Did You Know? – N°3 – September 2015

The voice of prostate cancer patients across Europe

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Editorial

by Malcolm Galloway Duncan – Newsletter Coordinator

The dominating article of the present edition of the Newsletter is undoubtedly the long term Strategic Plan devised by Prof Louis Denis, a founder member of Europa Uomo, which was promptly presented to a delegation of the European Parliament on 16th September. The implementation of the Strategic Plan by the Board will be coordinated by John Dowling, our new Secretary. Its main goals amount to achieving ever better care and general awareness of this sly and deadly disease which, today, is suffered by one man out of six.

Another important article and interview with the chairman of the European 40 member Task Force is

dedicated to progress already achieved in the development of Prostate Cancer Units throughout Europe. This innovation is indeed a milestone in the improvement of treatment of prostate cancer, in which the accent is no longer on the disease but on the patient himself. **As we are sure you will agree with this affirmation, we ask you to kindly contribute to the first ad hoc market survey which we intend to carry out. See the article for details on how to participate no later than 21st October. Many thanks!**

In fact this issue contains three new columns whose chief objective is to create intercommunications between the Newsletter and its readers, and thus favour regular input from our readership. They are respectively a Patients' Mailbox, Letters to the Editor and periodic Market Surveys. The first named will enable patients to pose delicate questions, like on sexual matters, to a medical expert and thus avoid any embarrassment, and anonymity is also assured if requested. Many of such queries are surely of interest to other patient readers. Letters to the Editor hopes to encourage readers to express opinions, make suggestions for the Newsletter and provide interesting news which may still be known by a very limited number of readers. The goals of the Market Surveys are obvious and are the reason why we have, from the start, emphasized the importance of a wide national mailing duly categorized.

We have been able to convey most positive news on the diatribe between the British Richmond Pharmacology company and the European proposal of an All Trials Register which will assure prompt disclosure of both ongoing medical research and final results. The opposition was promptly rebuffed by law.

A very honest and important exhortation is made by Per-Anders Abrahamsson, until recently Secretary General of EAU (European Association of Urology), on the need for the medical profession to work as a team and hopefully resolve the problem of the medical dinosaurs fighting to maintain their superiority in a disease second only to cardiovascular shortcomings for the premature death of members of the male sex. He also emphasizes the important role of advocacy groups like Europa Uomo in achieving such objectives and support for opportune early screenings throughout Europe.

At the annual assembly in Warsaw an invaluable contribution was given by a group of international medical experts in a most pertinent symposium dedicated to prostate cancer.

Our chairman, Ken Mastris, welcomed two new members of the Board, André Deschamps and John Dowling, respectively appointed as Vice Chairman and Secretary. He also expressed his most profound gratitude to Prof. Louis Denis for his dedication to Europa Uomo as Strategic Consultant as all our many goals and ways and means to obtain them are clearly outlined in the Strategic Plan. However our Chairman expressed his most sincere regret at the decision of our Special Advisor to step down from this important post, but was partly reassured by Prof. Denis's promise to remain on board as one of our Liaison Officers.

News is also supplied on the recent improvements in our website coordinated by Nancy Verbrugghe in order to render it more user-friendly. Gratitude is also expressed to Joaquim Cruz Domingos for his sterling efforts as webmaster ever since its inauguration.

The final article in this edition of the newsletter is the opening part of an article on prostate cancer and hormones kindly provided by Prof. Louis Denis.

EPAD meeting, September 16, 2015

The Strategic Plan in brief

by Malcolm Duncan

It is a very tough assignment to attempt to do justice to do justice to this document and to summarise the principal points contained in the Strategic Plan written by a leading European known urologist, Prof. Louis Denis, and one of the founder members of Europa Uomo. It is a document which has required much time and careful thought and reflection, but I will do my best to illustrate the main points contained in this detailed document which was presented to a delegation of the European Parliament on 16th September, after its prior and enthusiastic approval by Europa Uomo at its annual assembly in Warsaw last June.

Since its creation in 2003, Europa Uomo has developed close contacts and co-operation with many leading European professional institutions such as EAU, ICHOM, ESO, ECCO and others, which has favoured coordinated European research, the achievement of Centres of Excellence and notable improvements in the quality of treatment of patients throughout the continent. During this period of time Europa Uomo has also succeeded in aggregating advocacy groups like Europa Uomo in 23 of the 28 member states of the European Community.

In spite of the above successes, Europa Uomo decided on its tenth anniversary to review the situation in order to fully exploit its strengths and resolve its unresolved weaknesses: limited membership in many member countries and limited financial resources, and assigned the task of coordinating a medium and long term Strategic Plan to Prof. Louis Denis as Strategic Consultant.

The Strategic Plan has identified the following priorities and objectives:

- Positively contribute in the decision making process of the European institutions and authorities;
- Strive for the best treatment and quality of life of prostate cancer patients throughout Europe;
- Increase general awareness and visibility of this deadly disease which is at present suffered by one man out of six, also by achieving a major membership of each national association;
- Ensure the financial sustainability of Europa Uomo;
- Achieve annual European and national EPAD (European Prostate Awareness Days) events;
- Develop and implement a European fund-raising strategy so that Europa Uomo becomes a leading protagonist in the fight to resolve the prostate cancer dilemma;
- Establish an ongoing relationship with Members of the European Parliament (MEPs) who share our intent to resolve the prostate cancer problem;
- Identify and contact similar prostate cancer advocacy groups in the remaining 5 member states in order to achieve their aggregation;
- Strive to obtain closer contacts and the co-operation of women's European organisations;
- Set as one of our goals a 20 per cent improvement in our coverage of Europe year by year;
- Exploit our quarterly newsletter "*Did You Know?*" as a vehicle of education of this dreadful disease which is destined to grow further due to the general increase in the average longevity of life;
- Undertake appropriate surveys on this disease and the treatment of patients in co-operation with professional and patient organisations and support research;
- Develop and implement informative mechanisms for GPs in co-operation with EAU.

In this way we aim to exploit every opportunity to the full by ensuring that the national and European authorities are well aware of the diagnosis and treatment of prostate cancer and achieve ever better co-operation with interested professional bodies and physicians, and thus counteract the threat of being taken over by other organisations due to limited support and funding. An economic state possibly aggravated by the lasting downturn in European economies.

However, our ultimate goal and ambition is a future where no man suffers or dies from prostate cancer. In his closing remarks Prof. Louis Denis underlines that such ambitious goals and objectives require a dedicated and competent Board working together with an excellent team spirit.

The Chairman's Letter

By Ken Mastris

I hope you all had a memorable summer.

First and foremost I would like to thank all those that contributed to the success of our Warsaw annual assembly. I am also most pleased to welcome John Dowling and André Deschamps to the Board as the new Secretary and Vice Chairman. They have already made their mark on the running of the organisation.

André Deschamps	**John Dowling**
Vice Chairman	**Secretary**

On the contrary, I am very sorry to report that Louis Denis has decided to step down as our Strategic Advisor much earlier than expected. He believes that the Board is now well structured in order to move forward efficiently. I would like to take this

opportunity to thank Louis for helping me to put us back on track and on behalf of the Board wish him well for the future. Louis has however kindly agreed to continue to be involved as an Liaison officer together with Brigitte.

My thanks also goes to all those who have volunteered to act as Liaison Officers.

