



## Presidents's Message

During 2004 local interest in Endometriosis has been enhanced by the establishment of several national Endometriosis Societies and national meetings. These events have been inspired by members of the WES in those countries and help to highlight the importance of this condition to health care providers, but more importantly bring together clinicians and patient groups with an interest in the disease which should enhance networking and stimulate collaborative research. The forthcoming international conference in Maastricht in September - the World Endometriosis Society meeting - will enable experts around the globe to meet, share experiences and stimulate future research into endometriosis. We look forward to seeing you at the Congress in September, book early to ensure a place and make savings.

Best wishes for 2005

Professor Robert Shaw  
President WES  
Derby UK

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## Editorial

Dear Members

It is a great pleasure for me to take over the editorship of the WES e-journal. With your help I hope to make this journal an efficient channel of knowledge diffusion and a means for members to interact and exchange ideas. Our main goal is to stimulate research on endometriosis, a serious, enigmatic and fascinating disease. It is our responsibility as researchers and clinicians to communicate and combine our efforts to expand knowledge and to improve endometriosis diagnosis and treatment for the patients' well-being.

I believe it is important to have a more dynamic formula 1) by increasing the involvement of scientists working in the field through exchange, discussion and debate, and 2) to give the public as well as the scientists the best information about what is known and what is being done, with the accent on specific areas, for instance, basic research and epidemiology.

Concretely, in each issue of the e-journal, guest editorialists will be asked to write on a given subject of their area of interest. Members are encouraged to share their opinions regarding the editorial and other endometriosis-related issues in our discussion forum.

We wish to encourage WES researchers to submit comments/opinions, news and short articles summarizing what had already been published on a given subject or even describing new data that they wish to get diffused through the WES e-journal. Selected articles will be published and made available for discussion via our discussion forum.

We need to provide the visitor to our website with up-to-date information and would greatly appreciate any pertinent information of interest for our members (invitations for collaborative projects or multi-center studies, grant announcements, meetings, workshops, research opportunities for students, fellowships etc...).

The WES e-journal is yours, for the service of our members. So your active collaboration is a sine qua none condition for its success.

I'd like also to take this opportunity to ask for your active participation in our up-coming next meeting in Maastricht, The Netherlands on 14 - 17 September 2005. The scientific program included in the current issue of the WES e-journal is exciting! What a wonderful occasion to meet together and hear about the most advanced basic and clinical issues in the field.

(continued on page 2)

## Announcement

### Two Conferences of Particular Interest

- **21st Annual Meeting of the European Society of Human Reproduction & Embryology (ESHRE)**  
19-22 June, 2005  
Copenhagen, Denmark  
[www.eshre.com/emc.asp?pageId+206](http://www.eshre.com/emc.asp?pageId+206)
- **The 9th World Congress on Endometriosis**  
14-16 September, 2005  
Maastricht, The Netherlands

Endometriosis is on the increase. More and more women are suffering from it. Therefore, the 9th World Congress on Endometriosis is extremely timely. The central theme of the meeting -- which is being held in the mediaeval city of Maastricht



in The Netherlands -- will be "The Patient as a Partner". Learn all about new ways to diagnose and treat endometriosis. Collect new insights into its pathogenesis. Enjoy Old Europe. Walk on Roman cobblestones in Maastricht's traffic-free historical centre. Have a drink with old friends and meet new ones in the city's many beautiful tree-shaded squares. To access the scientific program and all relevant information please visit our website [www.conferenceagency.com/wce](http://www.conferenceagency.com/wce), and visit Maastricht.

...Welkom, gezellig !

## Editorial (continued)

Endometriosis is a hormone-dependent disease. Estrogens are known to favor eutopic and ectopic endometrial tissue growth; the finding of abnormal estradiol production by eutopic and ectopic endometrial tissue of women with endometriosis further adds to the prominent role of this steroid. Endometriosis-related changes in progesterone-dependent regulation of target genes is another critical aspect of endometriosis pathophysiology. Combination of E2- and P-related changes may be critical for endometriosis development, clinical manifestations and treatment.

In this issue of WES e-journal the topic is addressed by Dr Serdar Bulun in his article "Aromatase and Endometriosis". Members are encouraged to react and share their opinions via our discussion forum which can be accessed by clicking...

