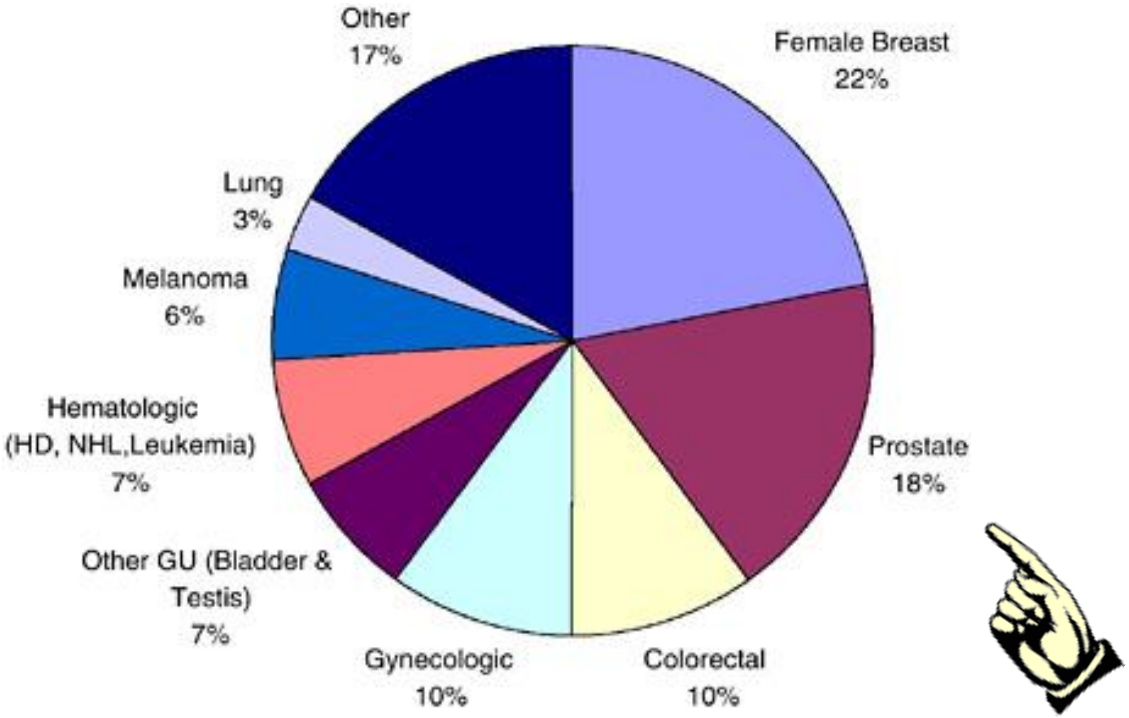
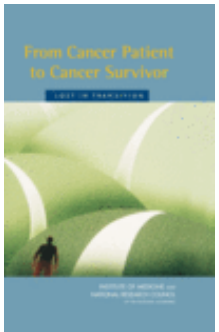
Is androgen supplementation feasible in the hypogonadal patient treated for prostate cancer?

Emmanuele A. Jannini
SCHOOL OF SEXOLOGY
University of L'Aquila
ITALY

www.issc.nu
The 2nd Rotterdam Symposium on Cancer and Sexuality
Controversies in Cancer and Sexual Function

Distribution of cancer survivors in the U.S. by site, 2002.





The famous book ***Cancer Patient to Cancer Survivor: Lost in Transition*** (2005) calls for implementation and evaluation of care plans addressing cancer survivors' needs across a broad spectrum, from ongoing medical care to psychosocial concerns

Radical Prostatectomy

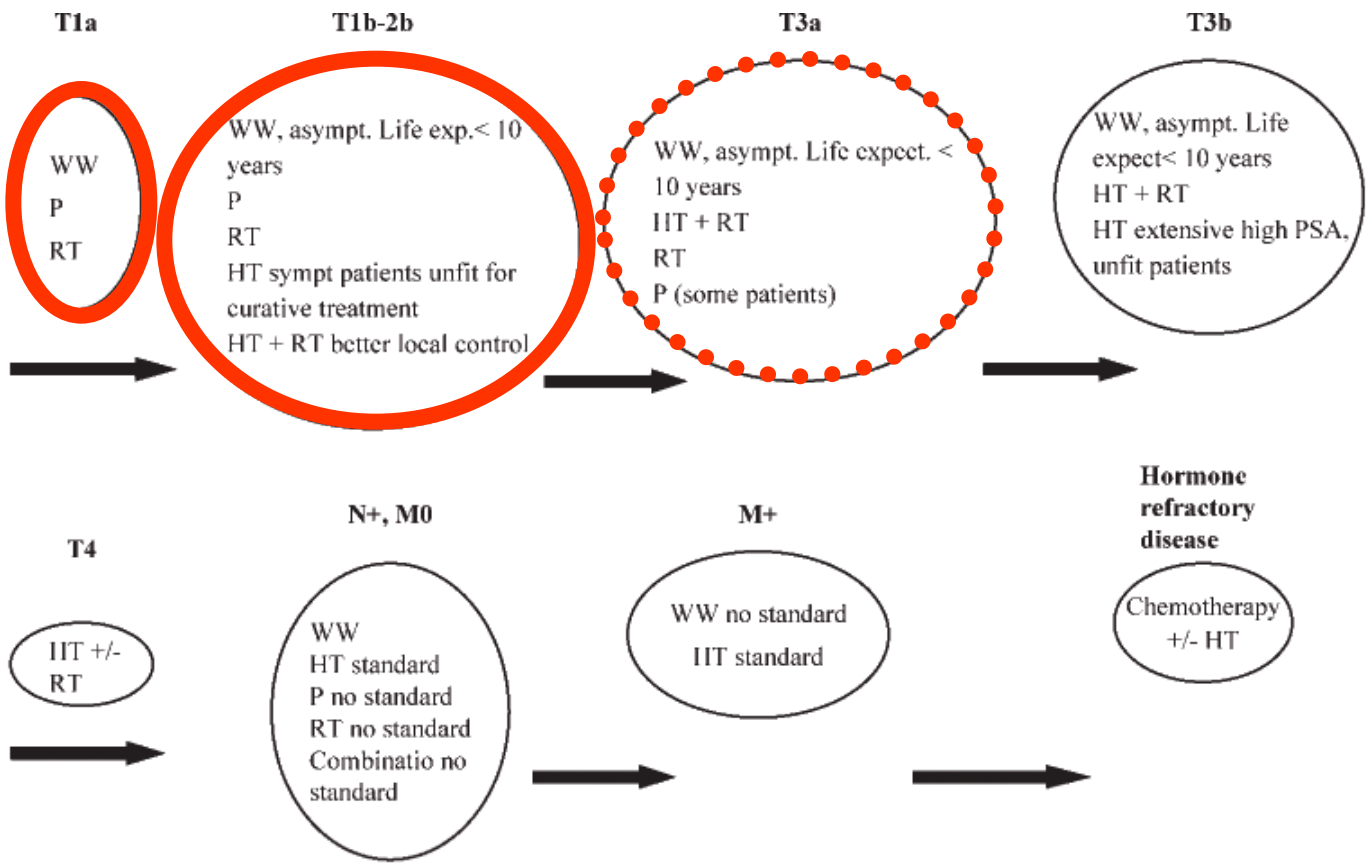
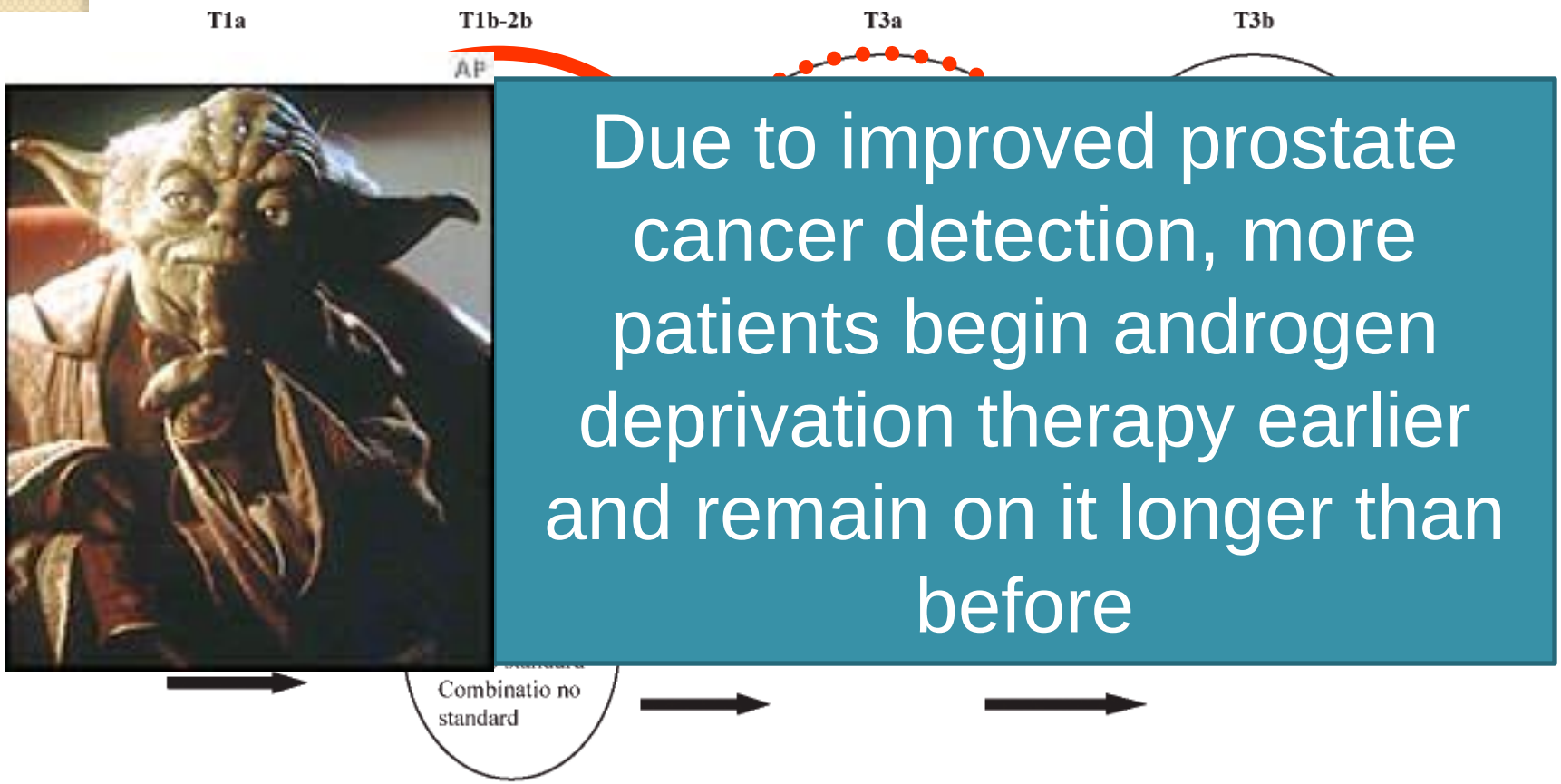