The Board is working hard to put the Strategic Plan in place together with the funding and communication strategies. In September we have had a most important annual EPAD event in the European Parliament. My thanks also goes to all our partners and sponsors who have helped to make it all happen. See our website for more details.

Since Warsaw we have developed our new website and I would greatly appreciate any comments or suggestions on the new site. Our new webmaster Nancy Verbrugghe has made the site more user-friendly and also duly updated it. I would also like to thank our previous webmaster Joaquim da Cruz Domingos for all his sterling efforts over many years.

Our newsletter is continuing to grow and receive most encouraging comments and our thanks goes to Malcolm Duncan for the work together with Anja Vancauwenbergh and the team in Italy.

Our Secretary has developed a two page Prostate Digest for member organisations which summarises the work of Board members and the roles they will play in the future development of the Strategy Plan – a strong team spirit will assure its success.

Finally I would like to thank you all for your support to me, your Chairman, to Europa Uomo and, above all, to all prostate patients and our most ambitious objective; *“ A world in which no man suffers or dies from prostate cancer*”.

A plea to the European Parliament

by Malcolm Duncan

The main objective of the recent Board meeting of Europa Uomo in Brussels, kindly organized by our special advisor Prof. Louis Denis on terminating the medium and long term Strategic Plan, was to sensitize the European authorities on the steady growth of prostate cancer among the male population, and we are very grateful for their response and hospitality in one of the main parliamentary auditoriums.
Philippe. De Backer (MEP) kindly chaired the opening session, and Nils Torvalds spoke at the closing dinner.

Concurrently with this Brussels EPAD encounter, a high level meeting took place in Luxembourg to commemorate the thirtieth anniversary of the first European Council’s decision in 1985 which paved the way for the first action at European level on cancer.

An exhaustive description of prostate cancer disease and its extent was given in two sessions. There were contributions by speakers from representative associations such as EAU, ESMO, ESTRO, EMHF, ECPC, EAPM and ESO. Thanks to their kind participation, Europa Uomo was able to give to the representatives of the European Parliament a detailed global update of the sly and potentially deadly disease of prostate cancer, the incidence of which is projected to rise steeply over the next two decades due to earlier diagnosis and increasing longevity.

It is very difficulty if not impossible to do justice to this important event in a mere “Did You Know?” article and the important news which transpired, and may advise the Europa Uomo Board to dedicate a second Special Issue on the contents of the various reports. However a copy of all the slides projected are now available in the Secretariat of Europa Uomo in its Antwerp head office.

I will therefore, for the moment, limit myself to a few of the most important points which were expressed by the speakers in the afternoon session. Dr. C. Chapple (EAU Secretary General) spoke of the importance of the quality of life, EAU’s commitment to research, and the important role of the genteel sex in this accomplishment. Dr. S. Joniau (EAU) stressed the success of the new robotic surgery employed in Sweden which now proved nerve-sparing in 80% of the patients, which is an important goal in order to assure a good quality of life post-surgery. Dr. J. Rees (EMHF) spoke of the PSA dilemma and the decrease in mortality thanks to opportune and regular screening in a few parts of Europe. Dr. C. Bangma spoke of the important role of Active Surveillance in order to avoid overtreatment. In fact many prostate cancer patients die of other illnesses and diseases. Finally Dr. K. Haustermans spoke of the important future role of imagery in the execution of screening.

Abbreviations:
EAU (European Association of Urology), ESTRO (European Society for Radiotherapy & Oncology), ESMO (European Society for Medical Oncology), ESO (European School of Oncology), EMHF (European Men’s Health Forum), EAPM (European Allied Personalized Medicine, ECPC (European Cancer Patient Coalition, EUomo, Europa Uomo.

Further mention of this important meeting and the intervention of other speakers will surely appear in the next issue of the Newsletter.

United Against Prostate Cancer

by Malcolm Duncan

In a session held on the eve of Europa Uomo's General Assembly 2015, which was held in Warsaw on 19th-21st June, a group of international experts, invited by EAU, ESO, ESTRO and Europa Uomo, spoke on the above theme and discussed various aspects of prostate cancer in a two day workshop (19th/20th). Europa Uomo was represented by Ken Mastris, our chairman, and Gunter Feick, ex officio member of the Board.

The first invited speaker was Prof. Monique Roobol, epidemiologist and research coordinator at the Erasmus MC University in Rotterdam. Though the incidence of prostate cancer has notably increased since the seventies, mainly due to increasing average longevity, she informed the meeting that death rates had nevertheless fallen slightly. She attributed this to improved medical treatment, earlier detection and the development of the Active Surveillance therapy which was being more used in low-risk prostate cancer cases before more drastic decisions such as radiotherapy or surgery are contemplated, this avoiding the danger of overtreatment. The worldwide promotion and development of Active Surveillance is chiefly the work of Movember by means of a Global Action Plan (GAP) which also aims to favour global research co-operation and the creation of a worldwide database which includes the validation of current Active Surveillance strategies.

Dr. Jens Deerberg Wittram, Senior Fellow at Harvard Business School, spoke of the worldwide efforts of ICHOM (International Consortium for Health Outcomes Measurement) to standardize cancer treatment. He also spoke at some length on the high rate of recourse to Active Surveillance in most of the world and cited, in particular, Sweden where it averages 63%, varying from practically 100% to a mere 25% in other parts of the country. In Stockholm, its capital city, it registers about 43% of all cases. He also mentioned the dramatic variation in nerve-sparing operations which now average about 80% of all surgical options in Sweden.

Clearly very patient oriented, Dr Deerberg spoke of ~~the~~ 3 core questions which every patient needs to consider with much attention and after carefully evaluating whether it is simply a localized, intermediate or advanced level prostate cancer.

The three fundamental questions are as follows:

a) What are my chances of survival and what will probably be the quality of life afterwards;
b) Which of the treatment options is the right one for me?
c) Which is the best place for me to go for treatment?

Prof. Didier Jacqmin from France spoke in detail of both Challenges and Chances in personalised treatment, very much in line with Dr Deerberg's emphasis on individual treatment and care. He informed the audience that while prostate cancer was the most prevalent form of cancer contracted by men, mortality was highest in the 4 Nordic countries, Iceland. Estonia, Lithuania, Ireland and France. However according to research the most mortal cancer for men was lung cancer including the trachea and bronchus.

Till 2004 the only options for advanced state prostate cancer were hormonal treatment or surgery. Since then new treatment choices have evolved such as chemotherapy and other hormonal manipulations and treatment options, which are duly adopted according to what is most indicated by PSA and Gleason score tests, staging and the characteristics of each and every patient. That is according to personal characteristics and those of the tumour. The tumours are classified as Low Risk where the PSA is below 10 and the Gleason score is under 6, whereas Intermediate Risk tumours have a PSA between 10 and 20 or a Gleason score of 7. Lastly, High Risk prostate cancer is where the PSA is above 20 or the Gleason score over 8.

Whereas, in the case of low risk cancers, Active Surveillance is the normal therapy choice, also in order to avoid unnecessary treatment, there are many new treatment options for advanced diseases and even multimodal solutions and a combination of treatment options, including hormonal treatment, brachytherapy and surgery.

The final choice in such cases is often left to the patient but this requires balanced and clear information being provided to the patient.

Prof. Jacqmin also spoke of improved imagery technology which should improve staging, which could be combined with genomic tests and which are on their way for approval and are of 3 types. New biomarkers will help urologists to identify patients who are perhaps resistant to certain treatments in order to reduce or eliminate possible side effects.

