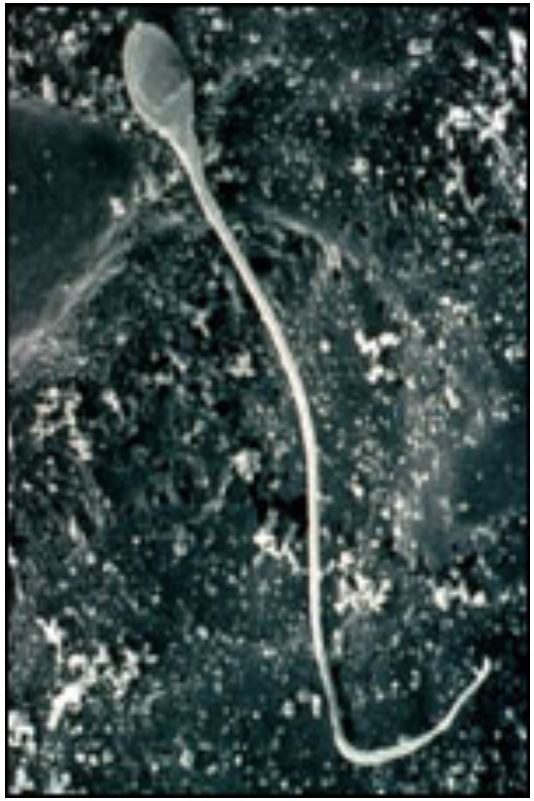



day 3
day 2
day 1
day 4
4 cells
2 cells
blastocyst
morula
zygote
day 7
inner cell mass of blastocyst
Fertilization
day 0
embryo
blastocyst implanting
ovulated egg
muscle layer
uterine wall
endometrium


V-2
Project Bumper
(V-2 plus WAC
Corporal)
Hermes
(Enlarged) →
(To Scale)


Catalase
and
Super Oxidase
Desmutase
Reactive
Oxygen
Species
Protection
Αντιοξειδωτικοί
παράγοντες
Demolition
Οξειδωτικοί
παράγοντες

Διατάραξη της προστασίας σε επίπεδο κυτταρικής μεμβράνης



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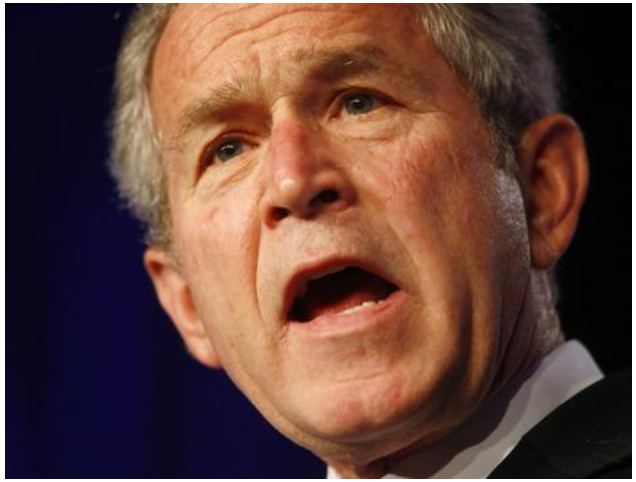


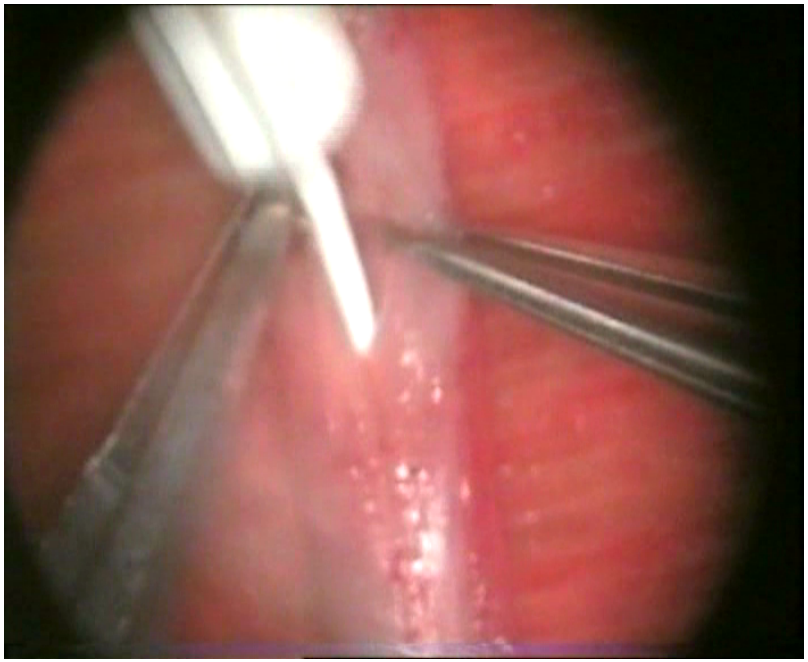
ROS

Κινητικότητα

- Η πρωτεΐνη **CatSper**, ευθύνεται για τις «δραστήριες ουρές», επιτρέποντας την είσοδο ιόντων ασβεστίου στο σπερματοζωάριο, όπου με τη σειρά τους ενεργούν σαν «καύσιμο» για την κίνηση της ουράς. Ακόμη ερευνάται το κατάλληλο φάρμακο που θα «αναστέλει» την CatSper

- Η κινητικότητα των σπερματοζωαρίων χρειάζεται μεγάλη ενέργεια από ATP, το οποίο προκύπτει από την γλυκόλυση στα σπερματοζωάρια. Διάφορα ισόμορφα ένζυμα στην γλυκολυτική οδό ερευνώνται

Ας βρούμε άλλον στόχο



- Συσκευή «Intra Vas Device» - IVD.
- Ο μηχανισμός αυτός παρέχει μια εναλλακτική μέθοδο προσωρινής στείρωσης προς εκείνη της βασεκτομής, μέσω δύο φυσιγγίων σιλικόνης που φράζουν τη δίοδο του σπέρματος στους όρχεις και μπορούν να αφαιρεθούν αν ο χρήστης τους αλλάξει γνώμη.
- Μετά από έξι μήνες ποσοστό **92%** των ανδρών δεν παρήγαγαν σχεδόν καθόλου σπέρμα. Έρευνες σε ζώα έδειξαν επιστροφή της γονιμότητας έπειτα από ολιγόχρονο χρήση, αλλά δεν υπάρχουν ακόμη στοιχεία για τη γονιμότητα ύστερα από μακροχρόνια χρήση.

- Epididymis is like a Medical School:

Immature Subjects Undergo Maturation