Department of Urology, Pediatric Urology and Andrology

JUSTUS- LIEBIG UNIVERSITY GIESSEN

DIAGNOSIS AND TREATMENT OF MALE ACCESSORY GLAND INFECTIONS

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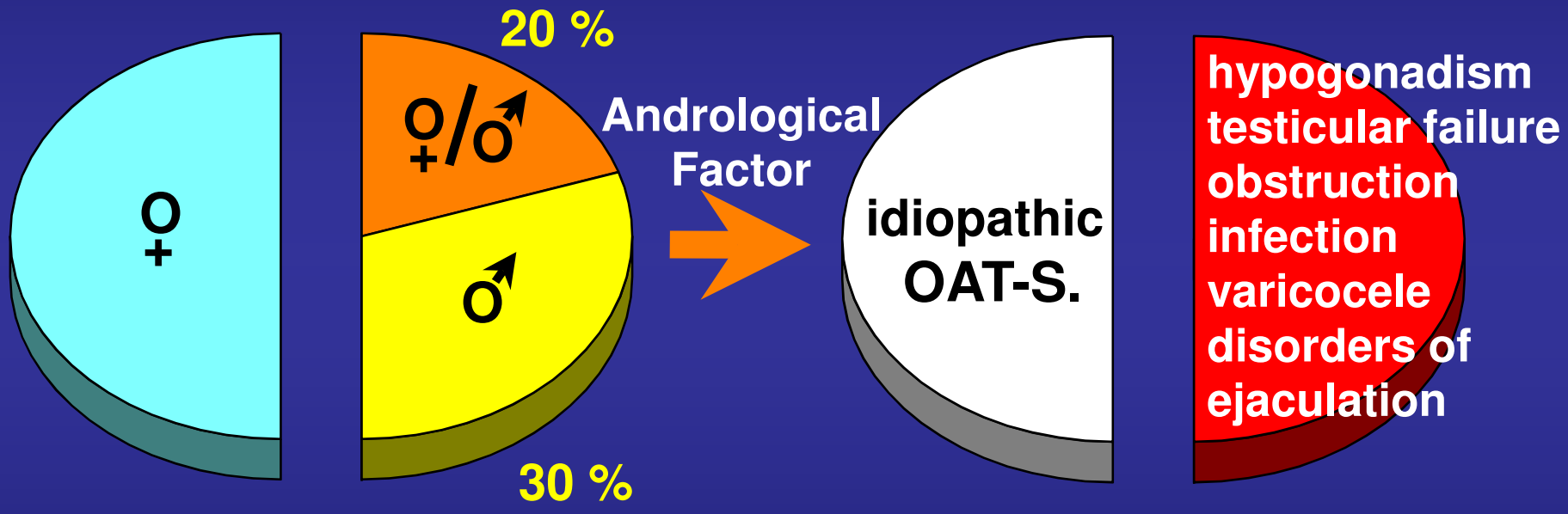
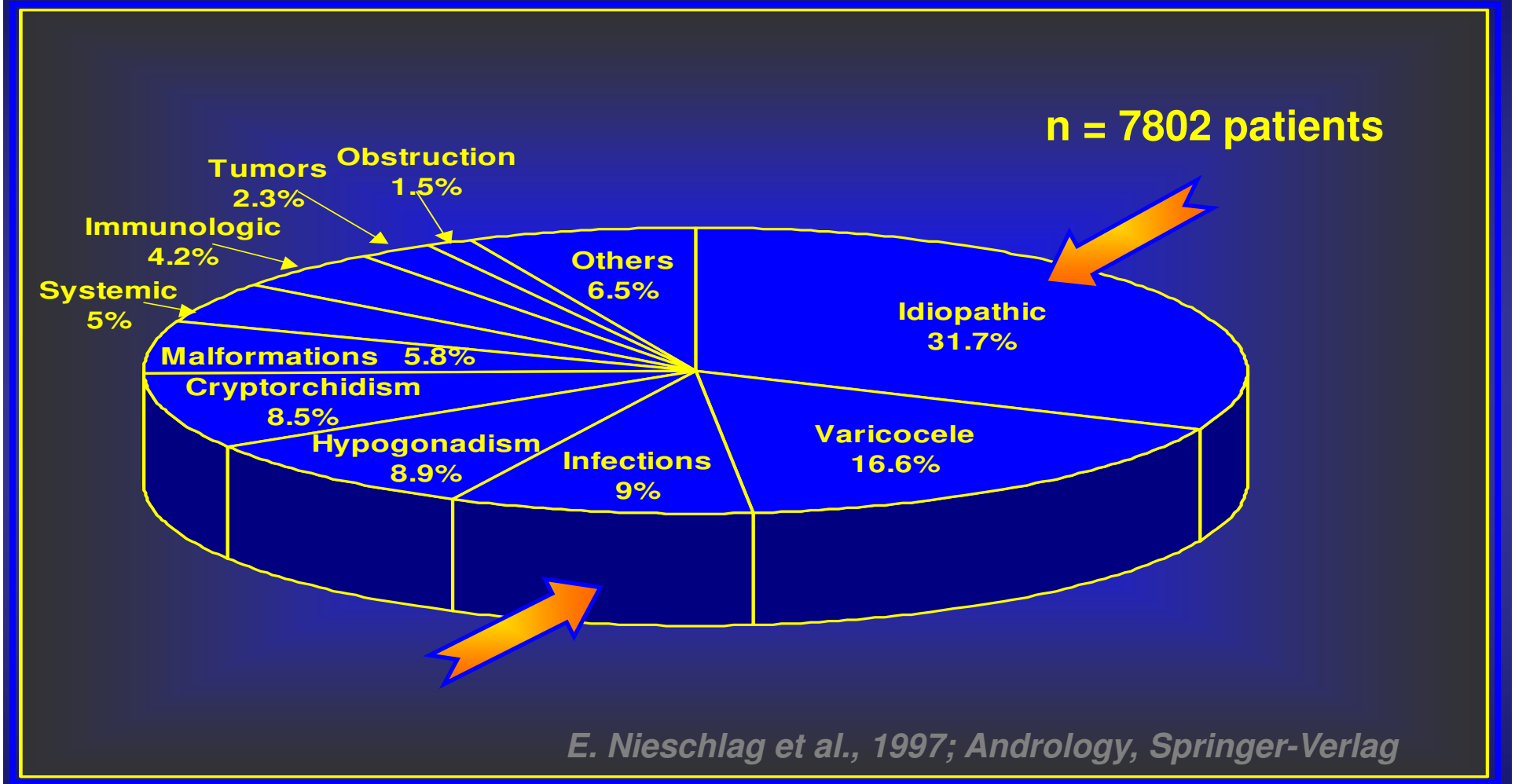
Androlological Causes for Infertile Partnership