Genomic tests will also reduce the risk of wrong information and therefore improve the decision making process as to which is the best therapy to adopt. They will also limit toxicity like the previously mentioned biomarkers.

Other new technologies still subject to evaluation such as HIFU, Cryotherapy, Interstitial laser and focal therapy. HIFU is particularly indicated for patients between 70 and 75 who are reluctant to undergo either surgery or radiotherapy.

Prof. Jacqmin terminated his presentation emphasizing the importance of early screening, which is not yet the case in France. Only about 30% of the men over 40 undergo PSA tests and 97% of such tests are advised by the patients' GPs. Every effort should therefore be made to convince national health authorities to promote an appropriate early screening in order to identify low risk tumours in good time.

The next speaker was Dr Silvia Villa, a psychologist at the Istituto Nazionale dei Tumori (IRCCS) in Milan, who spoke of holistic care and the importance of the Quality of Life.

She stated that cancer diagnosis challenges people's views the world over. One of the most common first reactions on hearing the dreadful news of having contracted prostate cancer was "Why me?" A general fall in overall health and also of mental health and self-esteem frequently follows and proves detrimental to both family and social roles. In 10-53% of the cases the patients become prone to psychological disorders like anxiety, depression, urinary and sexual dysfunctions, which sometimes lead to suicide.

In order to counteract such states of mind, it is of prime importance to avoid isolation and to seek professional help and family support.

The final speaker, Dr. Roman Sosnowski, was from the host country, Poland. He informed the conference that the likelihood of developing prostate cancer increased dramatically with age, and family and race genetics may help to establish why one man has a greater risk of contracting prostate cancer than another, as well as lifetime habits and vices. In 2008 8,500 prostate cancer deaths were related to smoking. In fact current smokers, and even those who stopped smoking less than 10 years before, have a two-fold higher risk of a recurrence of prostate cancer even after radiotherapy and surgery.

Although some factors that lead to prostate cancer are difficult or impossible to change, good nutrition and regular physical exercise in order to avoid obesity can help. Obesity in fact hinders and delays recovery after surgery. Men who are anxious to keep fit frequently have medical check-ups which undoubtedly helps to achieve an early detection of prostate cancer.

While the increased consumption of fruits and vegetables seem to have no overall effect in lessening the risk of getting prostate cancer, certain nutrients (plant phytochemicals such as antioxidants) as well as tomato-based foods and regular helpings of cruciferous vegetables can have positive effects and even slow down the progression of the disease.

Prostate Cancer Units (PCUs)

A Summary of the recently published Discussion Paper edited by Malcolm Galloway Duncan

The 30 member Task Force of prostate cancer experts, chaired and coordinated by Riccardo Valdagni* and Henk Hummel, recently published their Position Paper on the Prostate Cancer Units initiative, which contained 40 mandatory and recommended standards for the setting up of such centres in Europe. That is also bearing in mind what was feasible in an area in which health care varies considerably from country to country.

It began with a Discussion Paper produced by a team of experts gathered by the European School of Oncology in 2011 which stated the minimal requirements for the setting up of PCUs in Europe to be shared in the uro-oncologic community.

The task force which wrote the Position Paper was

composed of multiprofessional experts: urologists, radiotherapists, medical oncologists, psychologists, specialized nurses, patient representatives, hospital managers, and quality experts.

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Oncology Hematology

Prostate Cancer Unit Initiative in Europe: A position paper by the European School of Oncology

Riccardo Valdagni, Hendrik Van Poppel, Michael Aitchison, Peter Albers, Dominik Berthold, Alberto Bossi, Maurizio Brausi, Louis Denis, Lawrence Drudge-Coates, Maria De Santis, Günther Feick, Chris Harrison, Karin Haustermans, Donal Hollywood, Morton Hoyer, Henk Hummel, Malcolm Mason, Vincenzo Mirone, Stefan C. Müller, Chris Parker, Mahasti Saghatchian, Cora N. Sternberg, Bertrand Tombal, Erik van Muilekom, Maggie Watson, Simone Wesselmann, Thomas Wiegel, Tiziana Magnani, Alberto Costa

The work and dedication of the Task Force led to a consensus on the 40 standards considered as mandatory or recommended in several macro-areas, such as general requirements and critical mass, personnel and services (core team, non-core team and associated services), clinics, organisations and case management. The involvement of the advocacy group Europa Uomo was aimed to have the patients' perspective on key issues such as therapeutic and observational options for a disease which is diagnosed in around 417,000 new cases each calendar year and stressed a paradigm shift in cancer care from a disease focused management to a patient-centred approach which highlights the importance of a multidisciplinary team for the optimal coordination among professionals and communications with patients. Advocacy Groups could also prove most helpful in the lobbying process and thus have success with European legislators.

At least initially the standards had to be set at a reasonably attainable medium level, that is in the first phase in order to favour the acceptance and spread of PCUs in most European countries, and the feasibility of the criteria had to be thoroughly checked. The Task Force also had to bear in mind the impact of emerging technologies of which the most significant example was posed by the multiparametric Magnetic Resonance Imaging (mpMRI). Synergy among the various PCUs which must also be considered as an added value and should be pursued by encouraging close co-operation between Prostate Cancer Units.

It was also stressed that PCUs have to provide patients with clear and easy-to-understand written and electronic information on diagnosis, treatment and observational options, follow-up rehabilitation programmes, psychological care options, certified sperm preservation units on a regional basis, patient groups and other potential sources of support.

It was emphasized that clinical cases should be evaluated by the Interdisciplinary and Multiprofessional Team before starting any therapy or observational programmes.

Consensus was only possible in some cases by accepting a certain degree of compromise. Some urologists, for example, wanted to increase the minimum number of radical prostatectomies from 50 to 100 per year and introduce a minimum number of operations per surgeon to at least 25 per year. In the end the minimum numbers remained unchanged at least for the moment. Maximum contractual working times were also set for the main professionals of the core team.

If you agree that the creation of Prostate Cancer Units represents a milestone in the treatment and cure of prostate cancer, please give your name and country (in brackets) and brief comment like 'I fully agree" to the following email address:

europauomo.surveys@virgillio.it

**Riccardo Valdagni is Coordinator of the Prostate Cancer Programme of the European School of Oncology and is Director of the Division Radiation Oncology 1 and of the Prostate Cancer Programme at Fondazione IRCCS Istituto Nazionale dei Tumori, Milan (IT), where he also chairs the Prostate Cancer Unit.*

Prostate Cancer Units

Interview with Dr Riccardo Valdagni, President of the ad hoc Task Force

Author: Malcolm Galloway Duncan

Q. How long has it taken the Task Force to prepare the Position Paper so that the first Prostate Cancer Units (PCU), reflecting the new shared minimal requirements, may be created and which European medical associations participated in its preparation?