Figure 2. Stepwise treatment options stage by stage (according to TNM classification prostate carcinoma) for patients with prostate cancer. WW = watchf waiting; P = radical prostatectomy; RT = radiotherapy; HT = hormonal therapy.

D'Acona & Debruyne Hum Reprod Update 11:309-17, 2005

Radical Prostatectomy

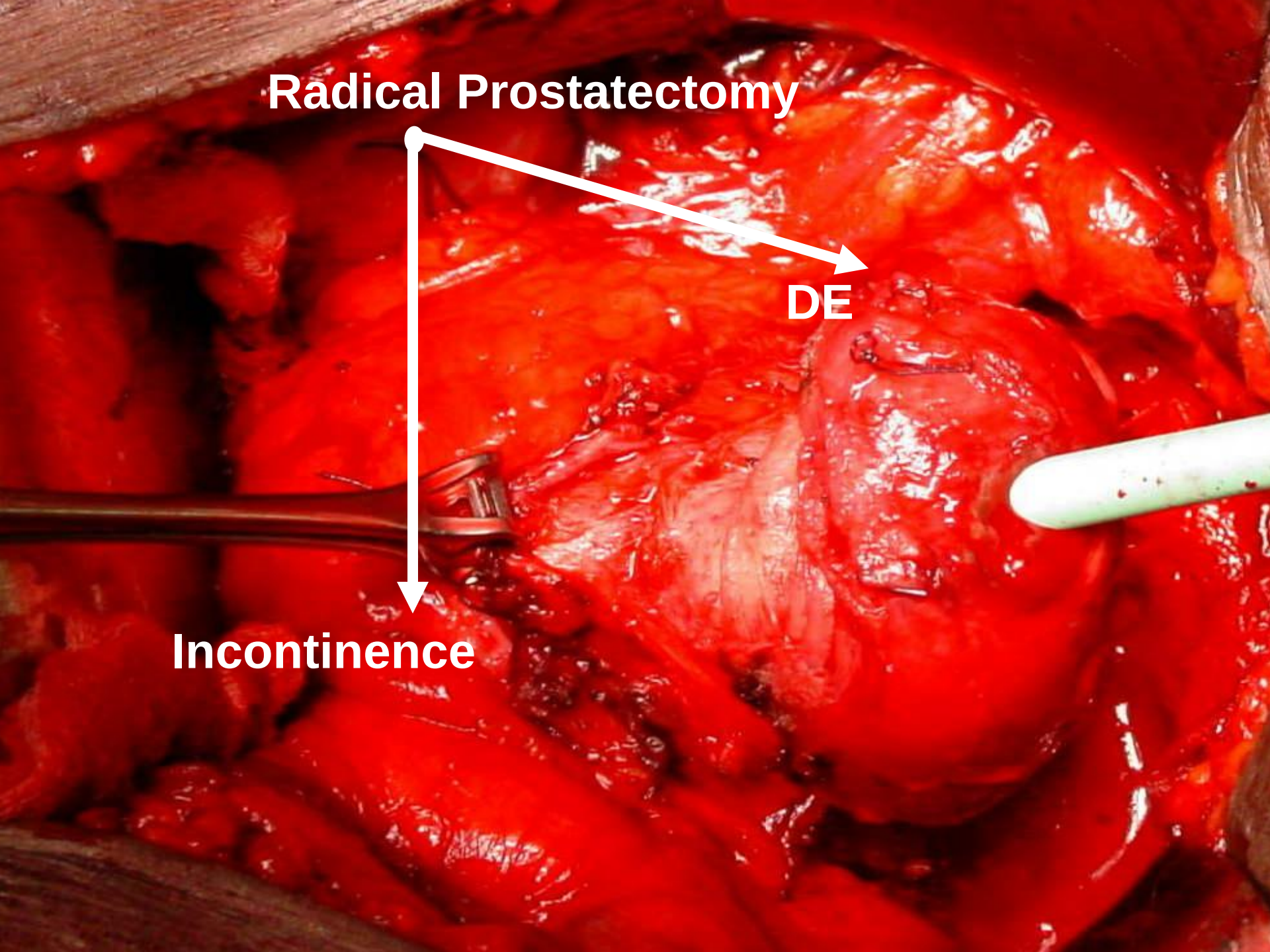


Due to improved prostate cancer detection, more patients begin androgen deprivation therapy earlier and remain on it longer than before

Figure 2. Stepwise treatment options stage by stage (according to TNM classification prostate carcinoma) for patients with prostate cancer. WW = watchf waiting; P = radical prostatectomy; RT = radiotherapy; HT = hormonal therapy.