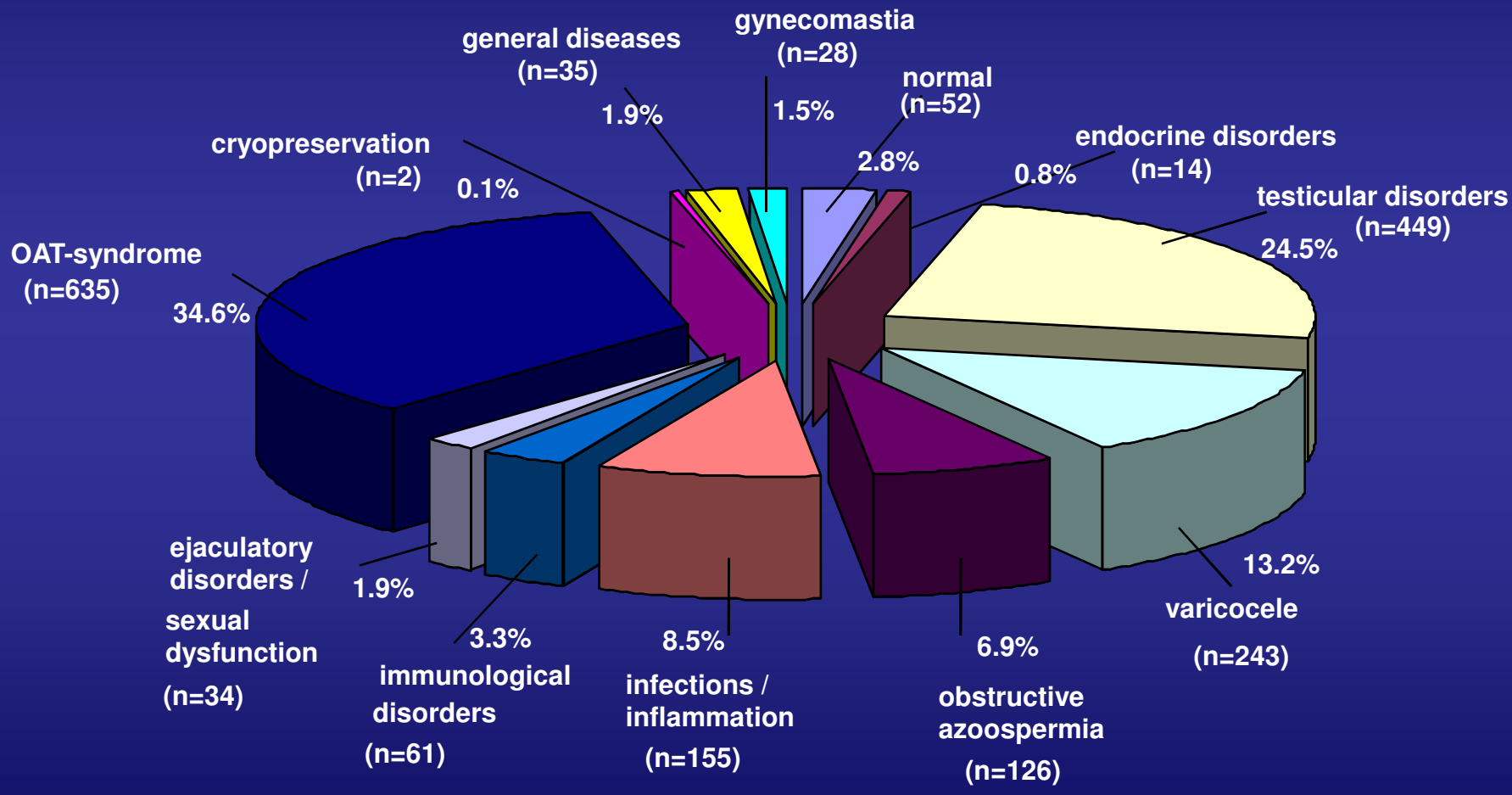
De Kretser, Baker, J Clin End Met 84: 3343 (1999)
Weidner et al., Eur Urol 42: 313 (2002)

Causes of Male Infertility



E. Nieschlag et al., 1997; Andrology, Springer-Verlag

Diagnosis of consecutive 1834 Men with Fertility Problems



Andrological Outpatient Department
Urology Giessen (2008)

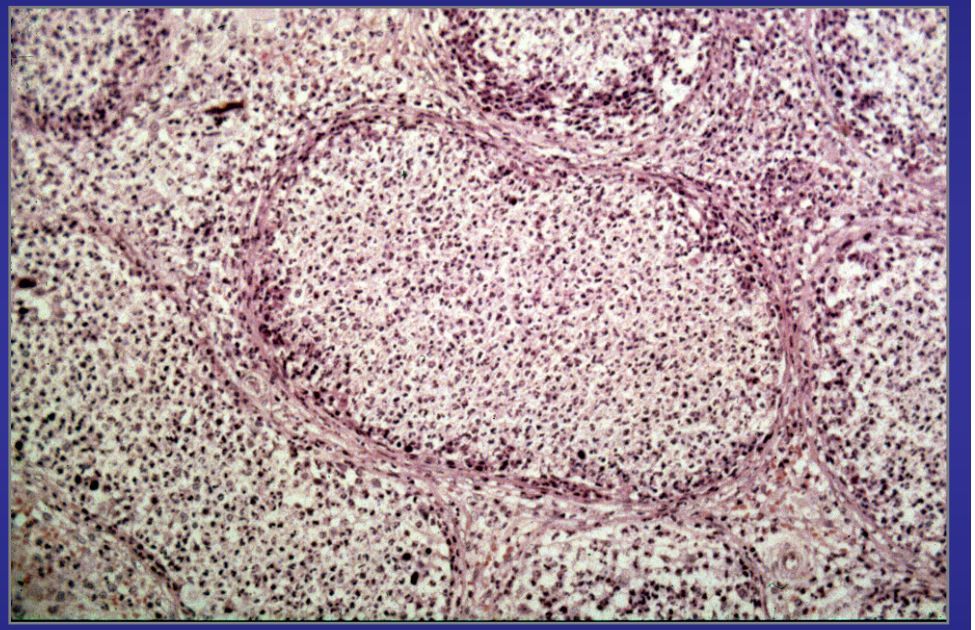
Infections and Male Infertility

- acute and chronic urogenital infections (frequent)
  - Orchitis and Epididymitis
  - Prostatitis, Chronic Pelvic Pain Syndrome
  - MAGI
  - (Urethritis)
- generalized systemic infections (rare)