A. Considering the starting point was the discussion paper "The requirements of a specialist Prostate Cancer Unit" published in the *European Journal of Cancer* in 2011, well, it took about 4 years. A long time which was necessary for the multi-professional Task Force to reach a consensus on standards that are not always evidence-based.
The Prostate Cancer Unit Initiative in Europe was first proposed by ESO to OECI (Organization of European Cancer Institutes) and DKG (Deutsche Krebsgesellschaft) which entered as partners. For ESO, though, it was important to have the support of Scientific Societies and for this reason EAU (European Association of Urology), ESTRO (European Society for Radiotherapy and Oncology), IPOS (International Psycho-Oncology Society), the two specialized nurses associations EAUN (European Association of Urology Nurses) and EONS (European Oncology Nursing Society), the patients' advocacy group Europa Uomo, and later, EBU (European Boards of Urology) were closely involved.
PCUs are meant to be structures able to manage patients with an interdisciplinary and multi-professional approach by means of a carefully organized team composed of Core members such as urologists, radiation oncologists, medical oncologists, pathologists etc., non-Core members such as psychologists, imaging specialists, supportive care specialists and advocacy representatives which participate on request by the Core Team.

Q. What is the Position paper?

A. The Position Paper establishes the 40 standards required for a PCU in order to facilitate the setting up of such advanced centres in prostate cancer care. Some have been considered as mandatory also in the first phase and the others as recommended. However a first report on progress will be made in 2016 which may already lead to some of the recommended standards becoming mandatory and new professionals entering the Core Team.

Q. How does the situation change from the patients' point of view?

A. The patients will be able to refer to centres where the specialists involved in their care work together in a coordinated way and where they can access all the medical services they need.

"We have to work as a team": Per-Anders Abrahamsson former Sec-Gen of the EAU retires

Turf wars that must come to an end and specialists who must specialise and work together with other disciplines in the interests of patients seem to be the burning issues for Per-Anders Abrahamsson. The tall distinguished Swede who has just stepped down after 11 years at the helm of the European Association of Urologists (EAU) was speaking to Cancer World[1]. Abrahamsson is quick to point out – as he has many times to European politicians – that urological cancers (including prostate, kidney, bladder, testicular and penile cancers) together constitute one-third of all cancers. In a world of scarce resources and scarcer attention spans, every form of cancer must make its case for primacy.

"We have to work as a team," says Abrahamsson, who is Professor of Urology at Lund University and Chairman of the urology department at Skåne in Sweden. "It has been a major task for me at EAU to try and help bring all the people in cancer under the same roof." He told Simon Compton of *CancerWorld* that he had just returned from a meeting of the European Cancer Organisation (ECCO) in Brussels, and is worried about ESMO's recent decision to hold its own congress every year rather than continuing to collaborate with ECCO on the organisation of the biennial European Cancer Congress. For Abrahamsson, building a strong ECCO and getting all disciplines to work together in the interests of patients are synonymous. But the cause is made more difficult by tensions created by the increasing role of organ-specific specialties in cancer.

Turf wars between medical oncologists and urologists are a particular source of vexation for Abrahamsson. In some European countries, urologists – normally surgeons by training – play the central role in treating urological cancers, even though more and more specialise in oncology. Many see little benefit in handing control of cancer patients to medical oncologists who have less knowledge of the prostate. Medical oncologists, they say, should be brought in attheir request rather than co-ordinating care.

So although "working together" is an Abrahamsson mantra, achieving it in urological cancer has been fraught with difficulty in Europe. "In some countries, there is a major battle," he says. "In Germany for

[1] This extract from the *CancerWorld* article of May 2015 is published by kind permission of *CancerWorld*.

example urologists are pretty well handling everything including chemotherapy, and they are not much working together with medical oncologists," he says, adding that there are urologists within EAU who want to be independent of all other specialities – not just medical oncology but areas such as imaging too. But Abrahamsson is adamant that this is not the way forward. "It's not going to happen," he says. "You cannot do everything."

"We organ specialists have to work closely with all the other specialties involved in cancer – imaging people, radiation oncologists, medical oncologists, basic researchers, nurses – which is why I think the multidisciplinary outlook of ECCO is so important," he says. He asserts that most urologists within the EU are indeed working in a multidisciplinary fashion. "It is the only way forward, because it is what patients want."

"It is clear that surgery cannot cure everything"

In urological cancers, it's all about using adjuvant and neo-adjuvant radiation, and in some cases, such as testicular cancer, chemotherapy. I remember a medical student on my course dying of testicular cancer in the 1970s, but now in Norway and Sweden we cure 99% of our testicular cancer patients. This is a wonderful example of why we need to work together, and I cannot understand this ongoing fight between different organisations." The last four years of Abrahamsson's term as Secretary General, which came to an end in March, has seen him turn his attention more and more to politics, and he jokes that his next role will be Secretary General of the United Nations. But he is hopeful the battles will end soon.

Consensual Working

"There are dinosaurs fighting to maintain what they have on both sides, but I'm optimistic that within five years it will be history. Patient organisations like Europa Uomo are getting better organised and asking for everyone to work as a team, and we have asked politicians in Brussels to look at the same thing." Abrahamsson doesn't have much time for dinosaurs, hierarchies or those who insist on being named as 'in charge'. He is from the Scandinavian school of open-necked informality, and proudly explains that everyone he works with at his hospital and the EAU headquarters in Arnhem, in the Netherlands, call him Per-Anders – or even Papa Pelle, a family nickname that somehow spread. When he took over as EAU's Secretary General in 2007, he changed its military-style top-down management model to a more level, consensual structure, with four team leaders who he "trusted with everything". It was based on the structures at his own hospital. "It's more time consuming, but I totally believe in it because it's about mutual trust."

So consensual working in urological cancer makes total sense to him. And in the field of prostate cancer, it extends to supporting the spread of specialist multidisciplinary prostate cancer units – along the lines already well established for breast cancer. In 2011, the European School of Oncology promoted the concept of prostate cancer units in an article in the European Journal of Cancer, and set out what was involved in terms of professional education and experience. The concept revolves around two principles: every surgeon and radiotherapist who treats patients with prostate cancer must specialise in the disease; and volume equates to quality.

Partnership with European School of Oncology

EAU met with ESO to discuss Prostate Cancer Units at the EMUC meeting in Lisbon last November. "We are working together on this, and I am convinced we will sign a partnership with ESO because we have the same goals. We are definitely behind the concept of units. In many countries already, for example the UK, you now have to operate a certain number of cases a year and demonstrate follow-up and outcome to be allowed to carry out a procedure. I am convinced this is what will happen in all European countries, but it will take some time. In Germany, for example, you currently have at least 120 centres carrying out radical prostatectomy, which is not acceptable. If you don't have on hand a whole range of other people – including qualified pathologists, imaging people, specialised nurses, and those who can help with the side effects of treatment such as incontinence – you shouldn't be allowed to perform surgical procedures."

Patient Pressure

Again, it is pressure from patients for evidence of good outcomes that will be the main force for creating Centres of Excellence. "Of course they are heading for the best centres, and that's going to happen in Scandinavia, as well as in the UK. That's why, in centres like our own, we are working like brothers and sisters with other disciplines."

Research into prostate cancer has been a central plank of Abrahamsson's career, continuing alongside his work as clinician and teacher. His innovative research in the 1980s and early 1990s identified new kinds of prostate cancer neuroendocrine cells and the peptides produced by them, and these were subsequently identified as promoting progression in some types of aggressive cancer.