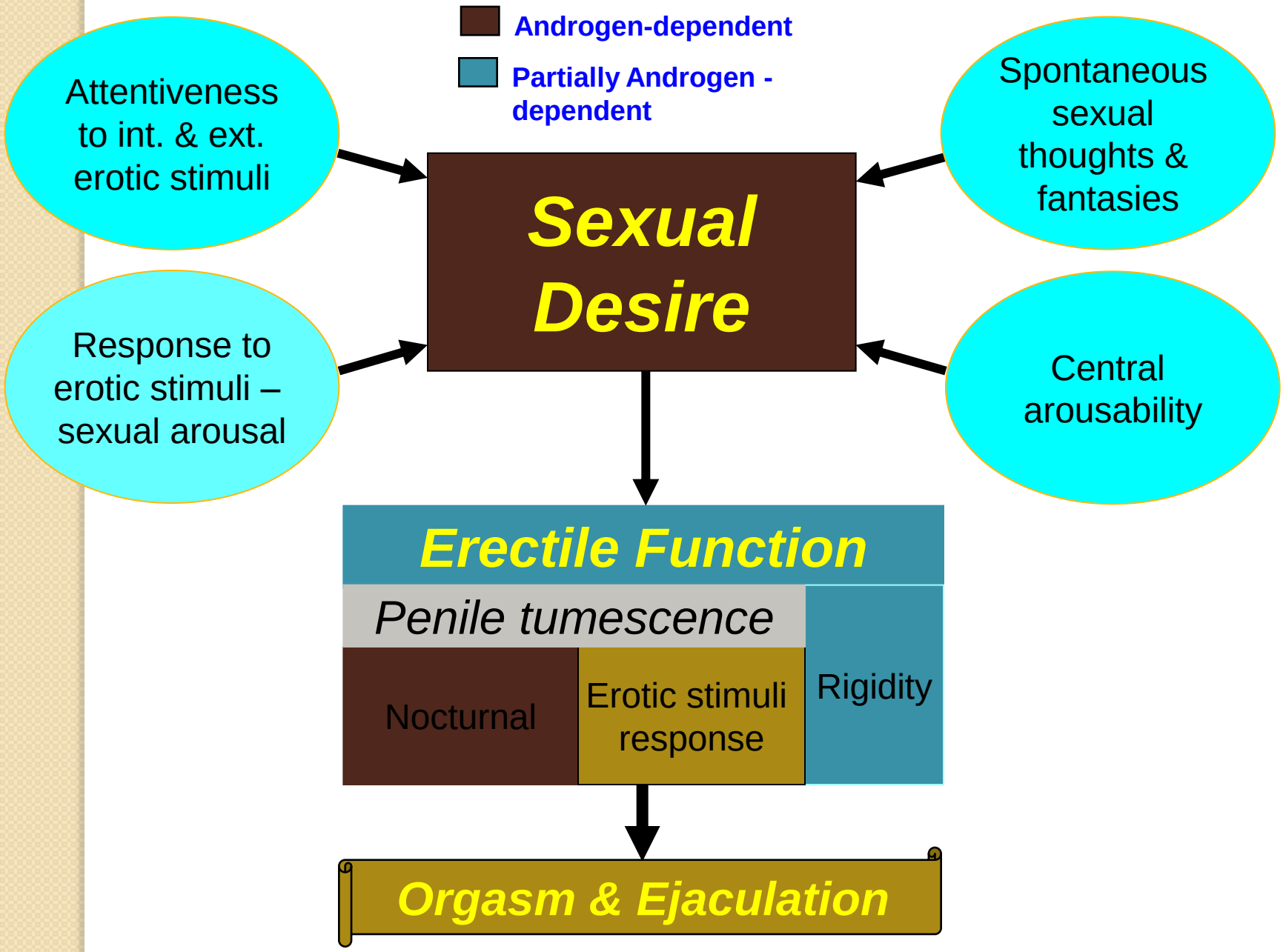
314

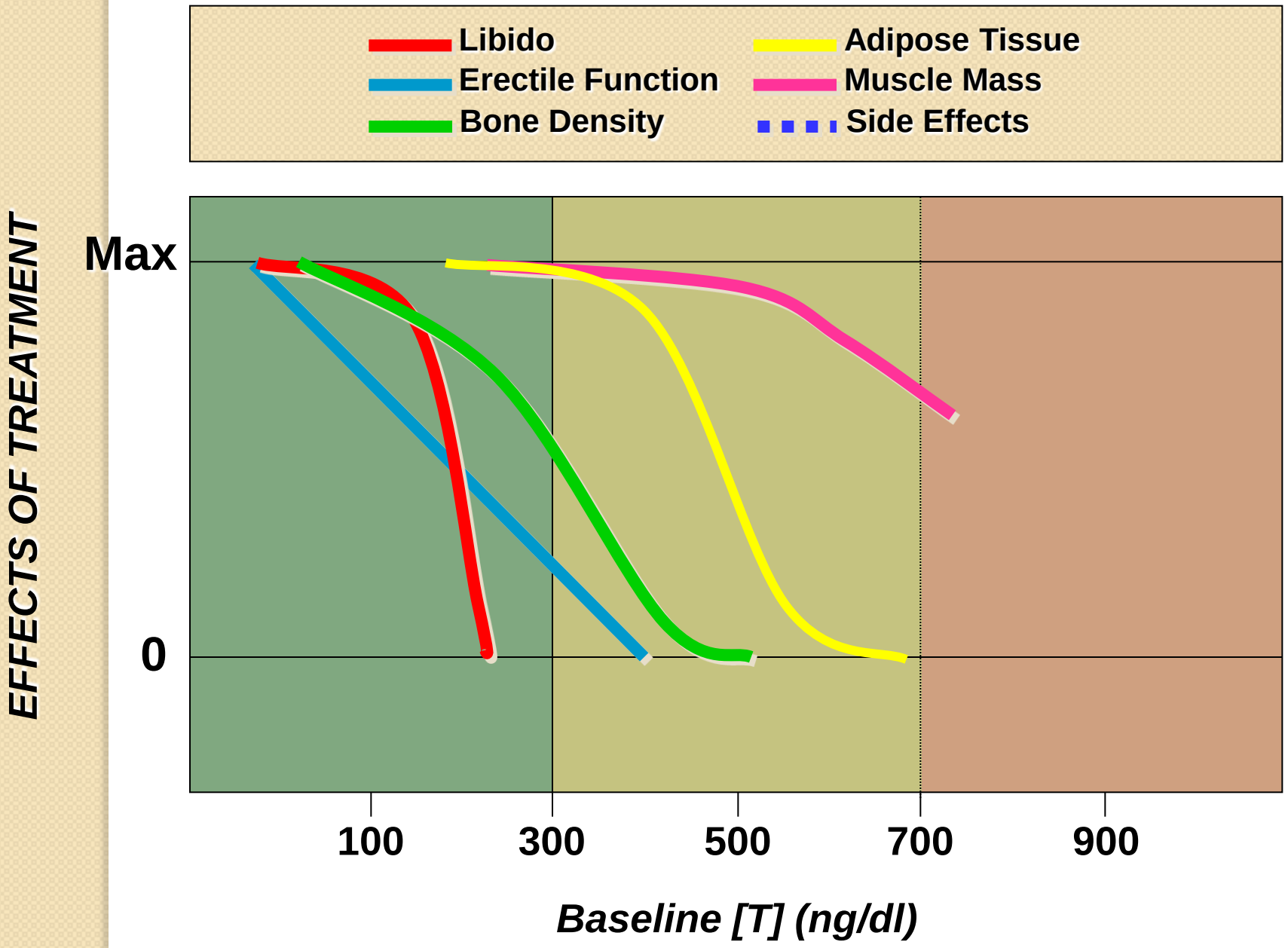
D'Acona & Debruyne Hum Reprod Update 11:309-17, 2005


Radical Prostatectomy
DE
Incontinence

TESTOSTERONE & HYPOGONADISM

The Role of Testosterone in Regulation of Sexual Function





Isidori AM, BJU Int 2005

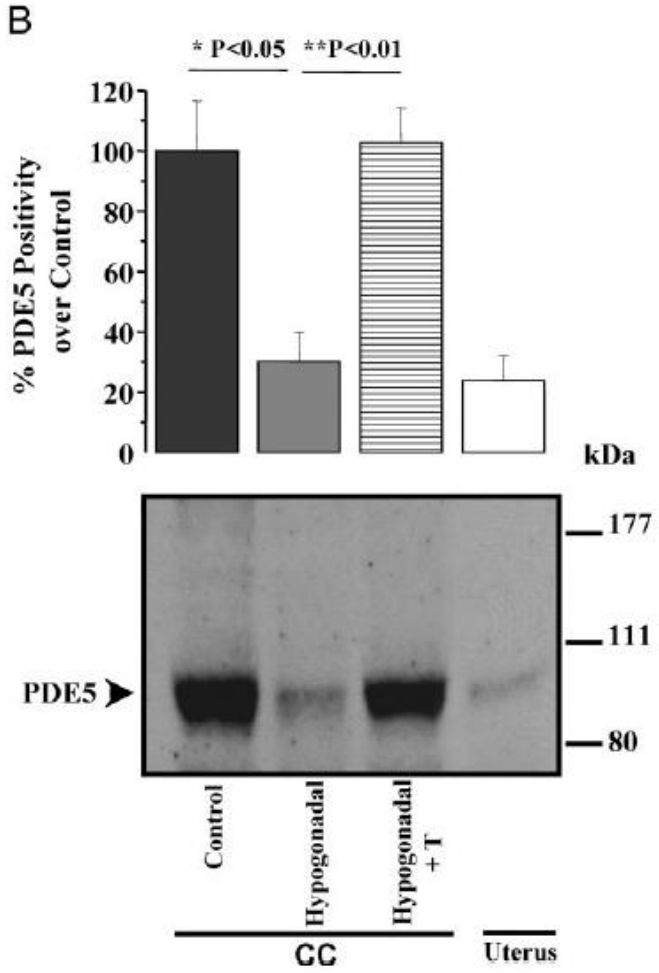
TESTORONE DEFICIENCY AND HYPOACTIVE DISORDERS (not necessarily low libido)

- The “That Viagra doesn’t work” syndrome:
  - His mind is not sexually aroused
  - Because his desire is low, or
  - His female partner is not enthusiastic/ not aroused, experiences no desire while sexually engaged: ED is very damaging to women’s sexual response.

Androgens Regulate Phosphodiesterase Type 5 Expression and Functional Activity in Corpora Cavernosa

ANNAMARIA MORELLI, SANDRA FILIPPI, ROSA MANCINA, MICHAELA LUCONI, LINDA VIGNOZZI, MIRCA MARINI, CLAUDIO ORLANDO, GABRIELLA BARBARA VANNELLI, ANTONIO AVERSA, ALESSANDRO NATALI, GIANNI FORTI, MAURO GIORGI, EMMANUELE A. JANNINI, FABRIZIO LEDDA, AND MARIO MAGGI

(*Endocrinology* 145: 2253–2263, 2004)



Hypogonadal men are less responsive to PDE-5i

Clinical Endocrinology (2003) **58**, 632–638

Androgens improve cavernous vasodilation and response to sildenafil in patients with erectile dysfunction

Antonio Aversa*, Andrea M. Isidori†, Giovanni Spera‡, Andrea Lenzi§ and Andrea Fabbri¶
**AFaR-CRCCS, Ospedale Fatebenefratelli Isola Tiberina, †Cattedra di Andrologia, ‡Cattedra di Medicina Interna III, §Cattedra di Patologia Clinica, Dipartimento di Fisiopatologia Medica, Università 'La Sapienza' and ¶Cattedra di Endocrinologia, Dipartimento Medicina Interna, Università 'Tor Vergata', Rome, Italy*

(Received 5 September 2002; returned for revision 13 November 2002; finally revised 18 November 2002; accepted 18 December 2002)

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Printed in U.S.A.
DOI: 10.1097/01.ju.0000132389.97804.d7