Epididymo-Orchitis

- Swelling, STD and UTI, chronic inflammation

Ultrasonography

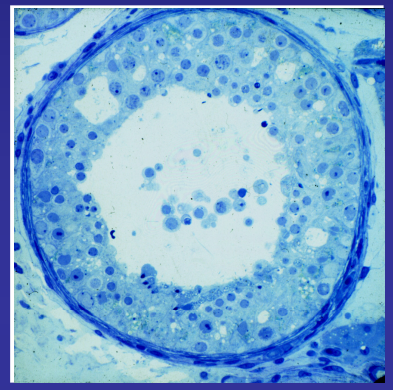


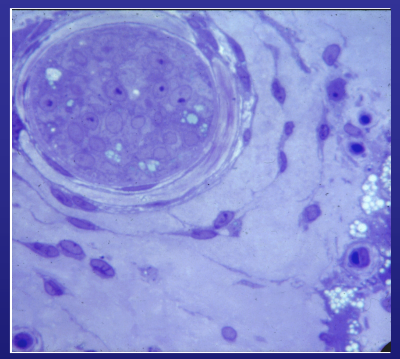
Biopsy

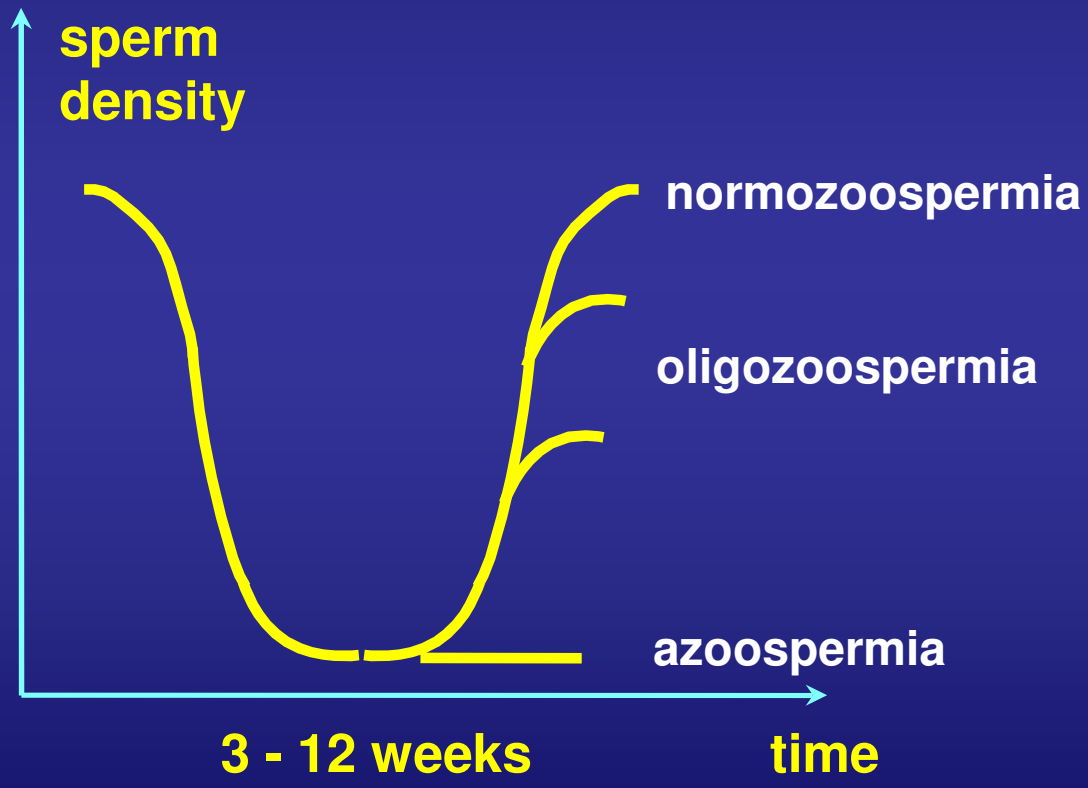
Recent results: 100 consecutive patients -> 70% positive microbiology

Pilatz et al., 2009
in press

Testicular Inflammmation and Spermatogenesis







Spermatological Outcome of Acute Epididymo-Orchitis

OAT - Syndrom	Testicular azoospermia	Obstructive (Epididymal) azoospermia
50 %	< 1 %	< 5 %

Weidner et al., Human Reproduction Update, 1999
Diemer and Desjardins, Encyclopedia of Reproduction, 1999
Paavonen and Eggert-Kruse, Human Reproduction Update, 1999

Chronic Inflammation in Testicular Biopsies Azoospermia

- Up to 14% peritubular lymphocyte-inflammation[1]
- Mast-cell increase[1,2]
- Interaction to dendritic cells[2]
- Association to spermatogenetic failure[2]