Today, there is increasing interest in neuroendocrine differentiation as a marker for prostate cancer aggression. But in 1980 he decided he wanted to be a urologist, not a general surgeon, and he began another residency, this time at Malmö University Hospital. "At that time I had no clue about the technologies and new surgical techniques that would transform my specialty," says Abrahamsson. "In the early '80s, we couldn't have imagined performing shockwave or laser lithotripsy for kidney stones, and we wouldn't have dreamed about performing radical prostatectomy to cure prostate cancer. We were using oestrogens for disseminated disease, and if you were diagnosed with penile cancer it was simply amputated." It was the urology chief at Malmö, Lars Wadström, who gave Abrahamsson the ambition to enter research, and it was his own doctoral thesis, completed in 1988, that established Abrahamsson's work on prostate neuroendocrine cells. On the basis of that, he was invited to the urology department at Rochester Medical Center in New York, becoming its laboratory director in 1991 and adjunct professor in 1993.

During his three years there, he brought in molecular biologists from all over the world, finalised 45 papers and – thanks to the influence of the department chief Abraham T.K. Cockett – made wide contacts in the urology world. Since then Abrahamsson has become known for his skills as an international networker. Returning to Malmö, however, he became dissatisfied that he could not get an appointment as a departmental chief, so began using his networking skills and giving talks about his research. At a talk in London in 1995, he met Frans Debruyne, then Secretary General of the EAU, who told him: "You are going to be Secretary General one day." Shortly after, he was asked to become a member of the Scientific Committee – and that is how his involvement with EAU began.

In 1998 he became chairman of the urology department at Malmö and Lund University hospitals, and then full Professor of Urology at Lund University in 2000. The two university hospitals have now merged, into Skåne University Hospital. "Now we are no longer competing against each other and we can cover all fields of expertise."

After 20 years, he is due to step down as urology chief later this year. His perspectives on the challenges of the past and the opportunities ahead have been moulded over 40 years of clinical, research, management and political experience. In the field of prostate cancer, perhaps most striking is his view that universal screening for prostate cancer is a realistic possibility – based on taking early and, if necessary, repeated PSA readings, but not normally intervening quickly with biopsies or surgery if raised levels are found (as has become the norm).

His view is founded on research from his own department, using stored blood serum samples from 20,000 men aged 35 to 45, 900 of whom were later diagnosed with prostate cancer at the hospital. Detailed analysis indicated that low PSA levels at age 45 indicated a very low risk of prostate cancer, but levels higher than 1.5 brought increased risk later in life.

"It shows clearly that you should have a baseline reading taken when you are fairly young. If it is low, then you can wait five years before you have it again. If it is higher, you have more tests on a more regular basis," says Abrahamsson. An international randomised trial with 18 years follow-up, being coordinated by Erasmus Medical Centre, Rotterdam (the European Randomised study of Screening for Prostate Cancer or ERSPC) indicates that such procedures reduce the chance of dying from prostate cancer by up to 50% – "that's more than any breast cancer screening study has shown."

Those wary of PSA testing say that it is an inaccurate indicator of prostate cancer, and that raised readings are often the result of other conditions or indolent tumours. It can lead to unnecessary anxiety, harmful biopsies, and unnecessary treatment, leading to incontinence and impotence. Supporters say it should be used widely because it is a better cancer marker than we have for any other type of cancer and can lead to life-saving early interventions.

Abrahamsson straddles the two camps. He wants national screening programmes that use PSA tests in a more considered way, alongside active surveillance. But he acknowledges this will require a change in attitudes to test results among clinical staff, as well as patients.

"There's a danger that, as soon as a PSA result presents a red flag, everything starts. The patient gets scared and things move very quickly. We don't want that to happen, so you need to educate patients, relatives, healthcare providers on how to proceed in a considered way. That will take time, and we cannot introduce mass screening programmes straight away. But eventually, in the future, I am convinced that testing decisions will be made on the basis of a PSA test in your 40s – unless, of course, you have a family history, in which case the need for regular testing is clear."

Abrahamsson is waiting for more results from the European randomised trials before taking the idea to policy makers. But he is about to present an award lecture on the subject at the American Urological Association meeting in New Orleans this May. The response will be interesting, given the fact that American doctors have a long history of responding to an early diagnosis of cancer with surgery rather than active surveillance.

Progress in Prostate Cancer is slowed by basic and gaping holes in research

In terms of treatments for prostate cancer, Abrahamsson has mixed feelings about the progress made. Remembering the "bloody mess" of radical prostatectomy when introduced into Sweden in 1987, he marvels at the precision of the Da Vinci robots on which surgeons today perform 500 prostatectomies a year in Malmö – and the resultant reduction in incontinence and impotence.

But for all the technological advances, progress in prostate cancer treatment is still slowed by some basic and gaping holes in research.

No randomised trials comparing surgery and radiation until now

"Those treating prostate cancer always have the problem that there is no randomised trial comparing radiation therapy with surgery. But we have started one here in the department, genuinely randomising patients to radiation or radical prostatectomy. It has to be done. Generally, around the world, people look to Scandinavia for the best randomised trials, the landmark studies – because of our health system, but also because our patients are historically more willing to be randomised. It's almost impossible to randomise patients in the United States."

Abrahamsson won't contemplate complete retirement. He will continue as a clinician at the hospital, and is hopeful that new-found time will allow him to pursue new research. He wants to investigate the stem-cell characteristics of cancer cells, test new combinations of treatments including chemotherapy, and find better ways of identifying the most aggressive cancers and tailoring treatments to them. His team has already begun the stem cell work in collaboration with Norman Maitland, Director of York University's Cancer Research Unit in the UK, and Jack Schalken, Director of Urology Research at Radboud University Medical Centre, the Netherlands.

"There are too many super egos among doctors, politicians and CEOs"

But he's wondering how he's going to cope without travelling. His role with EAU takes him tens of thousands of miles each year, and he wonders whether he might be addicted to travel. He started establishing international links early in his career, travelling to Poland on several medical relief missions during martial law and the economic crisis in the 1980s (he was awarded a Red Cross medal for his work). Since then, he has travelled regularly to central and eastern European countries to give lectures – not just Poland but Russia, Serbia, Ukraine and Romania. He has been awarded honorary professorships in most of these countries.

"The only real challenge in my career has been lack of time," he says. "Now, I think, if there's anything I could do in the next few years, it would be to continue to work in the international arena and offer them my experience and networks – I know so many opinion leaders in urology and oncology."

And it's here that he may need to take on the role of a United Nations-style peacemaker. "Time is so short, it's crazy. There are too many super-egos among doctors, politicians and CEOs. You find them everywhere. They have to down-size their egos. We need to sit down peacefully together, not fight each other.

This article is an edited version of a longer article by Simon Compton of CancerWorld. Europa Uomo is grateful to CancerWorld for permission to edit and use the article.

All Trials

John Dowling, 31 August 2015

Court Attempt to Block All Trials Publication Fails

The judicial review proceedings by the British-based,

Richmond Pharmacology, have failed to prevent the Health Research Authority from taking steps to register all trials in advance of the new regulations on the publication of information on all trials. These new regulations are now at an advanced stage of drafting and consultation. It is expected that at the final draft regulations will be due for consideration by the Board of the European Medicines Agency (EMA) before the end of this year.

There has been a very effective movement to ensure that information on all trials are published rather than the present practice of only publishing the outcomes of those trials where the product may be brought to market and is seeking regulatory approval.

Many trials are currently unpublished because they have been discontinued. This may be because the early results indicated the product was not effective or because it proved dangerous to the patient. In other cases the company (referred to in the literature as the "Sponsor") does not see that there is any commercial advantage in pursuing the trial or in some cases the trial is run to conclusion, but the company which developed it decides to not bring it to market for commercial reasons.