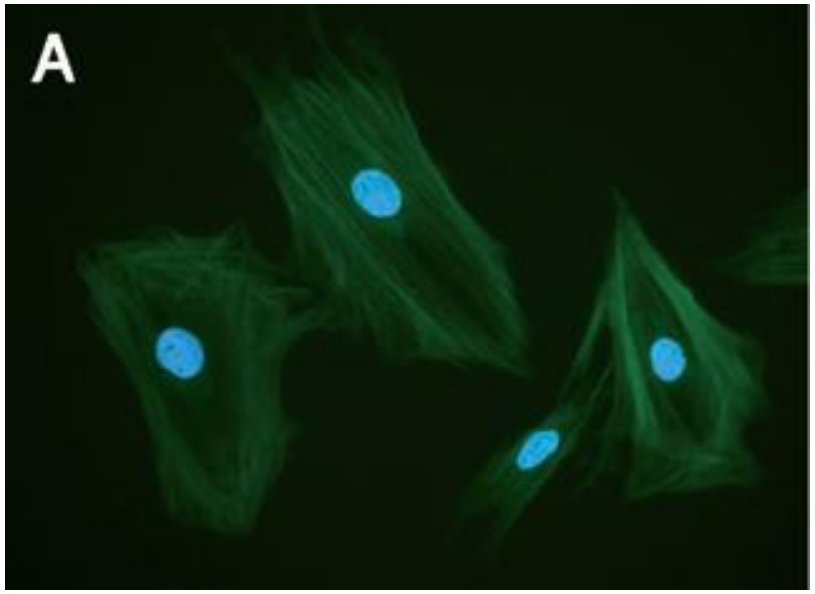
RANDOMIZED STUDY OF TESTOSTERONE GEL AS ADJUNCTIVE THERAPY TO SILDENAFIL IN HYPOGONADAL MEN WITH ERECTILE DYSFUNCTION WHO DO NOT RESPOND TO SILDENAFIL ALONE

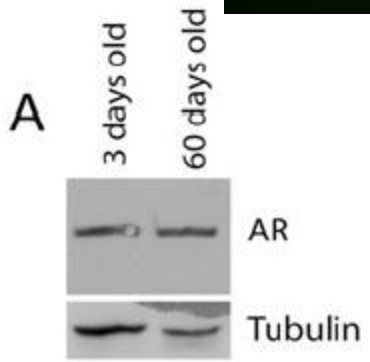
R. SHABSIGH,* J. M. KAUFMAN, C. STEIDLE AND H. PADMA-NATHAN

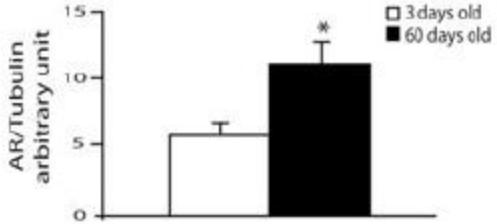
The Ontogenetic Expression Pattern of Type 5 Phosphodiesterase Correlates with Androgen Receptor Expression in Rat Corpora Cavernosa

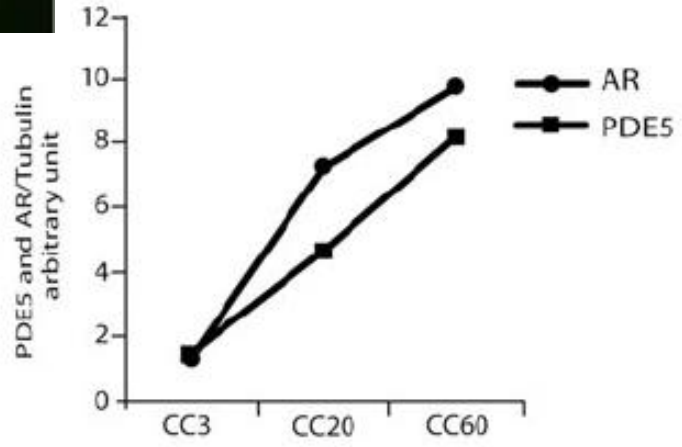
Eleonora Carosa, MD, PhD,* Simona Rossi, PhD,* Nadia Giansante, PhD,* Giovanni Luca Gravina, MD,* Alessandra Castri, PhD,* Susanna Dolci, MD, PhD,† Flavia Botti, PhD,† Annamaria Morelli, PhD,‡ Luigi Di Luigi, MD,§ Mario Pepe, MD,¶ Andrea Lenzi, MD,¶ and Emmanuele A. Jannini, MD*

J Sex Med 2009;6:388–396.





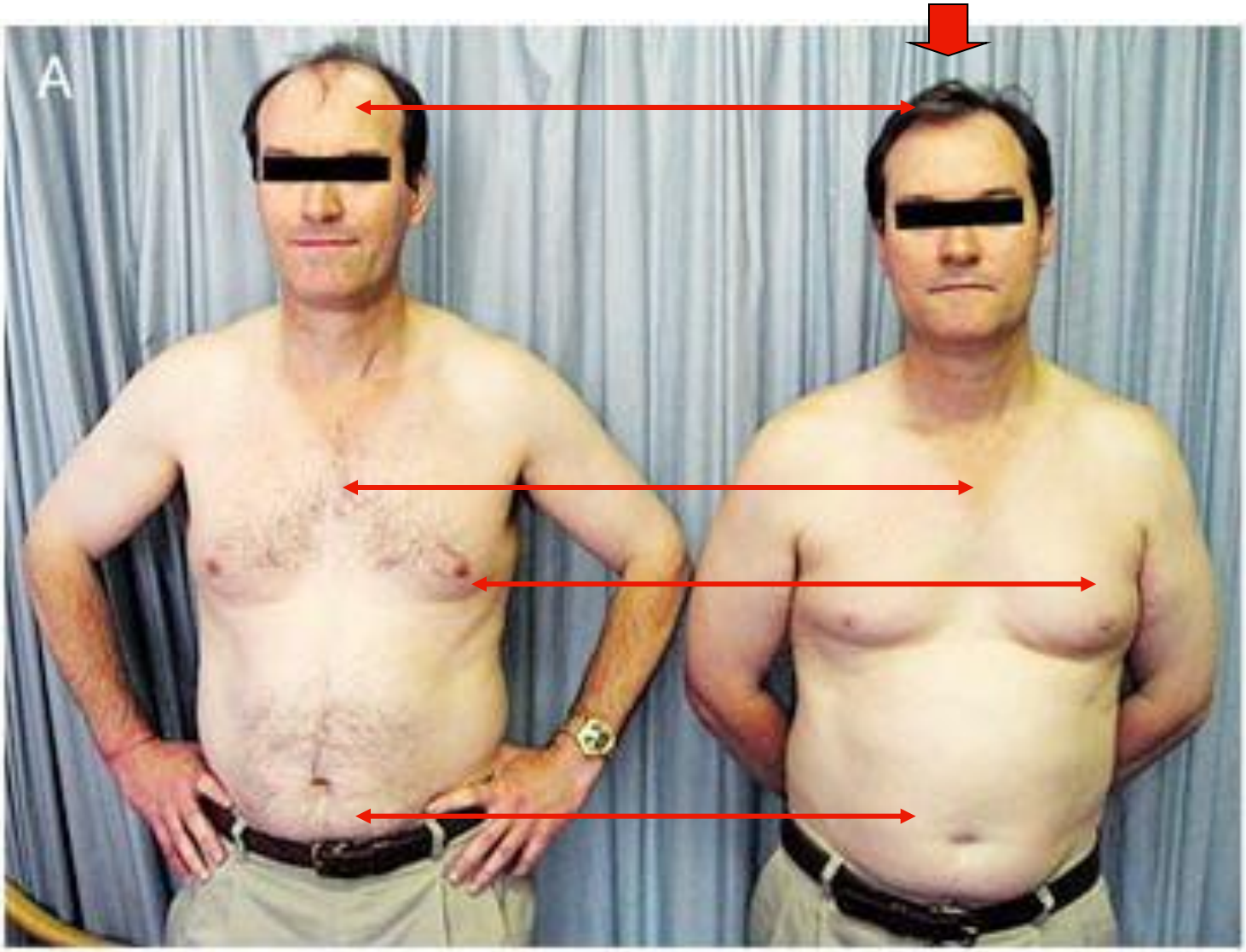




TESTORONE DEFICIENCY: overview

- Not only sexual desire
- Metabolic effects (diabetes)
  - Body Composition (obesity)
  - Bone Density.
- Erectile function
- Well-being
  - Anxiety
  - Power
  - Energy (osteoporosis, fatigue)
  - Mood (depression)

HYPOGONADISM IN IDENTICAL TWINS



Newnham, H.H. & L.M. Rivera-Woll (2008), *New Engl J Med* **359**: 2824.

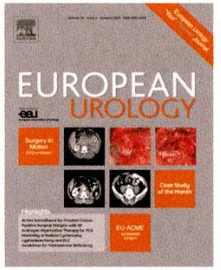
American Heart Association, American Cancer Society, and the American Urological Association.

