eJOURNAL

January / February 2011

THE PRESIDENT'S MESSAGE

Le Beaujolais Nouveau est arrivé!

Professor Hans Evers
WES President

Welcome to 2011. This year it will be exactly 25 years ago that, in the midst of the 1st World Congress on Endometriosis in Clermont-Ferrand, the big doors burst open and a red-faced burly chap in a blue apron bellowed: "***Le Beaujolais Nouveau est arrive!***" From then on there were only the speakers and the chairs in the otherwise deserted lecture halls...

Let's drink to a happy Jubilee Year for the World Endometriosis Society. The 11th World Congress (WCE2011) will take us back to France, this time to Montpellier from 4-7 September – just in time for the wine harvest, but (unfortunately?) a bit early for the most frolicsome and vivacious wine event of the year: the Beaujolais Nouveau will only arrive on the third Thursday in November, from hamlets like Villié-Morgon and Saint-Amour-Bellevue where millions of bottles of Beaujolais Nouveau will start their long journeys, first to Paris, Lyon, Bordeaux and Marseilles, and then to the wine restaurants of the world: *Le Beaujolais Nouveau est arrive!* But you can rest assured, our French hosts, vintners and viticulturists in their own right, will make use of every opportunity to introduce us to the oenological highlights of the Languedoc-Roussillon in Southern France. But this time … after the end of the scientific sessions!

In line with tradition WCE2011 is an abstract driven meeting, with few invited speakers, each moderating a seminar consisting of his/her keynote lecture, related free communications and a scientific wrap-up. So, if you want to get heard, please submit your abstract by 31 March 2011 at: **www.wce2011.com** – this enables as many of us as possible to share our work with colleagues in a relaxed and friendly atmosphere (a unique congress concept!).

Building on the success of WCE2008, Professor Peter Rogers will chair another workshop on "Research Directions in Endometriosis" at WCE2011. This consensus workshop takes place on 4 September 2011 (pre-congress) and is limited to 50 attendees only. To apply, please send an email to **wes@endometriosis.org** with your name, affiliation, and stating the two areas within the field of endometriosis which you feel you "specialise" in. The deadline is 28 February, and confirmation will be sent out in early April, so do register your interest now.

Please take five minutes to complete a short survey about what you want from the World Endometriosis Society: **http://www.surveymonkey.com/s/ejournal-survey**. We want to serve YOU—tell us if we are doing it right, please!

As president of WES I am, of course, at your service if you feel I can be of help as we work together to unravel endometriosis. Please do not hesitate to contact me if you feel I can be of assistance.

Looking forward to seeing you in Montpellier in September!

PS:
We appreciate that the so-called WSE2011 meeting, organised in an hotel in Atlanta only a few months before our world congress (WCE2011), has created a lot of confusion. It has no relation to WES, although it uses the same initials.

In this issue of the WES e-Journal

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A WORD FROM THE EDITOR

Tempus fugit!

Dr Luk Rombauts
WES e-Journal Editor

We are already more than a month into 2011. The countdown to WCE2011 has now begun. It's true, as our President points out in his contribution, that the Atlanta World Symposium on Endometriosis (WSE 2011), held for the first time in March, has perhaps caused some confusion. Let there be no mistake: The World Congress on Endometriosis is held every three years and brings together clinicians and scientists to discuss and debate the progress in this field.

The congress is heavily weighted towards abstract presentations, with several important prizes awarded. In particular, we expect there will be strong competition for the travel awards to assist the young (<40 years) and bright clinicians/scientists who would like to attend (see page 8). It also remains the best place to network with the best research groups from around the world. Perhaps you will discover your next job at the meeting? Your post-doc is leaving and you urgently need someone to continue your work? Come to WCE2011!

In the last edition I commiserated with the many unfortunates in the Northern hemisphere, punished by an unusually early and severe winter. In the mean time, La Niña has caused severe floods Down Under and in other continents. To get an idea of the absolutely massive scale of this cyclone, **click here**. It overlays the radar map of cyclone Yasi on the continental maps of Northern America, Europe and Asia. Mindboggling...

I wonder whether there is an analogy here with what endometriosis patients go through? By the time they have recovered from their last debilitating period, the next one is making its presence felt. The only difference is that the cycle of despair never ends, unless a sympathetic and skilful specialist can hopefully break the vicious cycle.

In this issue Robert Schenken has selected four abstracts for his guest editorial. The focus this time is on non-surgical approaches.