- Direct association to bacterial origin is lacking -

[1] Schuppe and Meinhardt, 2008

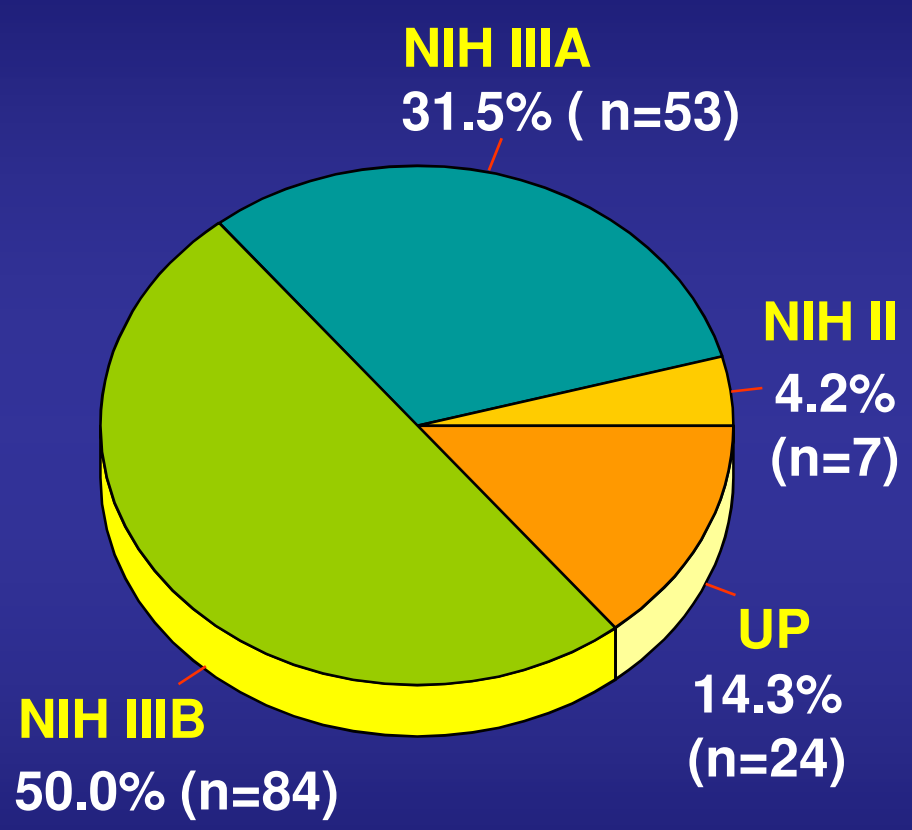
[2] Bhushan et al., 2008

Prostatitis
NIDDK / NIH Classification

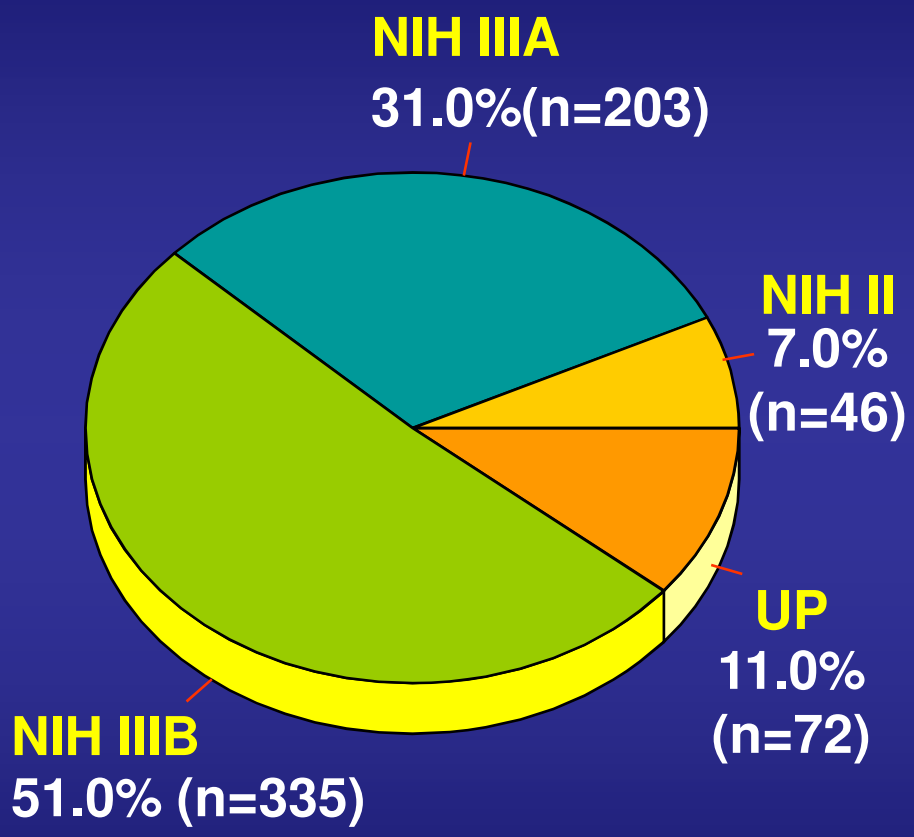
I	Acute Bacterial Prostatitis (ABP)
II	Chronic Bacterial Prostatitis (CBP)
III	Chronic Pelvic Pain Syndrome (CPPS)
A	Inflammatory (EPS, VB III, Semen)
B	Non - inflammatory
IV	Asymptomatic (inflammatory)

Krieger et al., JAMA 292: 236 (1999)