Circulation, 2010

- Several new studies reported an increase in CV events, including an increase in MI and cardiovascular death, in prostate cancer patients who were being treated with ADT
  - Keating NL et al. *J Clin Oncol*., 2006
  - Saigal CS et al. *Cancer*.2007
  - D'Amico AV et al. *J Clin Oncol*., 2007
  - Tsai HK et al. *J Natl Cancer Inst,* 2007
  - D'Amico AV et al. *Cancer*. 2008

EVIDENCE-AND OPINION-BASED CORRELATIONS BETWEEN TESTOSTERONE AND PCA

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



European Association of Urology

Guidelines

Investigation, Treatment, and Monitoring of Late-Onset Hypogonadism in Males: ISA, ISSAM, EAU, EAA, and ASA Recommendations

Christina Wang [a,*], *Eberhard Nieschlag* [b], *Ronald Swerdloff* [a], *Hermann M. Behre* [c], *Wayne J. Hellstrom* [d], *Louis J. Gooren* [e], *Jean M. Kaufman* [f], *Jean-Jacques Legros* [g], *Bruno Lunenfeld* [h], *Alvaro Morales* [i], *John E. Morley* [j], *Claude Schulman* [k], *Ian M. Thompson* [l], *Wolfgang Weidner* [m], *Frederick C.W. Wu* [n]

[a] *Division of Endocrinology, Department of Medicine, Harbor-UCLA Medical Center and Los Angeles BioMedical Research Institute, Torrance, California, USA*
[b] *Centre for Reproductive Medicine and Andrology, University of Muenster, Muenster, Germany*
[c] *Center for Reproductive Medicine and Andrology, University Hospital Halle, Martin-Luther-University Halle-Wittenberg, Halle, Germany*
[d] *Department of Urology, Tulane University, New Orleans, Louisiana, USA*
[e] *Department of Endocrinology, VU University Medical Center, Amsterdam, The Netherlands*
[f] *Department of Endocrinology, Academish Ziekenhuis, Gent, Belgium*
[g] *Centre Hospitalier Universitaire, Sart-Tilman, Liège, Belgium*
[h] *Faculty of Life Sciences, Bar-Ilan University, Ramat Gan, Israel*
[i] *Centre for Applied Urological Research, Queen's University, Kingston, Canada*
[j] *Division of Geriatric Medicine, St. Louis University, and GRECC, St. Louis VA Medical Center, St. Louis, Missouri, USA*
[k] *Department of Urology, Erasme Hospital, University Clinics Brussels, Brussels, Belgium*
[l] *Department of Urology, University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA*
[m] *Department of Urology and Pediatric Urology, University Hospitals, Justus-Liebig-University, Giessen, Germany*
[n] *Department of Endocrinology, University of Manchester, Manchester Royal Infirmary, Manchester, United Kingdom*

ISA, ISSAM, EAU, EAA and ASA recommendations Investigation, treatment and monitoring of late-onset hypogonadism in males

The very last sentence of introduction:

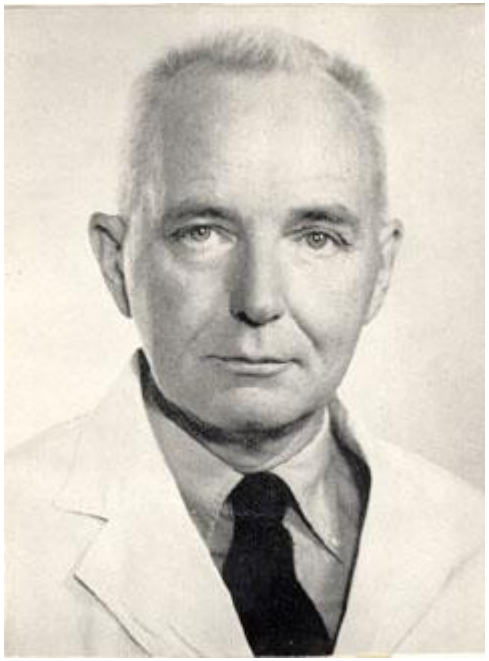
<<*Specific risk data on the prostate are needed*>>.

PARS DESTRUENS: TESTOSTERONE IS THE ENEMY OF THE PROSTATE

Androgens and PCa

60 years ago, the Nobel prize Huggins showed that suppression of testosterone causes regression of PCa…

He also recommended "the Huggins operation" -- castration



Historically androgen administration has been absolutely contraindicated in men suspected of harboring carcinoma of the prostate.

There is unequivocal evidence that T can stimulate growth and aggravate symptoms in men with locally advanced and metastatic prostate cancer?

YES !

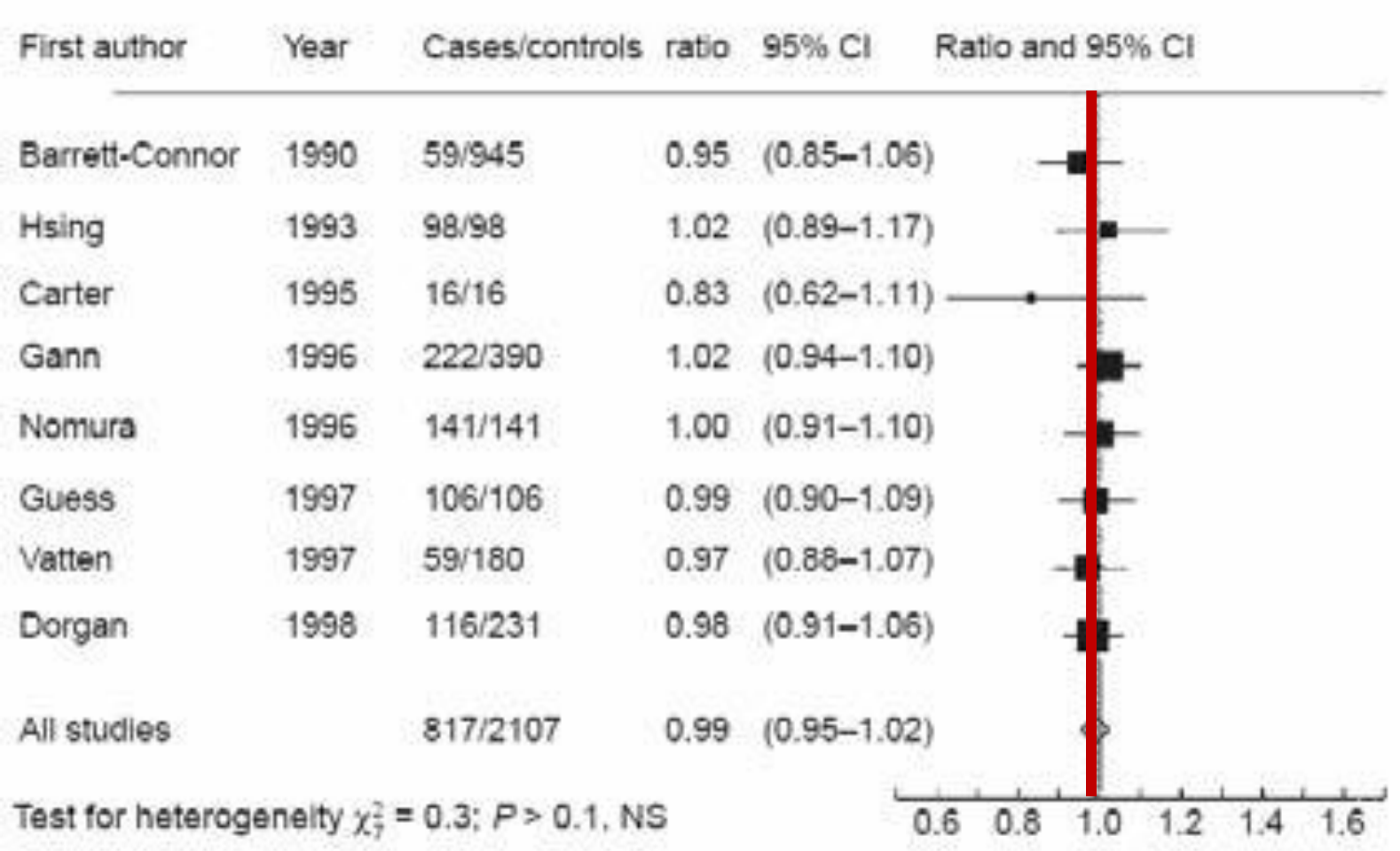
However, currently adequately powered and optimally designed long-term prostate disease data are not available to determine if there is an additional risk from normal T values in cured patients for PCa.

Can TRT convert an occult PCa to a clinically significant tumor ?

- Yes, in several anecdotal reports and opinion-based reviews.
- 1.1% 0ver 6-36 months: prevalence rate similar to general population rate
- BUT…only 36 months of follow-up!!

PARS COSTRUENS: TESTOSTERONE IS NOT THE ENEMY OF THE PROSTATE

No correlation between serum T & PCa



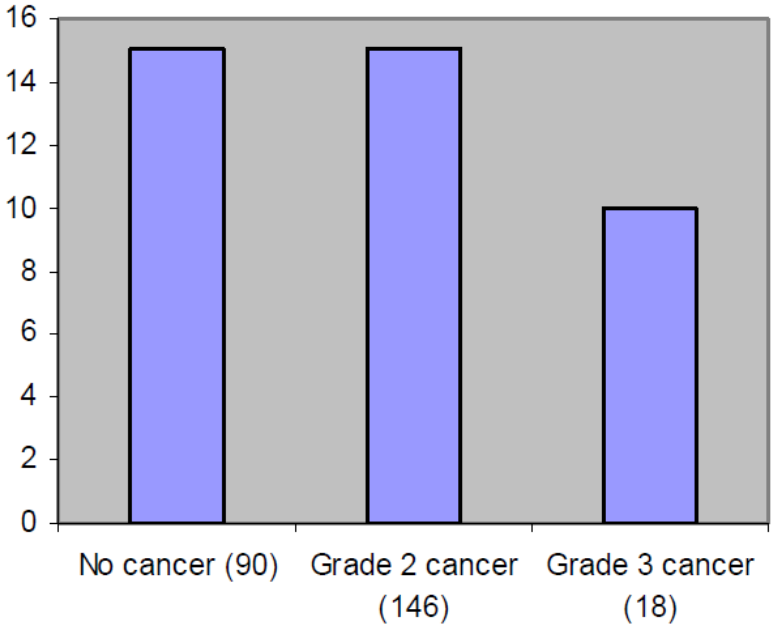
Gann Ph et al *Prostate* 1995 26:40
Eaton NE Br. *J. Cancer* 1999, 80:930