Last but not least, Bernard Hedon, the convener of WCE 2011, brings us another appetiser for Montpellier. He introduces us to the medical school which, as you will read, has a very long history. And apparently a most interesting collection of portraits.

Please enjoy.

UPCOMING MEETINGS

Annual Scientific Meeting of the SGI
16 - 19 March 2011
Miami Beach, USA

World Symposium on Endometriosis
24 - 26 March 2011
Atlanta, USA

9th Deutscher Endometriose Kongress
1 - 4 June 2011
Emmendingen, Germany

67th Annual Meeting of the ASRM
15 - 19 October 2011
Orlando, USA

>> COMPLETE CONGRESS SCHEDULE

Let's talk about sex and endometriosis: the science and surgery of deep disease
18 - 19 March 2011
New York, USA

10th International Pelvic Pain Society Annual Scientific Meeting
25 - 29 May 2011
Istanbul, Turkey

27th Annual Meeting of ESHRE
3 - 6 July 2011
Stockholm, Sweden

Endometriosis and IVF
28 - 29 October 2011
Rome, Italy

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GUEST EDITORS' RESEARCH DIGEST

Non-surgical approaches for the treatment of endometriosis

Robert S Schenken, MD

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Professor Robert Schenken

For this review, I have selected four recently published articles focusing on the medical management of endometriosis.

Despite years of effort, we remain in need of newer and more effective medical therapies.

This is a comprehensive review of dienogest for the treatment of endometriosis. Dienogest is a unique synthetic progestin that is widely used outside the United States.

It is highly selective for the progesterone receptor and has *in vivo* and *in vitro* inhibitory effects on proliferation of endometrial cells.

Dienogest appears to be as effective as GnRH analogues in the management of endometriosis-associated pelvic pain. Several studies confirm decreased dysmenorrhoea, dyspareunia, diffuse pelvic pain and tenderness on exam.

Studies have compared the 1, 2, and 4 mg/day dose. The 1 mg dose has unacceptable bleeding and there is no increased therapeutic efficacy with the 4 mg dose, so the 2 mg dose is recommended.

The primary drawback is the relatively common occurrence of irregular bleeding which may cause patients to discontinue therapy.

Other, rare, side effects include headaches, breast tenderness, depressed mood, and acne. It has only minor effects on liver function and carbohydrate metabolism making it suitable for long-term use.

Dienogest: a review of its use in the treatment of endometriosis
Drugs 2010;12(16):2073-88

McCormack PL

Dienogest (Visanne®) is a synthetic oral progestogen with unique pharmacological properties that is indicated at a dosage of 2 mg/day for the treatment of endometriosis. It is generally highly selective for the progesterone receptor and displays strong progestational effects and moderate antigonadotrophic effects, but no androgenic, glucocorticoid or mineralocorticoid activity. Dienogest has moderate affinity for progesterone receptors (10% that of progesterone) and at a dosage of 2 mg/day only moderately suppresses estradiol levels. It has high oral bioavailability and a half-life suitable for once-daily administration. In randomized clinical trials, oral dienogest was significantly more effective than placebo in reducing pelvic pain in patients with confirmed endometriosis. In trials comparing oral dienogest for 16 or 24 weeks with gonadotropin-releasing hormone (GnRH) agonists commonly used in the treatment of endometriosis, dienogest was noninferior to depot leuprorelin in reducing pelvic pain and was not significantly different from intranasal buserelin and depot triptorelin in improving combined symptoms/signs scores or revised American Fertility Society (rAFS) staging scores, respectively. Improvements were also noted in some measures of health-related quality of life. The efficacy of dienogest was sustained during long-term treatment for more than 1 year. Dienogest was generally well tolerated and was not considered to be associated with clinically relevant androgenic effects. It appeared to have fewer hypoestrogenic effects than the GnRH agonists. Dienogest was associated with a high incidence of abnormal menstrual bleeding patterns, although this was generally well tolerated by patients, with few discontinuing therapy, and the bleeding intensity and frequency decreased over time. Therefore, oral dienogest offers an effective, generally well tolerated therapeutic option for the long-term treatment of endometriosis.