These commercial reasons may be that the product, though efficacious, is no better or perhaps even inferior to the other products on the market; or the likely market for the product is too small to be of any long term interest in commercial terms; or the company already has another product on the market which would be adversely affected by the new product; or because the therapeutic benefit of the product is so minimal that regulatory approval, particularly for reimbursement, may not be forthcoming.

Patient and civil society groups have long contended that the policy of pharmaceutical companies in not publishing information on all trails conducted was not in the public interest. Legislation was enacted in the US several years ago but it has proved weak and ineffective and the All Trials movement in the US is now stronger than ever.

In Europe, the All-Trials agitation through the European Parliament resulted in the EMA commencing the current process which is now at a late stage of consultation and drafting. At the June meeting of the Patients' and Consumers' Working Party of the EMA (on which this writer is the Europa Uomo representative) the EMA briefed representatives on the present state of the draft directive. The EMA indicated that it expected to conclude the process by the end of this year. This will make it obligatory for all companies conducting drug trials in the European Union to register and publish these trials regardless of whether the company brings the product to market. The principal matters outstanding are around the issue of the timescale within which the company must publish a report of the discontinued trial.

Against this background a British company, Richmond Pharmacology, took Judicial Review proceedings in the High Court in Manchester, seeking an order against the Health Research Authority (HRA) and designed to prevent the new regulations from coming into effect in the UK.

Richmond contended that the ethical approval body for trials, the HRA, acted illegally in asking trial sponsors to declare that previous or ongoing trials in the UK had been registered; that by doing this HRA wrongly implied there was a legal requirement and so overstepped its duties as laid down in statute. HRA responded that it did not say that and did not intend that impression, and that its role in monitoring trial registration springs from its responsibility as the ethical approval body, not from law. The AllTrials group intervened by applying to the court to be allowed to set out the legal and moral case for trial registration and reporting. The judge permitted AllTrials to make written legal arguments.

AllTrials intervened because Richmond, whether intentionally or not, said it would be asking the court to decide a major point of principle about clinical trial registration. AllTrials lawyers saw a serious risk that the public's expectations of transparency, the hard won progress of two decades and new advances in patient safety would be unwittingly sacrificed in a squabble between a company and the regulator. AllTrials aim was to put to the court and to HRA the broader demand for transparency and monitoring of trials, and to challenge Richmond's and HRA's accounts of the basis for the registration and reporting. AllTrials contended that this is a matter that is far too significant to be negotiated as part of parties' settlement of a court case. AllTrials were intent that the court should not threaten trial registration or create loopholes through which more trials could flow, or the new European regulations be nullified.

Notwithstanding the Court's judgment – that the HRA has a clear legal right to monitor researchers' compliance with all their legal and ethical obligations – AllTrials remains concerned that there are parties who want to undermine the progress already made.

AllTrials and the Ethical Medicines Industry Group sent a joint letter: (http://www.pharmafile.com/news/498196/confronting-danger-blocking-progress-clinical-trial-transparency) in August to the HRA, setting out why it should not be dissuaded from its path. It was published in *Pharmafile* on 19 August (http://www.pharmafile.com/news/498194/hra-must-continue-progress-towards-clinical-trial-transparency). The Court was critical about some aspects of the HRA position and ruled that the Q&A and some of the HRA's material explaining the requirements were 'confusing'.

According to AllTrials "*monitoring compliance with regulations and good practice is one of the biggest challenges of trials transparency. Medical journals tell us that they still receive submissions from studies that have not been registered, and recent reviews have found big gaps in compliance on trial registries. The HRA had found a sensible and practical way of integrating some basic monitoring into the ethical approval process that they're responsible for. Regulatory bodies in other countries have been considering whether it is a way forward*."

"We hope our letter will also make it very clear to them that AllTrials supporters, the UK biopharmaceutical industry, and the English courts have all agreed that it is."

The Patients' Mailbox

The Editor has devised this column in order that patients may voice their views, opinions, queries and worries which they are perhaps reluctant or too embarrassed to mention to their doctors and urologists. Should they wish, the question may remain anonymous, provided they specific this preference on sending us their query to the attention of our secretarial office: europauomo@skynet.be.

1. Why has the British Cancer Drugs Fund delisted 25 treatment drugs including Cabazitaxel and what are the alternative solutions? According to a manufacturer's survey, 77% of the oncologists said Cabazitaxel fulfilled an unmet need for many patients. Patients like me think this is a mistake and that we risk being given cheaper unsuccessful drugs and will probably later need expensive palliative care in hospital, which will be more than the cost of the treatments provided. Patients who have had Cabazitaxel are still alive and well four years after first receiving it. (Hugh Gunn)

Comment:
Cabazitaxel is a new chemotherapy in addition to taxotere in the control of hormone resistant metastatic prostate carcinoma. Until a short while ago, this drug was given to patients after using taxotere, and had the advantage of prolonging life by 3 months more in respect of the mitoxantrone drug previously used.
Today there are at least 2 new drugs which are surely more effective and less toxic than Cabazitaxel and are given earlier. They are Abiraterone and Enzalutamide. Bearing in mind the increased cost of health and oncological care, the health authorities have posed the problem of cost and effectiveness (that is in reference to survival and the quality of life). The English health authorities are one of the most severe in making such considerations. If the relation between cost and benefit is below a certain level (QALY), the cost of the drug is no longer sustained by the English Health System (NHS). This in fact is the case for Cabazitaxel.

2. Can we reduce the need for expensive drugs? If so, how? (Anonymous)
Comment:
The first move in order to reduce the cost of new costly drugs is preventive care (no smoking, a correct nutrition, efforts to reduce exposure to pollution etc) and secondly by means of a timely diagnosis. New drugs tend to be very expensive as research and development prove to be very costly (generally speaking each new drug costs around 2 billion dollars by the time it is available for treatment).
In Italy we are in fact discussing with the pharmaceutical companies the relation between their cost and effectiveness (in other words, pay according to results, risk sharing etc.)

3. Why are 40% of new cases of prostate cancer incurable? (Hugh Gunn)
Comment:
Very often prostate cancer is not symptomatic on diagnosis and only becomes symptomatic when it is in an advanced stage locally or has become metastatic. That is when it can no longer be removed by means of localized treatments. The systematic therapies now in use are capable of combating the disease for many years but are unable to eradicate it.

4. I have been on Active Surveillance now for 4 years. How long can I persist with this treatment. Is it a physical or time factor? (Giuseppe Romoli)
Comment:
An observational study was recently published which indicated that 55% of the patients had been on active

surveillance for some 15 years and had had no need of any medical treatment. The duration of active surveillance depends entirely on the biology of the cancer and, in a biologically favourable cancer, it can last for even 20 years without any need for medical treatment.

5. Are there no statistics on how long one may live after the operation? (Armando Sforza)
Comment:
There are numerous statistics which measure survival after a surgical operation, but the data depend on a series of variables. First of all of the stage of the cancer (TNM) and the Gleason measurement. More recently there has been an attempt to correlate the prognosis with genetic data.

6. I have regular injections of Caverject. For how long can I use this therapy? (Michele Micoli)
Comment:
There are at present no precise indications on when to suspend this drug. However it is noted that continual traumatic effects which may occur on the injection of Caverject may render the human tissue more rigid and less elastic and lead to a certain deformity of the same tissue (like an induration penis). Should such phenomena occur, it is advisable to suspend the injections.