GIESSEN COHORT STUDIES

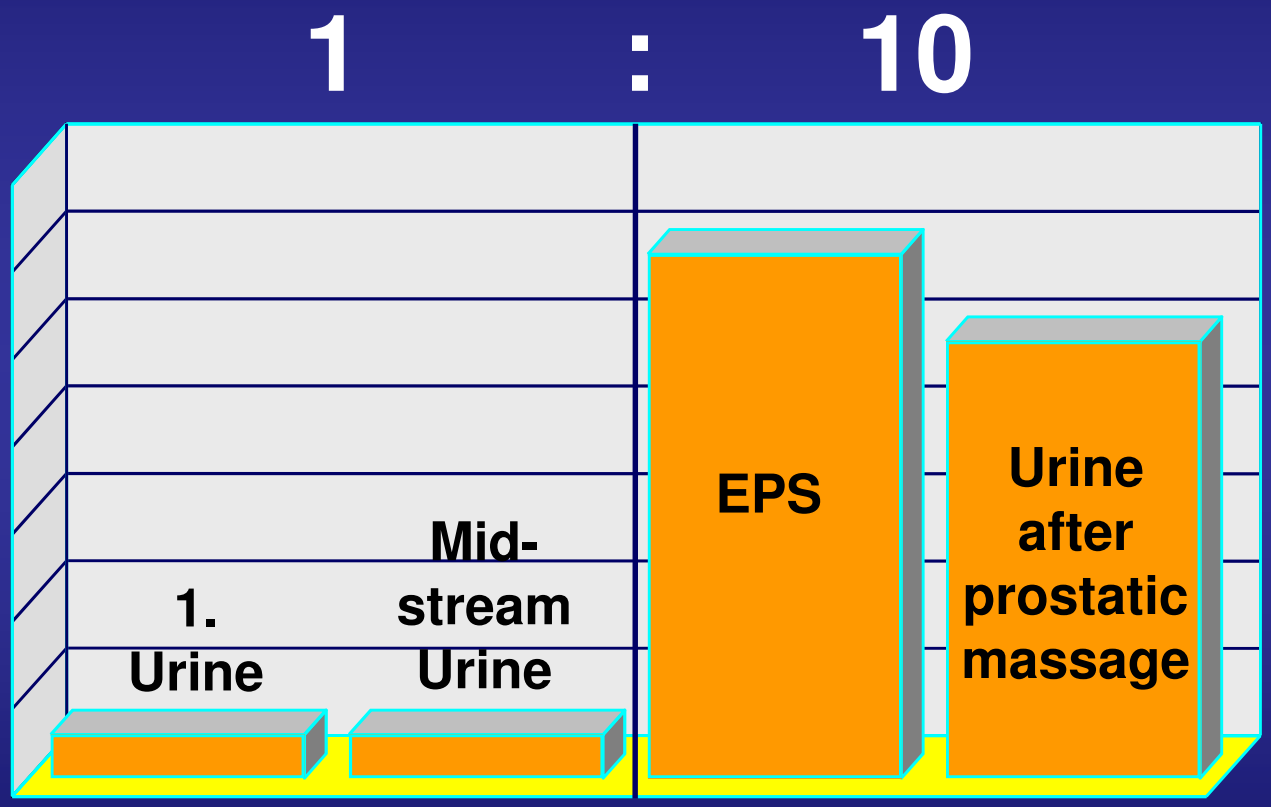


Study 2002
2001-2002
n = 168



Study 1992
1985-1990
n = 656

4 - SPECIMEN - TECHNIQUE



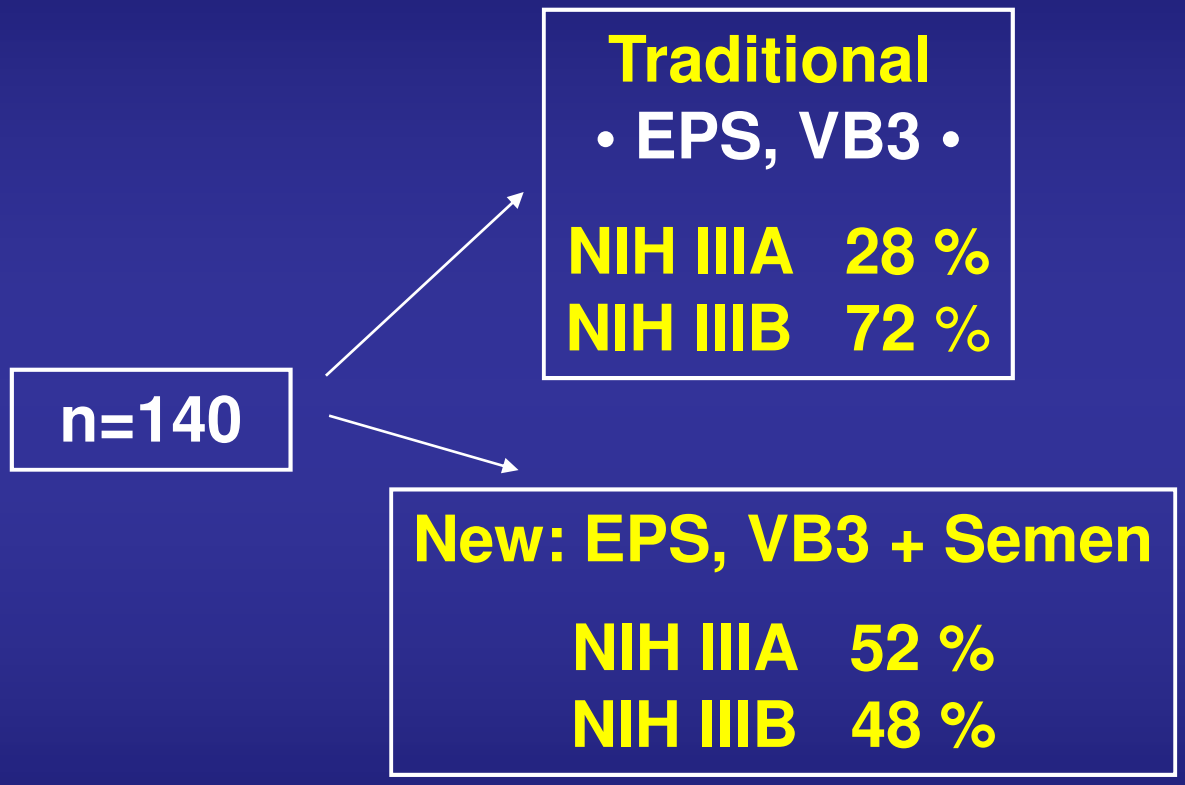
DIAGNOSTIC MANAGEMENT

INFECTIONS

- **NIH I** urine analysis, culture
- **NIH II** 4 and 2 glass test,
  semen culture,
  (significant bacteriospermia in about 50%)
- **NIH III** 4 and 2 glass test are an indicator for inflammation and infection
- **NIH IV** no suggestion