Waiting for Godot: a commonsense approach to the medical treatment of endometriosis

Hum Reprod 2011;26(1):3-13

Vercellini P, Crosignani P, Somigliana E, Viganò P, Frattaruolo MP, Fedele L

Conservative surgical treatment for symptomatic endometriosis is frequently associated with only partial relief of pelvic pain or its recurrence. Therefore, medical therapy constitutes an important alternative or complement to surgery. However, no available compound is cytoreductive, and suppression instead of elimination of implants is the only realistic objective of pharmacological intervention. Because this implies prolonged periods of treatments, only medications with a favourable safety/tolerability/efficacy/cost profile should be chosen. In the past few years, innumerable new drugs for endometriosis, which would interfere with several hypothesized pathogenic mechanisms, have been studied and their use foreseen. However, robust evidence of in vivo safety and efficacy is lacking and, at the moment, the principal modality to interfere with endometriosis metabolism is still hormonal manipulation. Regrettably, in spite of consistent demonstration of a major effect on pain even in patients with deeply infiltrating lesions, progestins are underestimated and dismissed in favour of more scientifically fashionable and up-to-the-minute alternatives. Moreover, oral contraceptives (OCs) dramatically reduce the rate of post-operative endometrioma recurrence and should now be considered an essential part of long-term therapeutic strategies in order to limit further damage to future fertility. Finally, women who have used OC for prolonged periods will be protected from an increased risk of endometriosis-associated ovarian cancer. To avoid the several subtle modalities for distorting facts and orientating opinions in favour of specific compounds, progestins and monophasic OC used continuously are here proposed as the reference comparator in all future randomized controlled trials on medical treatment for endometriosis.

The above mentioned paper is a thorough review of the literature comparing oral contraceptives, progestins, and Mirena to GnRH analogues.

Oral contraceptive and progestin should be considered in the long-term management of women with endometriosis. They are effective and less expensive than GnRH analogues. Several of the studies also demonstrate improved quality of life. Post-operative treatment with these agents also reduces recurrence of symptoms and reappearance of endometriomas.

Medical therapy does not influence reproductive performance. The authors suggest that future randomised trials should use oral contraceptive as the reference comparator.

Use of mifepristone to treat endometriosis: a review of clinical trials and trial-like studies conducted in China

Women's Health 2010;7(1):51-70

Guo SW, Liu M, Shen F, Liu X

China was the first country in the world that approved mifepristone (RU-486) for abortion. A total of 6 years after the report published in the Western world indicated that mifepristone may also be effective in treating endometriosis, the first paper on the same topic was published in China in 1997. Since then, over 160 studies on this topic have been published in China. We retrieved 104 papers on clinical trials and trial-like studies conducted in China evaluating the use of mifepristone to treat endometriosis that were published in the last 11 years. We found that the quality of these studies is well below an acceptable level, making it difficult to judge whether mifepristone is truly efficacious. There are intriguing signs that these studies, as a whole, have serious anomalies. The areas that are glaringly deficient are informed consent, choice of outcome measures, the evaluation of outcome measures, data analysis and randomization. The uniformly low quality is disquieting, given the large quantity of studies, the enormous amount of resource and energy put into these studies and, above all, the weighty issue of treatment efficacy that concerns each and every patient with endometriosis. Equally disquieting are the low-quality repetition, the absence of a critical, systematic review on the subject, the lack of suggestions for multicenter clinical trials and the seemingly unnecessary duplication of clinical trials without due informed consent. In view of this, it may be time to institute changes in attitude and practice, and to change education and training programs in the methodology of clinical trials in obstetrics and gynecology research in China.

RU-486
Mifepristone (RU486) has clinical potential in the medical management of endometriosis.

The mechanism by which RU486 modulates endometriotic tissue growth is poorly understood. Studies have demonstrated a direct antiproliferative effect on endometrial cell growth *in vitro* and RU486 also appears to have potent antioxidant activity, suggesting another potential mechanism of action.

Unfortunately, the available studies assessing clinical efficacy are hampered by small sample size, poorly defined primary outcomes, and many were not randomized. This underscores the need for a large randomized controlled trial to assess whether RU486 is truly an appropriate modality for treatment of women with endometriosis.

Alternative approaches
This last paper is an interesting review of alternative approaches to the medical management of endometriosis.

There is evidence for the effectiveness of n-3 fatty acids, vitamin E, vitamin B1, vitamin B3, and magnesium for dysmenorrheal.

These agents decrease the release of PGE2 and PGF2α.