7. With radiotherapy treatment, when can I consider myself as effectively cured and what side effects may later occur? In fact very often, though the various therapies are carefully outlined, the possible consequences for each treatment are rarely well explained. (Emilio Riva & Pippo Autera)
Comment:
Prostate cancer is a neoplasia which may develop very slowly so that the word "cured" needs to be used with some care, as it may reoccur even many years after having had radiotherapy treatment. Radiotherapy can produce chronic collateral effects such as cystitis and prostatitis, urine incontinence and impotence, which tend to materialize even several years after treatment.

8. Once operated, for how long after should I have regular PSA blood tests? (Armando Sforza)
Comment:
As I have already mentioned, prostate cancer may reoccur even many years after surgical or radiotherapy treatment and/or hormone therapy, so it is advisable to continue to have periodic PSA tests for many years. The regularity of such tests will depend on the nature of the prostate cancer and of the prognosis, and the degree of danger of a re-occurrence of the cancer.

Such medical comments and advice were kindly provided by Dr. Claudio Verusio, oncologist, and chairman of the Scientific Committee of Europa Uomo Italy and we thank him for the same.

Letters to the Editor

This new column aims to encourage our international readership to express opinions, make suggestions, give news of events and new discoveries which may not be generally known. We trust that you will contribute to its success and we thank you in anticipation of the same.

Dear Editor,

On reading "*Did You Know?* for the first time, a well-known famous saying immediately came to mind which, like many others, is attributed to George Bernard Shaw. It reads:" if I have an apple and you have a pear and we exchange them, each of us always has only one fruit. But if both of us has an idea and we exchange them, we both have two ideas. The multiplication of knowledge is at the basis of the spreading of knowledge in any and every intellectual sector, and I believe that your idea to encourage the inter-exchange of ideas, news and opinions among the readership of each national association belonging to Europa Uomo is sure to prove a success.

I also believe that many operators in this medical sector and, above all, many disease stricken patients will sincerely express their appreciation and, if you will permit me, your virtuous stubbornness, thanks to which you achieve such promising results.

We now have an additional responsibility. That is all of us who are involved in this great project to help and improve health care of prostate cancer not only within our own nations, but in the whole of Europe and, if possible, even beyond.

Congratulations Malcolm.
Marco Alberto Donadoni (Italy)

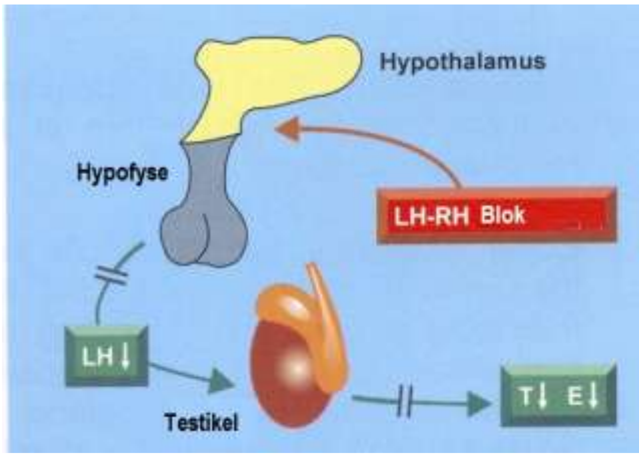
About Prostate and Hormones II: Anti-Androgens

Prof. Louis Denis

The most popular primary treatment for symptomatic and/or metastatic prostate cancer is still surgical or medical castration.
The surgical castration removes the most important source of testosterone (the male hormone T) by the

removal of both testicles. These are responsible for the production of 90 to 95 percent of the daily output in the male blood circulation (6 to 7 mgr/day).
The most popular medical castration is achieved by blocking the LH (Luteinising or gonadotropic hormone) in the hypophysis. LH stimulates the production of T in the testis. In women of course oestrogen. See Figure 1.

Figure 1: Scheme of the medical castration pathway T is lowered in the circulation to levels of < 50 ng/dl or < 1.7 nmol/L in the plasma)



This blockade is achieved by the administration of LH agonists (chemical simulation of the natural form) in adequate daily release doses by injections lasting one, three, six or 12 months. The one and three month injections are the most widely used in urological practice. The initial dose causes, of course, an extra stimulation of the LH production causing a temporary increase in LH (followed by T) that may in turn cause clinical problems in patients with symptomatic or metastatic prostate cancer. This is called a clinical flare (more pain or vertebral collapse). In these cases it is absolutely indispensable to administer complementary medication that prevents this clinical flare (see anti-androgens).
This clinical flare can be avoided by the administration of LHRH antagonists (LH releasing hormone) that bind directly to the LH receptors in the hypophysis.
The biological result of castration, be it surgical or medical, shall result in a low plasma testosterone value of at least less than 50 ng/dl.

Did you know that professor Andrew Schally (New Orleans, USA) also received a Nobel Prize in Medicine in 1977 for his successful research in the isolation/identification of the natural luteinising releasing hormone (LHRH) as a decapeptide (a protein consisting of only 10 amino acids) and the physiological results of administration in the male.

The actions of the LHRH agonists is described as paradoxal. Far from it. It is a normal expected reaction of any endocrine organ that stops producing if there is abundant end product present. In the physiological pathway the consequence leads to a halt in production of .i.T in the testicles. The great advantage of medical castration is its reversibility in contrast to surgical castration. It is flexible enough to allow for intermittent treatment. In these cases the hormones are given according to the reaction of the clinical results. In cases of good patient response, the treatment can be interrupted till we note a new tumoural activity.

Frequently it is forgotten that professor Charles Dodds created already in 1938 a chemical oestrogen (diethylstilboestrol, DES) that could be considered as the first chemotherapy in general and in prostate cancer in particular.

Before the era of the LH release hormones medical castration was achieved by administering oestrogens and progestogens, the two most important classes of female hormones. Out of a long list of publications with effective results we remember for oestrogens: DES, DES bisphosphonate, horse oestrogens and for long action substances poly-estradiol-phosphate. For the progestogens cyproterone (its acetate is an anti-androgen), medroxyprogesterone and chlormadinone. None of these substances achieved global status except DES that finally lost popularity by its side-effects such as nausea, breast formation and cardio-vascular complications. The final demise was given by the results of the VACURG (Veterans Administration, USA) studies demonstrating a clear cardio-vascular toxicity (especially blood clots) with daily doses of 5 and even 3 mg of DES. These side-effects were confirmed in several EORTC (European Organisation for Research and Treatment of Cancer) studies. Still we were interested in the positive results and minimal toxicity of 1 mg DES daily but trials with this dirt cheap medication were never pursued. However research with parental oestrogens is still pursued to avoid the liver intoxication of the oral forms and its described activity in the cancer cell not related to the effect of castration.

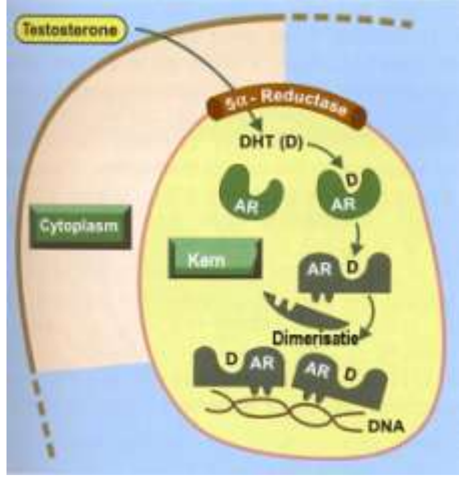
Did you know that testosterone and derivatives sometimes improve patients with prostate cancer. My advice is never try it on an active, extended cancer. Of course they have the same effect on the hypophysis – testicle axis. The reason that body builders with testosterone sometimes end up with two peanuts.