Similar results for BPH

Massachusetts Male Aging Study

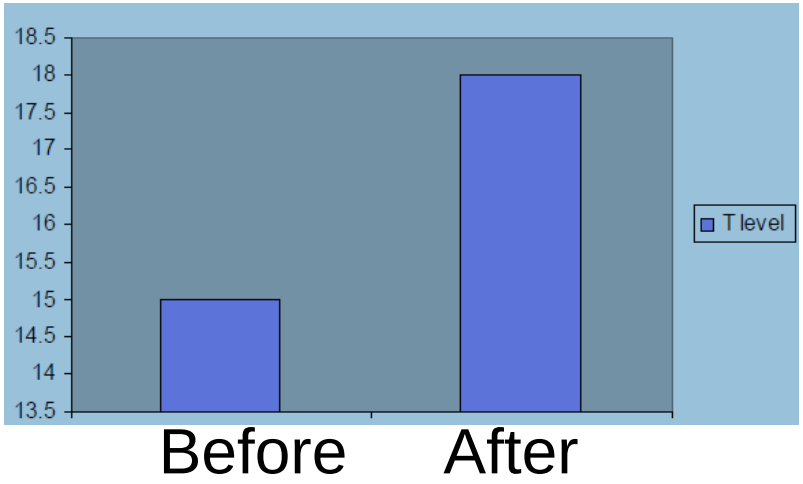
- Prospective, population based study of aging in 1576 men 40-70 years old (8 years of follow-up)
  - 4% developed Pca
  - 17 hormones assessed for PCa risk
- **No association of testosterone level and PCa risk**
- Only one hormone (androstenediol) was associated with PCa Risk

PCa may suppress serum testosterone…



Zhang et al assayed testosterone levels prior to biopsy (Prostate 2002)

Levels of testosterone following radical prostatectomy (79 patients)



Is occult PCa more prevalent in hypogonadal men ?

- Biopsy of 77 men hypogonadal men with normal PSA
- 14 had PCa
- Higher than the expected rate in men with normal PSA

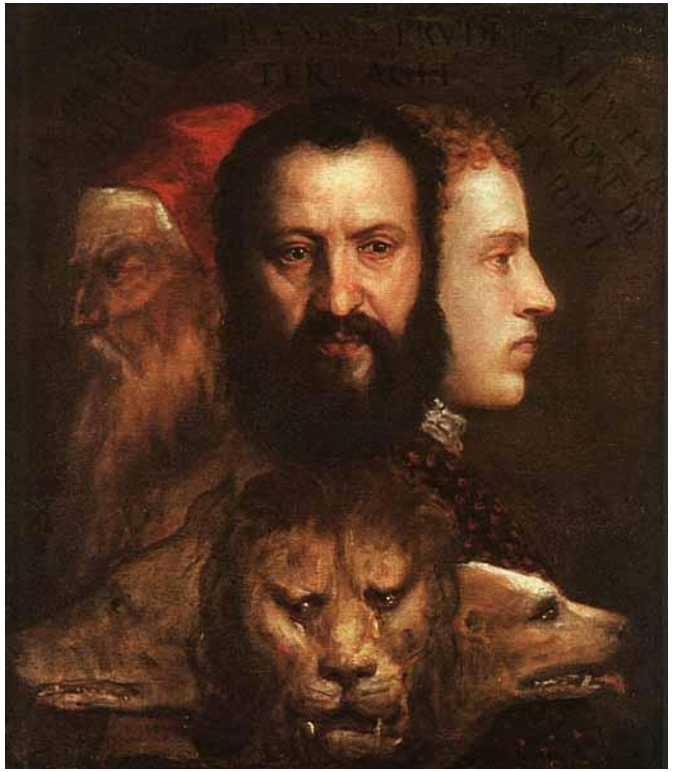
Checking for occult PCa is mandatory in hypogonadal men before TRT

Morgentaler, *Jama*, 1996

Androgen supplementation and PSA

- Trials have inconsistently shown a rise in PSA
- The mean increase: 0.3-0.43 ng/mL
- The possible rise occurs in the first 6 months and remains stable thereafter

Study	Duration	Increase in PSA	
		Placebo	Testosterone
	mo		*number/t*
Hajjar et al. (1997)[32]	24	–	–
Sih et al. (1997)[9]	12	0/15	0/17
Dobs et al. (1999)[11]	24	– –	1/33 0/33
Snyder et al. (1999)[8]	36	7/54	13/54
Snyder et al. (2000)[6]	36	–	–
Wang et al. (2000)[20]	6	– – –	0/76 1/73 4/78
Kenny et al. (2001)[7]	12	3/33	8/34