Only one randomised trial has assessed the efficacy of dietary therapy following conservative pelvic surgery for endometriosis. The treatment groups included:
1) placebo
2) dietary therapy with nutritional intake of vitamins (B6, A, C, and E) mineral salts, and VSL3 lactic ferments and fish oil
3) GnRH analogue, and
4) low-dose monophasic oral contraceptives.

Hormonal suppression and dietary were equally effective and more effective than placebo in relieving pelvic pain and improving quality of life.

Consideration should be given to non-prescription medications especially antioxidants.

Dietary therapy: a new strategy for management of chronic pelvic pain
Nutr Res Rev 2010;25:1-8

Sesti F, Capozzolo T, Pietropolli A, Collalti M, Bollea MR, Piccione E

Chronic pelvic pain (CPP) can be identified as a chronic nociceptive, inflammatory and neuropathic pain characterised by spontaneous pain and an exaggerated response to painful and/or innocuous stimuli. This pain condition is extremely debilitating and usually difficult to treat. Currently, the main approaches to treatment include counselling supported by reassuring ultrasound scanning or psychotherapy, attempting to provide reassurance using laparoscopy to exclude serious pelvic pathology, hormonal therapy and neuroablative treatment to interrupt nerve pathways. Dietary supplementation has been suggested as a means to treat chronic medical illnesses that are poorly responsive to prescription drugs or in which therapeutic options are limited, costly or carry a high side-effect profile. A comprehensive search of the PubMed database was performed using the search terms 'chronic pelvic pain', 'oxidative stress', 'antioxidants' and 'dietary therapy'. The systematic review focuses on both randomised and non-randomised controlled trials from 2005 onwards, in which CPP was the end point. Given the complexity and not well-understood aetiology of CPP, its treatment is often unsatisfactory and limited to partial symptom relief. Dietary therapy with antioxidants improves function of the immune system and in fighting free radical damage. Agents with antioxidant activity are able to improve CPP without undesired effects and any important metabolic changes associated with hormonal suppression therapy. In conclusion, dietary therapy with antioxidants could be considered as a new effective strategy in the long term for CPP, and may be better accepted by patients. Further randomised trials with larger series and long-term follow-up to confirm these observations are needed.

Celebrating 50 years of the human clinical use of gonadotrophins: a tribute to Professor Bruno Lunenfeld

In 1961 the first baby was born after being treated by Professor Bruno Lunenfeld with Pergonal, the first human gonadotrophin drug that enabled ovulation to take place. Until then the many causes of infertility were not fully understood, and there was little that could be done for women unable to conceive.

Professor Lunenfeld was part of the team which, in the 1950s, unravelled the workings of gonadotrophins and consequently paved the way for their use in the treatment of infertility, including therapies facilitating IVF to this day.

The 50th anniversary of this clinical breakthrough in the field of fertility was celebrated at the 10th International Symposium on GnRH, in Salzburg, in early February.

Any regrets?

We caught up with Professor Lunenfeld at the meeting and, rather than asking him to reflect on his long and distinguished career, chose to enquire if there was anything – looking back – that he would have done differently or, indeed, felt he could have done better?

"Yes, most probably there was", responded Lunenfeld. "Professor MC Shelesnyak, who was at the Weizmann Institute, invited me to join him there, whilst I was still in the army. He was working on implantation and had just discovered a very interesting situation that with Ergocornine and Ergocryptine he could inhibit implantation in rats and mice and had started to think about how to work on this in humans.

Lone Hummelshoj, Professor Bruno Lunenfeld and Dr Klaus Bühler at the 10th GnRH meeting, Salzburg, 8 February 2011

"So I joined the Weizmann Institute in 1957 and we started working on this. But my interest was still also, on one hand, on gonadotrophins, so we developed an anti-serum to hCG and thought this was a good idea because with this we could again influence implantation.

"As I continued to work with Professor Shelesnyak suddenly Professor Harel, the head of endocrinology at the Sheba Medical Centre, was appointed as the Israeli Ambassador to Romania, and I was subsequently offered the position to replace him at the hospital. I quickly concluded that someone who gets to be an ambassador will never return as a head of a hospital department, if anything he'd return as head of the hospital itself.

"So, I accepted the appointment even though the scientists at the Weizmann Institute called me a prostitute accusing me of leaving basic research for this silly clinical work. But I did it, and that is how I stopped my work on implantation and continued my work very rapidly on gonadotropins. The latter moved forward with the help of grants from the Population Council, the Ford Foundation, and the NIH. This enabled us to develop human menopausal gonadotrophins together with Piero Donini from the R&D department of Serono, finally helping so very many infertile women – and of course our work has, directly and indirectly, resulted in the birth of more than four million babies.