So we remain with a correct surgical or medical castration with a residual 5 to 10 percent of the daily testosterone production (± 0.3 to 0.6 mg) by the surrenal production or peripheral conversion in our fat tissue but also in the prostate and even the cancer itself.

Before we can define castration resistant prostate cancer (CRPC), it is mandatory to measure the T values in the serum that should be below (< 50 ng/dl or 1.7 nmol/L) the accepted castration values coupled to progression of the cancer. Progression can be defined as an increase in the PSA serum values, increase in volume or number of metastatic sites.

To conclude this long introduction it is appropriate to discuss the function of the androgens in the prostatic tissue. The famous studies of Wilson, Bruckovsky and Farnsworth revealed the function of T but the real male prostatic hormone was 5 alpha-dihydrotestosterone (DHT). This DHT is converted from T by an enzyme 5 alpha-reductase (5AR). Around the same time the studies of Dorfmann confirmed that specific proteins, called androgen receptors, bonded with DHT. This DHT-AR complex binds in the cell nucleus with the androgen elements on the DNA with activation of the related genes. See figure 2.

Figure 2: The DHT binds to the androgen receptors that activate the responsive DNA domain.



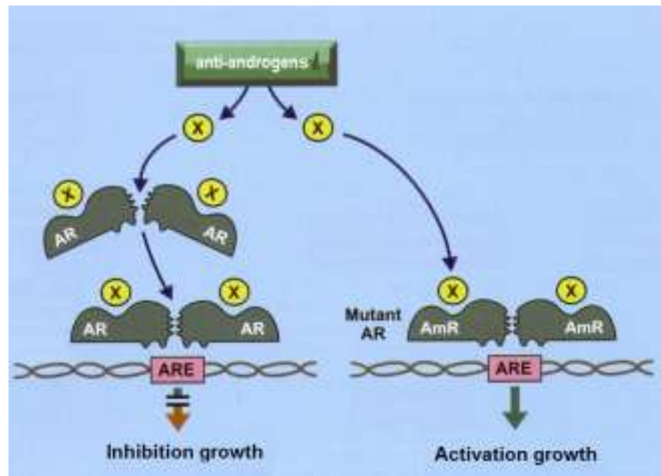
The discovery and application of a 5 AR inhibitor (5 ARI) for its two enzymatic forms lead to a 80 percent decrease of available DHT in the prostate. This led to an innovative treatment of benign prostate hyperplasia (BPH). Some specialists use the drug, finasteride or dutasteride, in the treatment of prostate cancer. However this treatment is not listed in the guidelines of the European Association of Urology (EAU) in the treatment of extensive, relapse or CRPC (*European Urology*, 65, 2014: 467-479) or in general treatment of prostate cancer in normal praxis.

Definition of Anti-androgens

Anti-androgens are substances that block the effect of the androgens on specific locations. They are different from the substances that decrease the substances (hormones) released from the hypothalamus and hypophysis or have a direct action on the gonads (testicles) to block the synthesis and secretion of T.

This definition refers to the so called pure androgens as flutamide, nilutamide, bicalutamide and enzalutamide but not cyproterone acetate that by its steroid structure also exerts a progestogenic influence on the hypophysis – testicle axes. Figure 3. Their function is well studied and bound to DHT they reach the nucleus to couple to the specific domain on the DNA to stimulate the male phenotype that includes the function and growth of the prostate.

Figure 3: Anti-androgens are able after mutation in the AR to stimulate instead of blocking cancer activity.



We know that an increase in the number of androgen receptors points to a possible evolution towards CRPC an end-station in the control of this cancer but also that mutations in the receptor may lead to activation of weak androgens, oestrogens, cortisone and yes anti-androgens in the AR elements on the DNA.

If the patient receives anti-androgens they need to be stopped before the diagnosis as these substances may change from antagonist to agonist (stimulating the tumour).

In simple terms anti-androgens, that normally block the biological activity of cancer, may after some time in the treatment start to activate the growth. This is

the reason why on relapse of the disease based on a PSA increase we stop the anti-androgen and control of the PSA after three to six weeks.
An important aspect of the treatment with anti-androgens is that serum T, instead of decreasing, increases slightly. Though appreciated both by patients and treating physicians, secondary effects such as breast formation (painful nipples to start with) as the increased end-product from T are estrogens which cause this side-effect.

From the first generation anti-androgens, bicalutamide proved to have the least side-effects. Less liver toxicity, though lung and visual problems were noted. It was preferred in Europe and finally advocated at 150 mg/day as an alternative for surgical castration. The most popular steroid anti-androgen is cyproterone acetate (CPA) that was the first used as monotherapy but is nowadays rarely used.

In 1996 the European School of Oncology (ESO) brought the discoverers of the then used anti-androgens together in a symposium (F. Neumann, R. Neri, B. Furr, M. Gaillard) to investigate the future of the anti-androgens in prostate cancer (L. Denis, *Anti-androgens in Prostate Cancer. A key to tailored treatment*. Monographs ESO, Springer, Berlin, 1996).

Consensus was reached on the indications of anti-androgens in the treatment of extensive prostate cancer (Table 1).

Table 1: anti-androgens indications in extensive prostate cancer

Non-Steroidal Anti-Androgens	
Monotherapy	
MAB	(maximal androgen blockade, a combination with LHRH A. Also called CAB (Complete Androgen Blockade)
Monotherapy and 5 ARI	
Prevention 'flare-up' LHRH A	
Castration resistant prostate cancer (CRPC)	

The main controversy was combining LHRHA & AA
Traditional doctors prefer to combine different active treatments in one disease hoping to obtain increased results in controlling the evolution of the disease. The drawback is of course that one also modifies the side-effects increasing the patient's burden and the cost of treatment. The combination of castration and anti-androgens has caused a lot of debate. In the new millennium we have collected 23 randomised trials in a meta-analysis published in the *Lancet*. The conclusion was the advantage gained was very small, less than 5 percent, in survival thanks to the combination.
The term CAB (Complete Androgen Blockade), preferred in the US, is a misnomer as other androgen sources remain intact.
The EORTC preferred a simple castration followed by the addition of an anti-androgen when the primary therapy showed failure.
A secondary response, mainly on the PSA marker, is noted in 7 to 10 percent of cases.

List abbreviations:

AA	Anti-Androgen
ADT	Androgen Depletion Therapy
AR	Androgen Receptors
5 AR	5-alfa-reductase
CAB	Complete Androgen Blockade

A new website for Europa Uomo

Nancy Verbrugghe, Webmaster EUomo

www.europa-uomo.org

On August 12 we launched a brand new website. Running on a professional platform and more flexible to update.

This new version is also mobile ready, which means it is easily readable on tablets and smartphones.

More content will be added in the coming days and weeks. We hope you enjoy it.

Please feel free to use the contact form (http://www.europa-uomo.org/contact/) for any remarks and/or suggestions.

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