Paris, 2005
Consensus Conference
NIH, EAU, WHO

INFLUENCE OF LEUKOCYTES IN THE EJACULATE ON CP / CPPS CLASSIFICATION

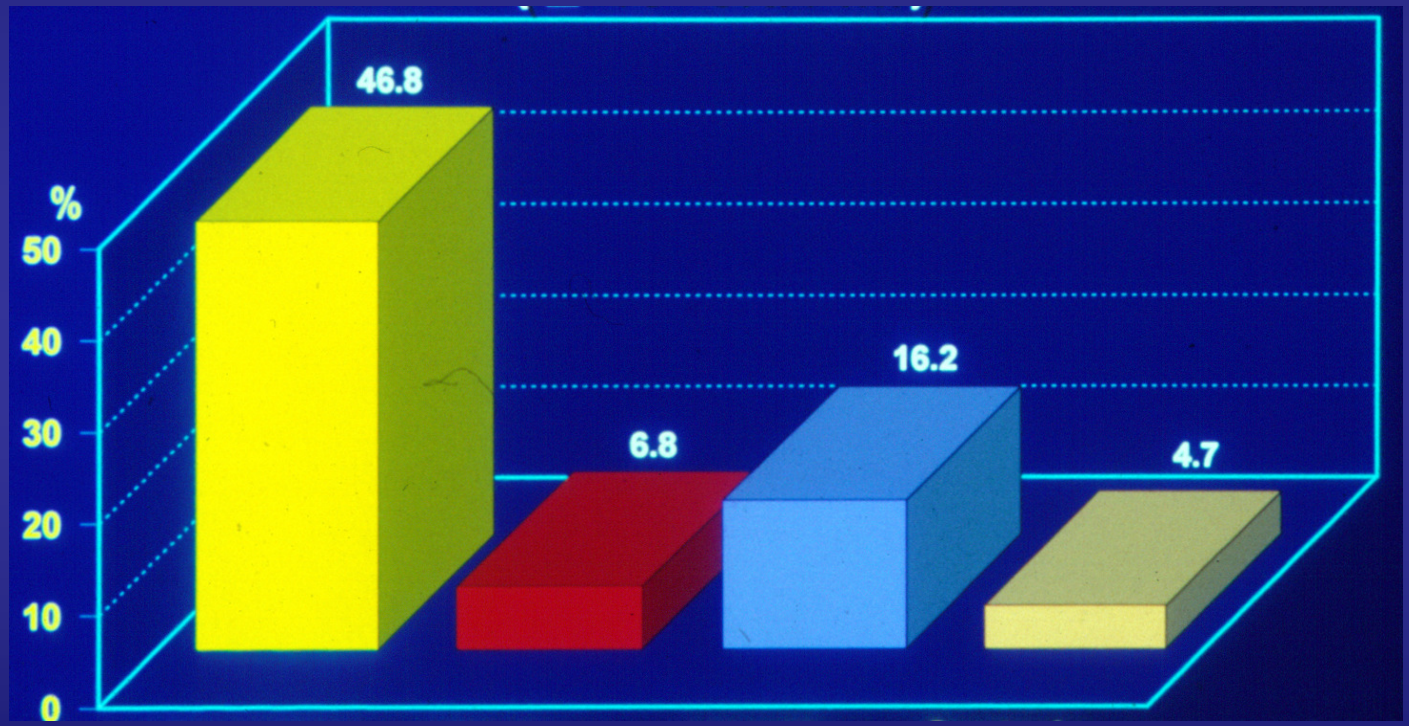


1.9 fold more patients to have inflammatory CP / CPPS

Krieger et al., 2003

Bacteriospermia in CBP

($\geq 10^3$ cfu/ml)



Weidner et al., Arch. Androl., 26: 173 (1991)

DIAGNOSTIC PROCEDURES

NIH III / CP-CPPS

Ejaculate

Ejaculate quality	no influence
Evidence of leukocytes	Improves the accuracy for classification in category IIIa and IIIb
Autoimmune markers (complement, T-cells) Immunoglobulines cytokines	only research

Paris, 2005
Consensus Conference
NIH, EAU, WHO

Cutpoints for EPS, urine after P.M. (VB3) and ejaculate/seminal plasma parameters indicative for inflammation

	parameter	cutpoint
EPS	leukocytes	≥ 10-20/1000 x
VB3	leukocytes	≥ 10/mm^3
Semen	PPL	≥ 0.113 x 10^6/ml
Seminal plasma	Elastase	≥ 280 ng/ml
Seminal plasma	IL-8	> 10600 pg/ml

Wagenlehner and Weidner, 2008

Inflammatory Parameters in CP/CPPS and Infertile Men

	NIH IIIa N34	NIH IIIb N140	Infertile Men N77
Age	45 (19-69)	42 (18-69)	40 (15-71)
PPL (mill./ml)	0.23 (0-8.24)	0.04 (0-12.08)	0.07 (0-23.04)
Elastase (ng/ml)	188 (7-1.708)	95 (4-1001)	91 (2-400)
IL-8 (pg/ml)	2,969 (27-10,001)	1,588 (7 – 10,001)	1,602 (13-10,001)

ongoing study
Wagenlehner et al.
Dresden 2009

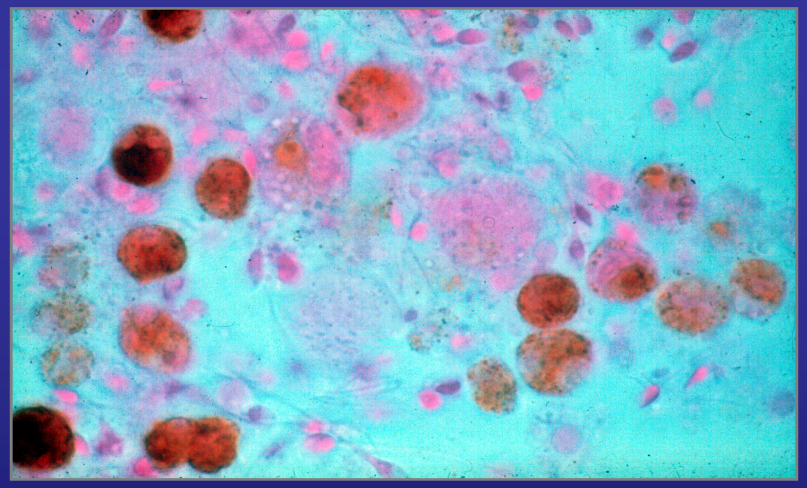
Altered Sperm Parameters and „Prostatitis“