"But today I am very sorry that I did not work on implantation because, as I told Professor Shelesnyak back in 1958, I wasn't doing implantation only to prevent pregnancies but I also wanted to study implantation because I wanted to prevent metastasis implanting anywhere in the body", said Lunenfeld.

Six years later in Chicago when he met Professor Melvyn Cohen, who was doing the first laparoscopies and showed him endometriotic tissue in the pelvis, Lunenfeld commented: "Listen! This is a very interesting thing, maybe we should work on implantation and then we could probably prevent implantation of endometriosis wherever it comes from?"

Any chance of going back to work?

It was too tempting not to ask this energetic Professor what is now stopping him from returning to the work of implan-

tation, a question which he responded to in good humour.

"You know, at my age today at 84, I don't think that anybody would ever give me any funds to work in a laboratory, so I can only use my brain to analyse data, which is coming out and give advice to other people who do research. But personally, unfortunately, my research period in the lab, on the bench, has ended.

However, I think there are enough good people around, and I am always happy to discuss things and I talk to Hans Evers and others – and I love to discuss science since it is an intellectual exercise for me. But whereas I would be delighted to help anywhere I can, I think younger people should go do these things themselves and my generation should only act as advisors or consultants", commented Lunenfeld.

So, what about endometriosis?
When Lunenfeld is asked what the single most important thing that has happened in the field of endometriosis in last 50 years is he didn't hesitate with his response.

"Since the discovery of modern laparoscopy and laparoscopic surgery I think that nothing much new has happened unfortunately. We still do not know enough about this disease. We still do not know how it develops and even when it starts.

"You know there are the three theories, which probably all have some kind of validity. There is retro-implantation of menstrual blood. There is a more logical theory, the genetic theory, as well as an environmental theory.

"I think that all of these have something to do together but the entire story of course we do not know yet. I am sure that working on factors which can control angiogenesis and factors which can prevent implantation have a future.

"We are learning to control pain through certain progestogen agents and GnRH analogues, as we have also heard during this meeting, but for the time being the only thing that we really have, and which really works, is surgical removal of the disease. Through laparoscopy you can diagnose and treat at the same time, removing lesions as good as you can. But it is still surgery and I only hope in the very near future endometriosis can be treated medically".

What is the meaning of life?
The editor of the WES e-Journal has been keen to understand the meaning of life, and who better to ask then someone who has made it to the age of 84?

"This is very interesting" responded Lunenfeld, "because for me adult life started at the age of 11 when I was forced to leave home. My father had given me five pieces of advice:


Professor Bruno Lunenfeld

1. Never underestimate anyone;
2. Respect everyone;
3. Keep your dignity at all times;
4. Do not expect anything from others – don't ever ask what others can do for you, but what you can do for others (just like JF Kennedy said it, except my father said it long ago before to me);
5. Try to be as honest as possible.

"I took these five messages with me all my life and I tried to live by them. This was my youth. When I became older and a student I was influenced by Jean Paul Sartre, of course, and learned that we had to live for today because we do not know what tomorrow brings. This again influenced my way of life and how I look at life. I am thankful every morning that I am alive and I try to enjoy my current situation.

"Finally, I was influenced by Professor De Watteville, who was my chief and boss, and who really showed me how to think onwards; but, in the end, it is all about what my mother always told me. In German you say *Der Mensch denkt und Gott lenkt* (man thinks but God decides). Whatever you call God – or whether it is god, destination, nature, whatever... – I think this is the way we have to look at life. For me this means continuing to live in good health and with dignity. That is all", concluded Professor Lunenfeld.

Further reading:
"Baby boomer" article by Bernard Dichek for Israel21c, 8 February 2011

Lunenfeld B. Historical perspectives in gonadotrophin therapy. Hum Reprod Update 2004;10(6):453-67.

In celebration: 50 years of the clinical use of human gonadotrophins. RBM Online 2011;22 Supplement 1

WES announces four travel grants for WCE2011

Through generous donations, not least a part of the profits from the 3rd Nordic Congress on Endometriosis, WES is delighted to be able to announce four travel grants for WCE2011. These grants will be allocated to clinicians and/or scientists, who specialise in endometriosis but who are unable to raise funding to come to Montpellier in September to present their work.