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[www.endometriosis.ca](http://www.endometriosis.ca)

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## Forthcoming Meetings in 2005

March 10-13

XII World Congress on Human Reproduction  
Venice, Italy.

April 14-17

Obstetrics Gynaecology & Infertility  
6th World Congress  
Athens, Greece.

May 7-11

53rd Annual Clinical Meeting of the American College  
of Obstetrics & Gynecology  
San Francisco, USA.

May 12-15

Advancing the ART of Human Reproduction:  
Physiology & Technology of the Future  
Miami, USA.

June 19-22

21st Annual Meeting ESHRE  
Copenhagen, Denmark.

July 24-27

38th Annual Meeting Society for the Study  
of Reproduction  
Quebec, Canada.

14-17 September

9th World Congress on Endometriosis  
Maastricht, The Netherlands.

15-22 October

American Society for Reproductive Medicine  
Annual Meeting  
Montreal, Canada.

### AROMATASE IN ENDOMETRIOSIS

Serdar E. Bulun, Gonca Imir, Hiroki Utsunomiya, Steven Thung, Bilgin Gurates, Mitsutoshi Tamura and Zhihong Lin. Department of Obstetrics and Gynecology Northwestern University, Chicago, IL 60611

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Key Words: Aromatase, aromatase inhibitor, letrozole, anastrozole, endometriosis, estrogen, estrogen biosynthesis, endometrium, uterus.

**Pathologic relevance.** Aromatase P450 (P450arom) is the key enzyme for estrogen biosynthesis<sup>2</sup>. The significance of aromatase in human disease has recently been underscored by six randomized clinical trials published since 2000 and demonstrating the superiority of aromatase inhibitors to tamoxifen in the treatment of breast cancer<sup>3</sup>. There are two intriguing implications of these results. First, it is pharmacologically more efficacious to block estrogen formation rather than its action at least by currently approved estrogen antagonists or SERMs. Second, the local effect of aromatase inhibitors at the target tissue level to block local estrogen formation may represent the most critical mechanism for the superior therapeutic potential of aromatase inhibitors. Thus, elucidation of molecular and cellular mechanisms that regulate local estrogen formation in pathologic hormone-dependent tissues (*e.g.*, breast cancer and endometriosis) is essential to understand the pathogenesis and develop novel therapeutic strategies. The molecular mechanisms responsible for estrogen biosynthesis in breast cancer and endometriosis are distinct, and their investigations require a thorough knowledge of the microenvironment in each disease.

Endometriosis is an estrogen-dependent disease that affects 10% of U.S. women of reproductive age (approximately 6 million) and is the most common cause of chronic pelvic pain<sup>4,5</sup>. Endometriosis is a systemic disorder that is characterized by the presence of endometrium-like tissue in ectopic sites outside the uterus, primarily on pelvic peritoneum and ovaries, and linked to chronic pelvic pain, pain during sex and infertility. In the U.S., endometriosis is the third most common gynecologic disorder that requires hospitalization and a leading cause of hysterectomy<sup>5</sup>. Only 50% of women with endometriosis achieve pain relief in response to existing hormonal treatments or conservative surgery<sup>5</sup>. Thus, there is a clear need to develop novel and effective therapies for endometriosis.

We recently demonstrated abundant aromatase expression and local estrogen production in endometriosis tissue<sup>6-10</sup>. This led our team to use aromatase inhibitors for the first time to successfully treat women with endometriosis resist-

ant to other existing therapies<sup>11</sup>. Thus, as in breast cancer, aromatase seems to be a critical therapeutic target in endometriosis.

**Mechanisms of growth and inflammation in endometriosis.** Two basic pathologic processes, namely growth and inflammation, are responsible for chronic pelvic pain and infertility, which are the primary devastating symptoms of endometriosis. Estrogen, growth factors and metalloproteinase enhance the growth and invasion of endometriosis tissue, whereas prostaglandins and cytokines mediate pain, inflammation and infertility<sup>4,12</sup>. Research work from our laboratory over the past 10 years uncovered a molecular link between inflammation and estrogen production in endometriosis<sup>10</sup>. This is mediated by a positive feedback cycle that favors continuous local production of StAR/P450arom, E2, COX-2 and PGE<sub>2</sub> in endometriosis tissue.