Sperm Parameter	Proven	Questionable	No hint	Comment
Bacteriospermia	+			CBP
OAT-S.		+		totally unclear
Leucocytospermia	+			CBP, NIH IIIa
Cytokine response	+			NIH IIIa
ROS formation		+		no new data
Sperm antibodies			-	recently reconfirmed
Inflammatory obstruction	(+)			rare

Male Accessory Gland Infection

- Asymptomatic (silent ejaculate infection)
- Leukocytospermia

WBC > 1 x 10^6/ml
Peroxidase Staining



WHO, WHO Manual
Cambridge University Press, 1992

Unsolved Problems
of Leukocytospermia

- Only associated with bacterial infections in 20 %
- high rate of spontaneous resolution in infertile men

MAGI – CLASSIFICATION SYSTEM

Group A	Group B	Group C
Typical History/ Physical Signs	Urine after P-Massage	Ejaculate signs
e.g. UTI, Epididymitis, STD Epididymal swelling Abnormal prostate	Increased PML C. trachomatis	PPL Bacteriospermia C. trachomatis Biochemistry Inflammation

C. trachomatis PCR
PPL > 1 Mill./ml
Bacteriospermia > 1000 cfu/ml
Elastase > 250 ng/ml

MAGI =
a) 2 signs,
each from a different group
b) at least 2 ejaculate signs

(WHO 1993, 2000)

PATIENTS / METHODS

- 258 infertile men (age 24-69 years)
- Ejaculate analysis according to WHO
  → analysis of PPL (1 Mill./ml), bacteria (10^3 cfu/ml), elastase (250 ngl/ml)
- Exclusion of urethritis (1. voided urine: PML, C. trachomatis, N. gonorrhoeae)
- Diagnosis of NIH II prostatitis and CP/CPPS
  → NIH-CPSI, 4-glass-technique
- Diagnosis of chronic epididymitis
  → palpation, scrotal ultrasonography

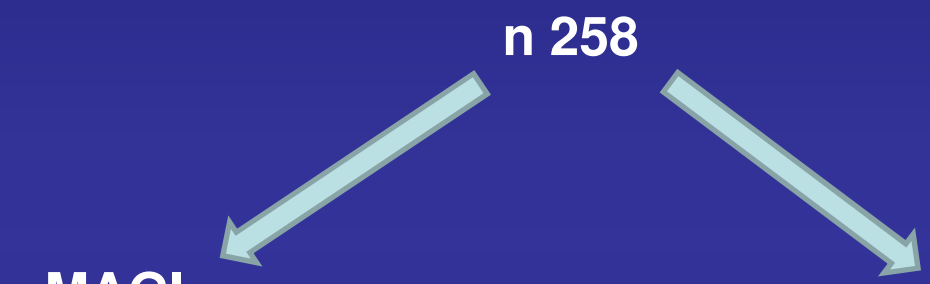
RESULTS

DIAGNOSIS OF UROGENITAL INFECTION / INFLAMMATION

including
25 epididymitis
14 urethritis

RESULTS

DIAGNOSIS OF PROSTATE RELATED INFECTION / INFLAMMATION



excluding
25 epididymitis
14 urethritis

"prostatitis"	
NIH II	26 (10 %)
NIH IIIa	36 (14 %)

RESULTS

EJACULATE DIAGNOSIS OF UROGENITAL INFECTION / INFLAMMATION IN DEFINED ENTITIES

	n	Evidence of Bacteriospermia	PPL	Elastase	C. trachomatis
NIH II	26[x]	none[xx]	12	15	none
NIH IIIa	36	none	24	20	none
Epididymitis	25	9	9	8	2
Urethritis	14	1	4	4	12

[x] 15 x E. Coli [xx] > 10^3 cfu/ml

CONCLUSIONS

- The WHO diagnosis „MAGI“ detects urogenital infection/inflammation in about 20% of patients.
- In this figure, cases of epididymitis and urethritis are included.
- Prostate related infections (NIH II) are detectable in 10% of infertile men.
- Questionable prostate-related inflammatory changes (NIH IIIa) have to be noted in further 14%.
- Ejaculate analysis demonstrates leukocytal activity in about two thirds of these cases.
- The MAGI classification of the WHO clearly underestimates the percentage of infections/inflammatory prostatitis and/or CP/CPPS in male infertility.

CONCLUSIONS

To exclude male urogenital infections and inflammation in infertile men

- ejaculate analysis
- clinical investigation of the epididymis
- a 4 glass test for prostatitis diagnosis

are mandatory.

THERAPEUTIC DILEMMA

- Antibacterial therapy works in about 70%
- The persistence of inflammation can not be predicted.

SUGGESTED ANTIBIOTIC IN CBP (NIH II)

fluoroquinolones	1. choice
trimethoprim / sulfamethoxazole	in FQ resistence (2-3 months)
macrolides	gram positives, atypical m.
tetracyclines	atypical m.
aminoglycosides	not suggested

EAU guidelines 2009

Fluoroquinolones in CBP

	Dosage/day (mg)	Days	n	Eradication (%)	Follow up (mo)	
Norfloxacin Schaeffer et al	800	28	14	64	6	1990
Norfloxacin Petrikkos et al	4-800	174	42	60	8	1991
Ofloxacin Pust et al	400	14	21	67	12	1989
Ciprofloxacin Weidner et al	1000	14	15	60	12	1987
Ciprofloxacin Weidner et al	1000	28	16	63	21-36	1991
Ciprofloxacin Pfau	1000	60-150	7	86	12	1987,1991
Ciprofloxacin Naber et al	1000	28	34	76	6	2000
Ciprofloxacin vs.	1000	28	78	72	6	2001
Lomefloxacin Naber et al	400	28	75	63	6	2001
Levofloxacin Bundrick et al	500	28	136	53	6	2003
Naber et al	500	28	116	84	6	2008