Applicants must be under the age of 40, have at least one publication on endometriosis in a peer-reviewed journal, as well as an accepted abstract for WCE2011 (deadline for submission of abstracts is 31 March 2011) in order to qualify. Applicants will also need to justify their need for travel support.

Please apply online at: **www.endometriosis.ca/rodolphe-maheux-travel-fund.html**.
Successful applicants will be notified mid-May.

Rodolphe Maheux Award for best clinical presentation at WCE2011

The World Endometriosis Society (WES) established an award in 2008 in the memory of the Society's co-founder, Rodolphe Maheux. This award, which carries a prize of €1,000 towards a future meeting, will be presented to the best clinical presentation or poster at WCE2011 by an author under the age of 40.

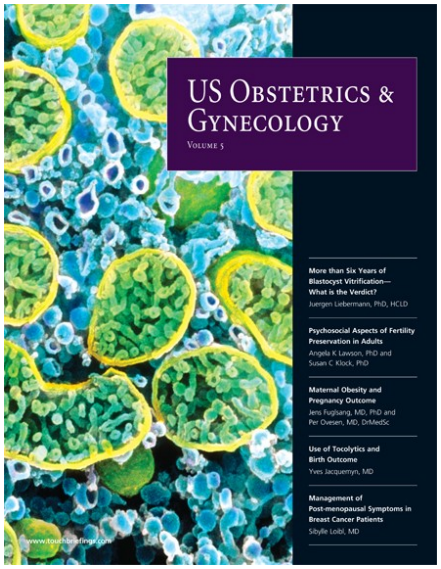
CLICK HERE to submit your abstract(s) now — the deadline is 31 March 2011.

ASRM announces e-Learning programme

ASRM eLearn

The ASRM has launched an online learning programme for reproductive healthcare professionals, including online CME, PEER, and Nursing CE credits (with discounts for ASRM members).
View a video demo at www.asrm.org

Free eBook access to Touch Briefings' *US Obstetrics and Gynecology*



WES has entered into a collaboration that provides its members with free access to Touch Briefings' publications.

Their latest issue of *US Obstetrics & Gynecology Volume 5* is now available in full, and for free for WES members, in eBook format at **www.touchbriefings.com/ebooks/A1q1te/usobsandgynreg5/**

In this issue, two informative articles discuss the use of blastocyst vitrification in assisted reproduction in some depth, whilst Angela K Lawson and Susan C Klock examine "Psychosocial Aspects of Fertility Preservation".

Elsewhere in this edition, Udo B Hoyme provides a fascinating exploration of the prevention of pre-term birth by vaginal pH self-screening.

Enjoy reading!

Most ancient medical faculty "in the world" hosts world congress of endometriosis

by Bernard Hédon, WCE2011 president

Yes, Montpellier is the most ancient medical faculty in the world. To be honest, I should add: "still active". Because there are competitors from Italy, Salerno and Bologna who claim the same. You have to ask yourself how this is possible, because in this historical competition, you either are or you are not.

Let history be the referee.

As for Salerno, the case is simple: the medical faculty was established before the one in Montpellier, somewhere around the start of the 13th century.

But, it is no longer a faculty; the reason for the "still active" addition! And Montpellier started its activity before Bologna. At least, this is what we believe here in Montpellier. I remember my surprise when, visiting Bologna, I suddenly realised that the Bolognese believe the exact opposite!

Today, in any case, the claim has little value in regard with the incredibly rich testimonies of the glorious past of our medical faculty of Montpellier.

Its history is paved with prestigious professors whose names ring familiar in the international medical community. Many break-through discoveries have been made in Montpellier, starting with the topical use of alcohol by Arnaud de Villeneuve in the prevention of wound infection.

The interesting thing is that the initial donation of his painted portrait to the faculty upon retirement has become a tradition throughout the centuries. There are now thousands of portraits and not enough walls to display them all.

The participants in the World Congress of Endometriosis will have the privilege to visit the faculty with its astonishing architectural design alongside the cathedral (here again, there is a reason for that, because the bishop of Montpellier was also the dean of the faculty), its portrait galleries and its famous Anatomy Museum, host of the most precious collections of venereal diseases and foetal monsters.

The visit will be presented by modern-day medical professors, yet far-away descendants of Rabelais and Lapeyronie, during the opening of the gala dinner served in the very heart of the faculty.

Register for the 11th World Congress on Endometriosis here: **www.wce2011.com**