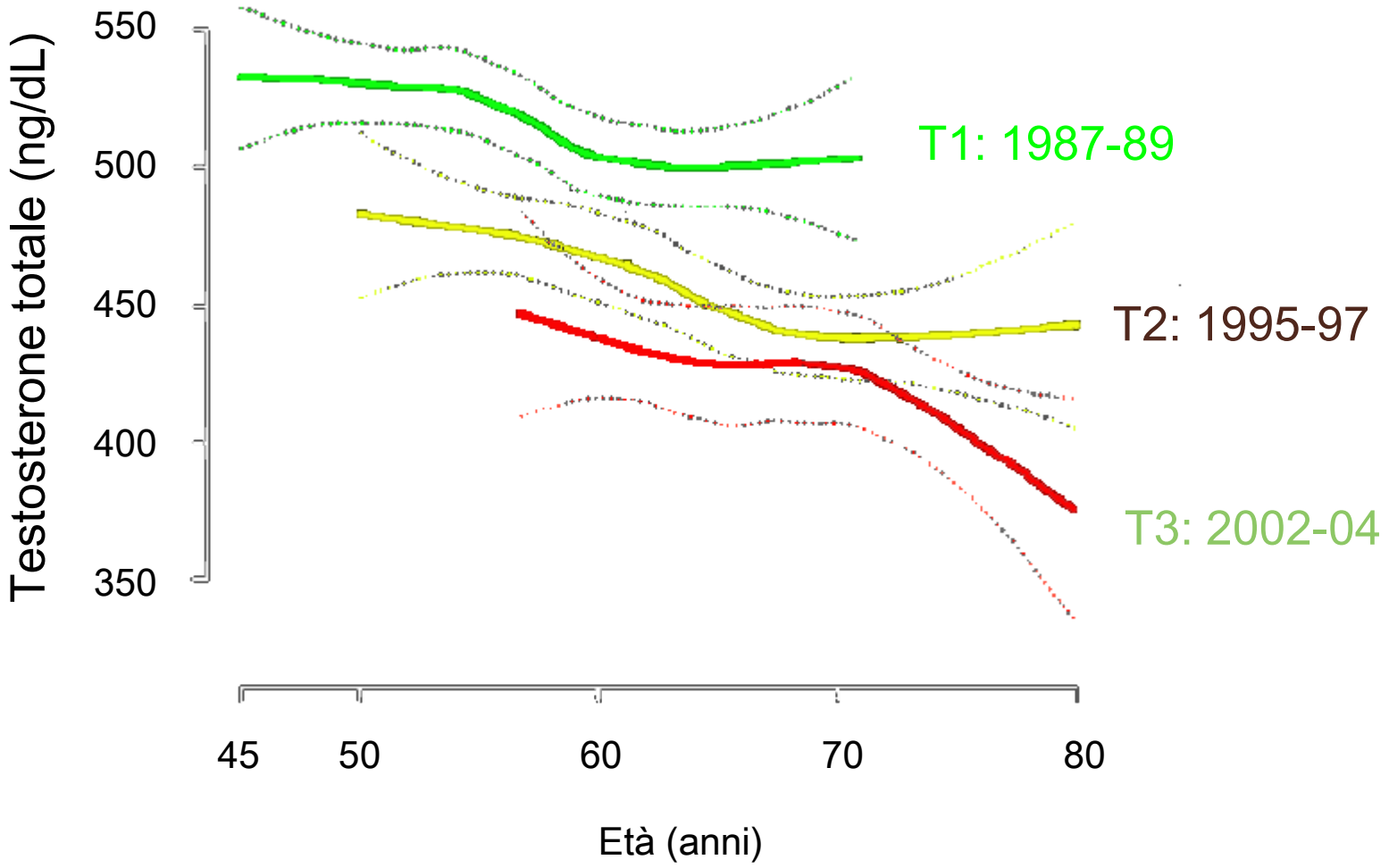


AGE, TESTOSTERONE, AND PCA

A Population-Level Decline in Serum Testosterone Levels in American Men

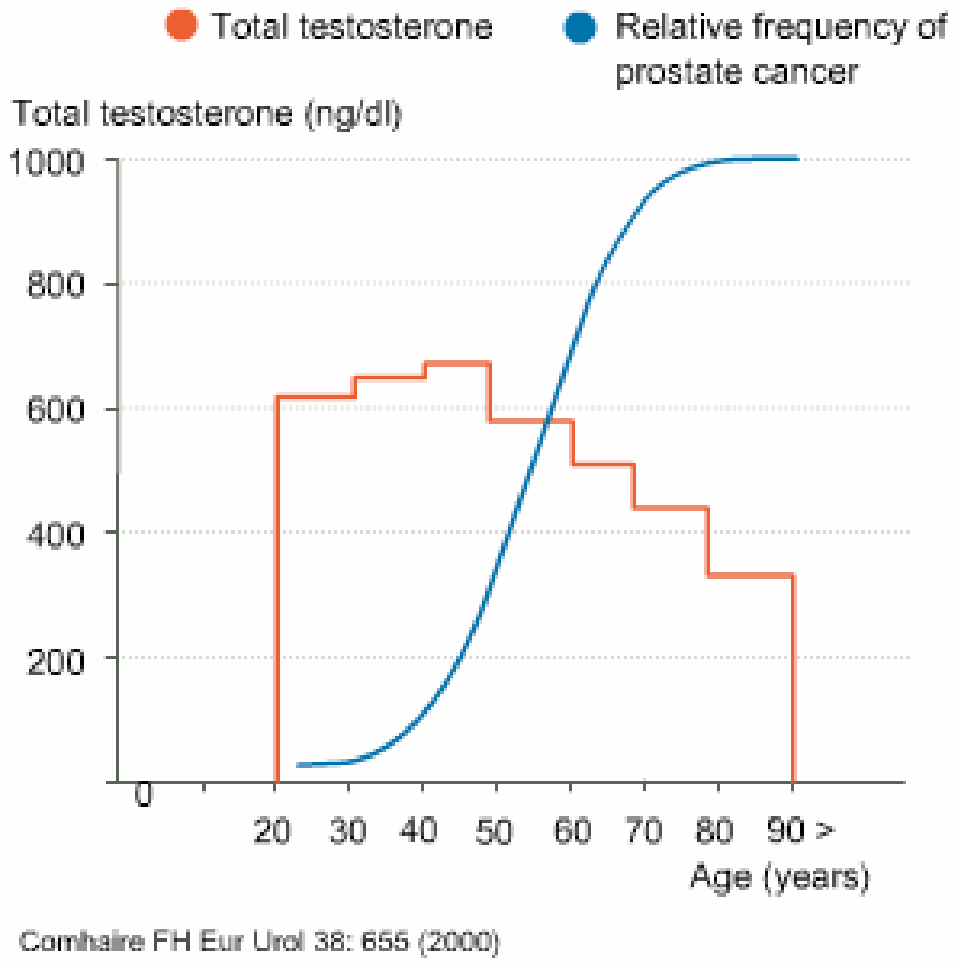
Thomas G. Travison, Andre B. Araujo, Amy B. O'Donnell, Varant Kupelian, and John B. McKinlay

New England Research Institutes, Watertown, Massachusetts 02472



PCa ↑ when serum T↓

Hypogonadism,
as PCa, is more prevalent
in older populations



Comhaire FH Eur Urol 38: 655 (2000)

sexual activity and prostatic health

- The equation ↑ sex = ↑ T apparently does not fit with the equation

  ↑ sex = ↓ prostate cancer.
- Prostate cancer is an age-dependent disease. This means that it is more likely to correlate with low sexual activity and low T than with the opposite.

Controversies in Sexual Medicine

Is Sex Just Fun? How Sexual Activity Improves Health

Emmanuele A. Jannini, MD,* William A. Fisher, PhD,† Johannes Bitzer, MD,‡ and Chris G. McMahon, MBBS FAChSHM§

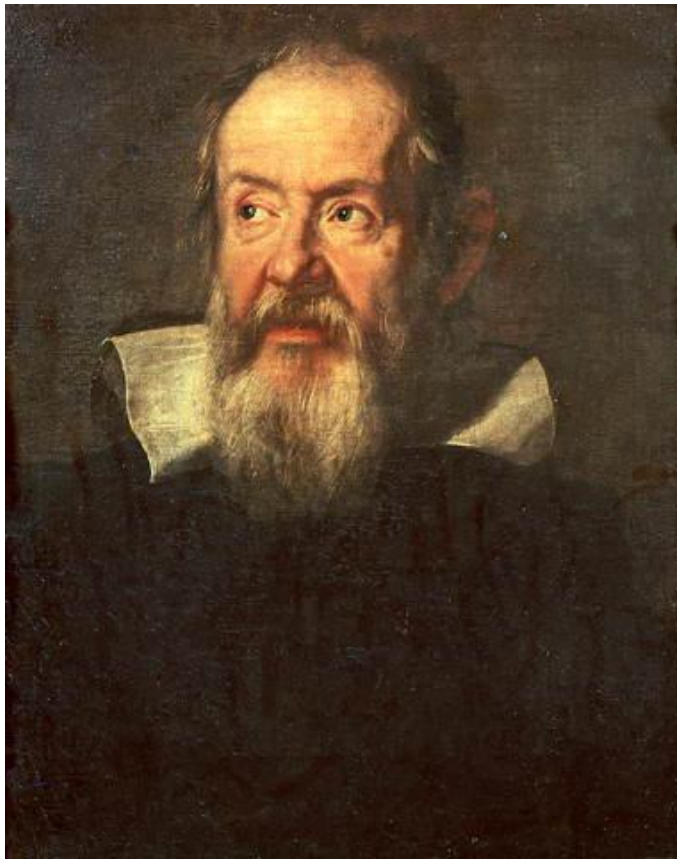
J Sex Med, 2009

Is prostate a really T-dependent tissue?

- Yes, but T stimulates the prostatic tissue in a dose-dependent fashion only until a saturation point, achieved at low T concentrations.
- At these low T concentration, stimulation is near maximal, and testosterone supplementation above this level would not lead to significantly greater stimulation

Morgentaler A. Testosterone and prostate cancer: an historical perspective on a modern myth. Eur Urol 2006;

DATA ON TRT IN TREATED PCA



Kaufman JM, Graydon RJ. **Androgen replacement after curative radical prostatectomy for prostate cancer in hypogonadal men.** J Urol. 2004

- A retrospective review of clinical records of 2 busy private urology
- The case records of 7 hypogonadal men who had undergone curative radical prostatectomy were identified.
- After variable followup periods no biochemical or clinical evidence of cancer recurrence was found.

Agarwal PK, Oefelein MG **Testosterone replacement therapy after primary treatment for prostate cancer.** J Urol. 2005.

- 10 hypogonadal patients after radical retropubic prostatectomy
- Asseed periodically for changes in PSA and TT
- At a median followup of 19 months no patient had detectable (greater than 0.1 ng/ml) PSA.

Sarosdy MF. Testosterone replacement for hypogonadism after treatment of early prostate cancer with brachytherapy. *Cancer* 2007

- 31 receiving TRT from 0.5 to 4.5 years after seed implantation
- Stage T1c tumor and Gleason 6, 32% had palpable disease and 29% had Gleason 7 or higher.
- Median duration of TRT and follow-up were 4.5 and 5 years, respectively.
- No patient stopped TRT because of possible or confirmed cancer recurrence or progression.

Sarosdy MF. Testosterone replacement for hypogonadism after treatment of early prostate cancer with brachytherapy. *Cancer* 2007

- 31 receiving TRT from 0.5 to 4.5 years
- 2%
- d
- -up
- No patient stopped TRT because of possible or confirmed cancer recurrence or progression.

Theoretically, TRT after radiation therapy could be riskier than after radical prostatectomy because of the residual prostatic tissue.

Androgen Replacement in Men Undergoing Treatment for Prostate Cancer

Ernani Luis Rhoden, MD, PhD, Márcio Augusto Averbeck, MD, and Patrick E. Teloken

J Sex Med 2008;5:2202–2208

Rhoden EL, Averbeck MA. Testosterone therapy and prostate carcinoma. *Curr Urol Rep*. 2009.

- <<In summary, in the three available case series describing T replacement after treatment for PCa, no case of clinical or biochemical progression was observed.>>
- <<The available data suggest that TRT can be cautiously considered in selected hypogonadal men previously treated for curative intent of low-risk PCa and without evidence of active disease.>>

Androgen Replacement in Men Undergoing Treatment for Prostate Cancer

Ernani Luis Rhoden, MD, PhD, Márcio Augusto Averbeck, MD, and Patrick E. Teloken

J Sex Med 2008;5:2202–2208

Rhoden EL, Averbeck MA. Testosterone therapy and prostate carcinoma. *Curr Urol Rep*. 2009.

- <<In summary, available case series de after treatm al or bioch ed.>>
- <<The RT can be cautic ted hypogonadal m treated for curative intent of low-risk PCa and without evidence of active disease.>>

Just 48 patients!

…WHEN GUIDELINES ARE DIPLOMATIC

International Consultation on Sexual Medicine

Paris, 10-13 July 2009

Committee 14

Endocrine Aspects of Men Sexual Dysfunctions

Chairmen:

J Buvat, M Maggi

Members:

A Morgentaler, C Schulman, M Zitzmann

Consultants:

L Gooren, A Guay, J Kaufman, HM Tan, LO Torres, A Yassin

International Consultation on Sexual Medicine

- At the present time, there is no conclusive evidence that TRT increases the risk of PCa or BPH (Roddam et al. 2008; Carpenter et al. 2008).
- There is also no evidence that testosterone treatment will convert sub-clinical PCa to clinically detectable PCa (Level 4, grade C).

International Consultation on Sexual Medicine

- Hypogonadal men > 45 years old should be counselled on the potential risks and benefits of TRT before treatment, and carefully monitored for prostate safety during treatment (L3, Grade A)

International Consultation on Sexual Medicine

- However, there is unequivocal evidence that T can stimulate growth and aggravate symptoms in men with locally advanced and metastatic PCa (Fowler, Jr. et al. 1982; McConnell, 1995) (Level 2a, grade A).

Recommendation 25. Testosterone Therapy after treatment for PCa

- Men successfully treated for PCa and suffering from confirmed, symptomatic hypogonadism are candidates for TRT, after a prudent interval, if there is no evidence of residual cancer.
- The risks and benefits must be clearly understood by the patient and the follow-up must be particularly careful.
- No reliable evidence exists in favor or against this recommendation. The clinician must exercise good clinical judgment together with adequate knowledge of the advantages and drawbacks of androgen therapy in this situation.
  L3, GradeC

WHICH (EVENTUAL) TESTOSTERONE FOR PCA?