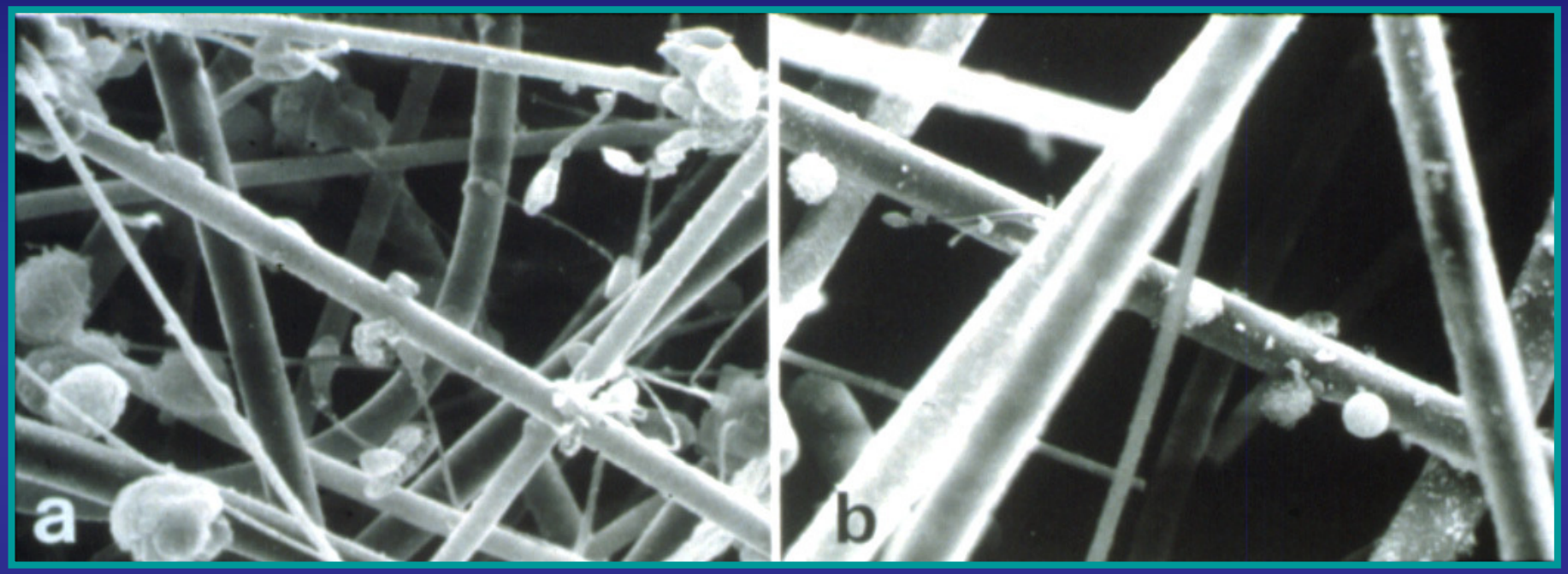
NIH II

- **NIH II** antibiotics, α-blockers (4 weeks)
  → 63-76% bacteriological cure

- **failure**
  - intermittent antimicrobial therapy (acute symptomatic)
  - low dose suppression
  - radical TUR-P or prostatectomy

Paris 2005

Sperm Preparation: Glasswool



Henkel und Schill, Andrologia 30 (Suppl 1): 91 (1998)

TARGETS OF THERAPY

- Eradication of Microorganisms
- Normalization of Inflammatory Parameters ?

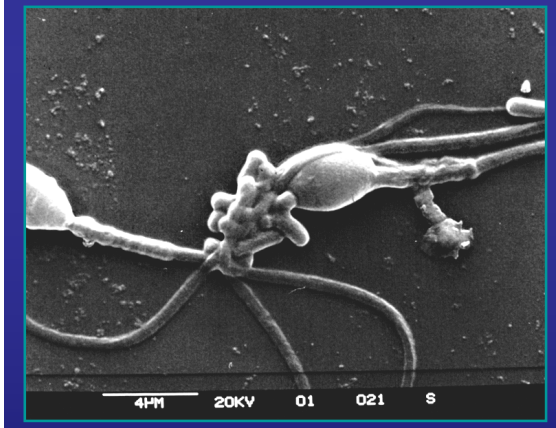
↓

Normalization of Symptoms

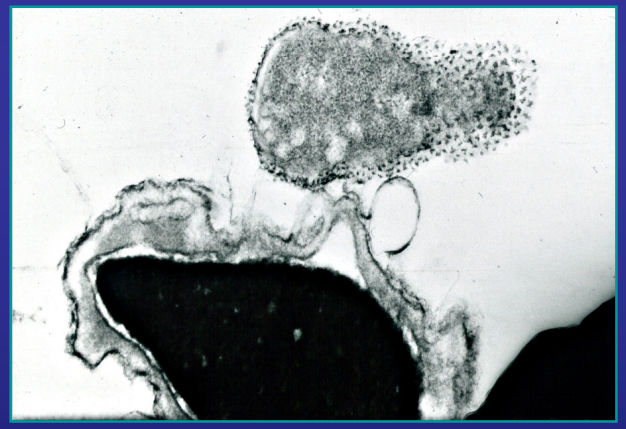
Bacteria - Sperm - Interaction

→ Motility and Morphology ←

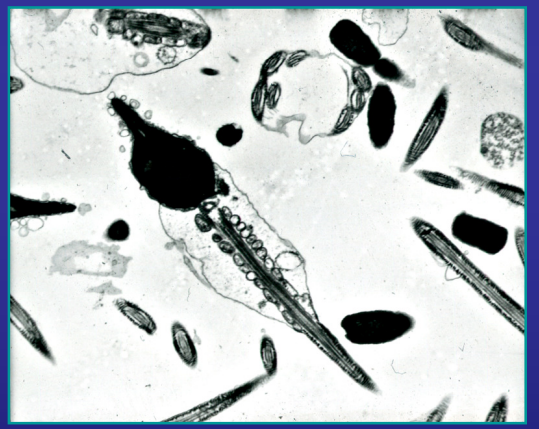
Agglutination



Adhesion



Membrane damage



Diemer, Weidner et al.,
Int J Androl 19: 271 (1996)
Int J Androl 23: 178 (2000)
Andrologia 35: 100 (2003)

Bacteria - Sperm - Interaction

Motility and Morphology

Depending upon

- **Species**
  + E. coli, C. trachomatis
  - E. faecalis, Staphylococcus spp.
- **Number**
- **Time**

Diemer, Weidner et al.,
Int J Androl 19: 271 (1996)
Int J Androl 23: 178 (2000)
Andrologia 35: 100 (2003)

Bacteriospermia