Recommendations for T Therapy in patients not in PCa

- Oral methyl testosterone should not be used
- Injections with T enanthate /cypionate not recommended if T levels supraphysiological
  - Give lower doses (50 or 100 mg) Q 1-2 weeks
  - Use T undecanoate injections
- PSA rise > 20% or > 0.75 ng/mL per year should be regarded as suspicious

WHICH TESTOSTERONE PREPARATION AND FOR WHOM?

All Young Adults

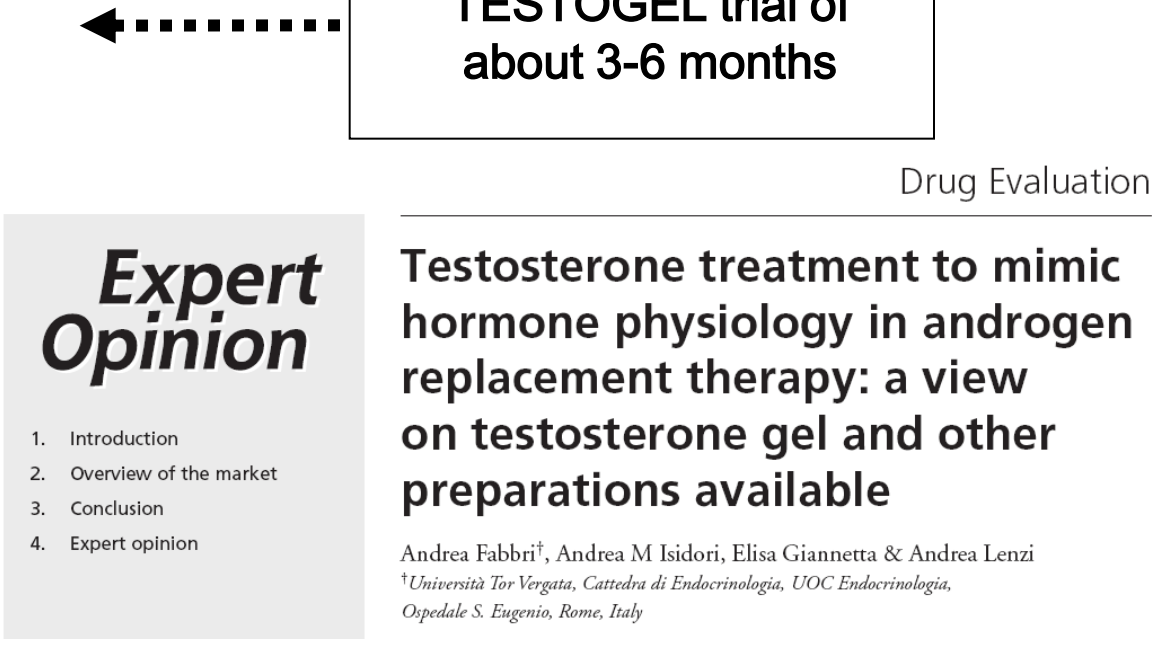
& All Severe Hypogonadism

Elderly subjects

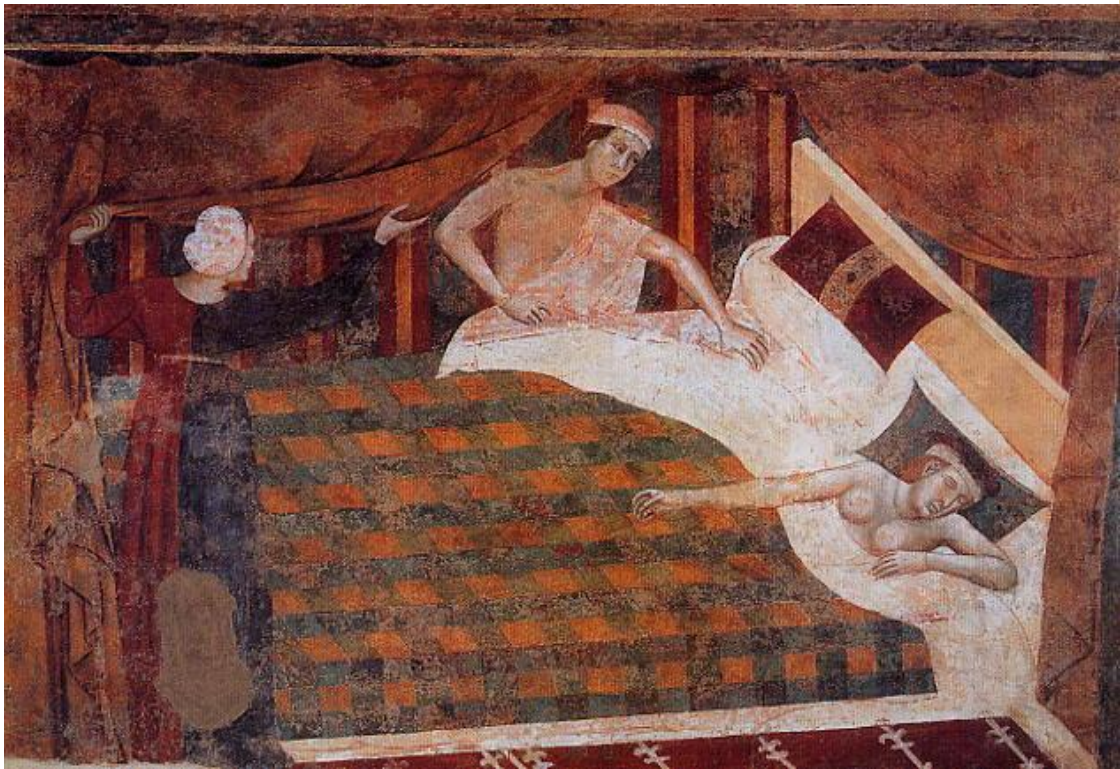
& Mild Late on-set Hypogonadism

Nebid®

TESTOGEL trial of about 3-6 months



WHEN T CANNOT BE USED: HANDLING SYMPTOMS OF ADT



Body Feminization

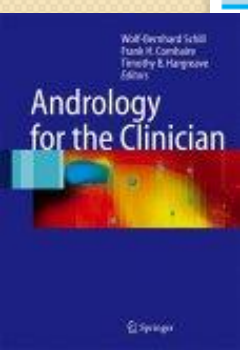
- gynecomastia and mastodynia → Mastectomy or liposuction, Preventive radiation treatments
- Weight gain, altered fat distribution, loss of muscle mass, physical weakness, and loss of body hair → Diet, Physical exercise
- hot flashes → No caffeine, hot drinks, chocolate, spicy or hot foods and alcohol, Use SSRI
- Loss of penile volume and length, testicular atrophy. weight gain can further reduce visibility of the penis for the patient → PG, vacuum therapy, PDE5i

Sexual Changes

- HSDD → Sexual therapy techniques invoking sexual fantasies
- Iatrogenic double ED (surgical and endocrinological) ~85% of the population on ADT → PDE5i PG
- Ejaculatory troubles (surgical and endocrinological) → Counselling

Table II.4.19. Coaching cancer patients about sexuality and fertility

1. Setting	Create privacy and confidentiality, be aware of cultural differences, be non-judgemental and respectful, avoid jargon (Sundquist 2003)
2. Education on the impact of serious systemic diseases on sexuality	The patient should be aware that any important disease might affect sexuality. This is an adaptive mechanism, but it is a good prognostic sign to resume sexual activity
3. Education on the impact of cancer on sexuality	The patient should be aware that the disease process (weight loss, muscle loss, anaemia, pain, fatigue, incontinence, neurological impairment, ascites, loss of sensation, depression) might affect sexual life, so that he can face it in the best way
4. Education on the impact of cancer treatments on sexuality	The patients must know a therapy's impact on sexual performance beforehand. However, he should also be informed that there is great variability in this
5. Education on the impact of cancer treatments on fertility	In patients with both good and bad prognosis, preservations of gametes before chemotherapy, radiotherapy and surgery should be discussed in counselling
6. Suggestions on improving intimate communication	Sex should be regarded as part of an intimate relationship, particularly important when facing cancer
7. Suggestions on resuming sex comfortably and how to mitigate sexual handicap	This is of particular importance in patients whose treatment has caused or will cause mutilation. In some cases, the importance of non-penetrative sex should be stressed
8. Self-help strategies to overcome specific sexual problems	A minority of patients may need specialized, intensive psychological treatment
9. Use of pro-sexual drugs as antidotes to anticancer therapy's side-effects	The use, when indicated, of hormones, PDE5 inhibitors, prostaglandins, even prostheses should be encouraged
10. Follow-up	For most patients, discussion of their quality of life and sexual issues after treatment is particularly important (Aass et al. 1993)



II.4.19 Behavioural Therapy and Counselling

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Medical optimization of ADT to minimize side-effects

- transdermal estradiol through the use of LH-RH agonists (experimental)
- Referral to appropriate psychosocial resources
- referral to an appropriate clinical psychologist, counselor, sex therapist, or sexual medicine expert
- Follow the sexual rehabilitation principles for persons with chronic illness

In conclusion

- Is prostate a T-dependent tissue?
  - Yes, but just at low [T]
- Is PCa induced by T?
  - No !
- Is PCa metastasis T-dependent?
  - Yes!!!
- Can TRT be used in cured PCa?
  - Possibly yes, at least in selected patients carefully monitored

De Libero Arbitrio Diatribe sive Collatio (*Of free will*, 1524)

In the "Diatribe“ the Great from Rotterdam did not encourage any definite action. For him, the essential point is to have the freedom of choice…