**Definitions of tissues showing molecular and biologic abnormalities.** We demonstrated a number of molecular abnormalities in endometriosis. The prototype abnormality was the presence of significant levels of P450arom enzyme activity and expression of protein and mRNA in the stromal cell component of endometriosis, whereas P450arom expression was either absent or barely detectable in the eutopic endometrium of disease-free (normal) women. The eutopic endometrium of women with endometriosis contains low but significant levels of P450arom mRNA and enzyme activity and represents an intermediate state of this disease. It appears that upon retrograde menstruation and implantation of this inherently abnormal tissue on pelvic peritoneal surfaces, P450arom expression and enzyme activity are amplified by up to 400 times<sup>13,14</sup>. We would like to clarify the terminology to be used in this manuscript in reference to the tissues and cells that are studied. The terms, “endometriotic tissue,” “endometriotic cell” and “endometriosis” will refer to the pathological ectopic endometrium-like tissues isolated from the pelvic peritoneum or ovaries during surgery. The term, “endometrium” refers to eutopic endometrial tissue that lines the uterine cavity. “Normal endometrium” and “normal endometrial cells and tissues” refer to the eutopic endometrium from disease-free women. The term, “endometrium from an endometriosis patient” refers to eutopic endometrial tissue or cells from patients with endometriosis. “Endometriotic stromal cells” are isolated from the walls of cystic endometriosis lesions (endometriomas) in the ovaries<sup>15</sup>. These cells in primary culture have been characterized extensively in Dr. Robert Taylor’s and our laboratories<sup>14,15</sup>. Endometriotic stromal cells display the differentiation markers observed in eutopic endometrial stromal cells in

culture. For example, progestin-treated endometriotic stromal cells express prolactin mRNA (readily detectable by northern), albeit in significantly lower levels compared with eutopic endometrial cells; whereas control ovarian granulosa cells do not show detectable prolactin mRNA.

***PGE<sub>2</sub> biosynthesis in endometriosis.*** The rate-limiting step for PGE<sub>2</sub> biosynthesis is catalyzed by the cyclooxygenase enzyme that is encoded by two distinct genes, referred to as COX-1 and COX-2. COX-2 is the inducible gene that is regulated by a whole host of factors. An *in vivo* association was reported between levels of P450arom and COX-2 expression in breast cancer tissues. PGE<sub>2</sub> synthesized in breast cancer epithelial cells was proposed to stimulate P450arom expression in breast fibroblasts<sup>16,17</sup>. In endometriotic stroma, COX-2 is upregulated in comparison with normal endometrium<sup>18</sup>. Moreover, we demonstrated during the past funding period that IL-1b and PGE<sub>2</sub> itself induce COX-2 in endometriotic/and endometrial stromal cells, whereas VEGF and E2 induced COX-2 in uterine endothelial cells<sup>19,21</sup>. Thus, a large number of pathways in endometriosis induce COX-2 to increase PGE<sub>2</sub> formation in this tissue.

***PGE<sub>2</sub> action in endometriosis and eutopic endometrium.*** Both endometriotic and eutopic endometrial stromal cells express similar mRNA and protein levels of the known PGE<sub>2</sub> receptor subtypes including EP<sub>1</sub>, EP<sub>2</sub>, EP<sub>3</sub> and EP<sub>4</sub>. Use of receptor-selective agonists, however, showed that only EP<sub>2</sub> receptor is responsible for PGE<sub>2</sub>-mediated StAR and P450arom expression in endometriotic stromal cells<sup>22</sup>. Stimulation of the EP2 receptor rapidly increases intracellular cAMP<sup>14,23</sup>. Treatment with PGE<sub>2</sub> or a cAMP analog gives rise to comparable increases in P450arom enzyme activity and mRNA levels<sup>14</sup>. On the other hand, neither PGE<sub>2</sub> (despite the presence of EP<sub>2</sub> receptors) nor cAMP analogs can induce P450arom (or StAR) in normal eutopic endometrial stromal cells. Thus, the block for PGE<sub>2</sub>-dependent steroidogenesis in eutopic endometrial stromal cells is mediated by inhibitory mechanisms downstream of cAMP.

***Estradiol (E2) biosynthesis in endometriosis.*** The biologically active estrogen estradiol (E2) is produced from cholesterol through six serial enzymatic conversions in two ovarian cell types that cooperate in a paracrine fashion. The rate-limiting two steps include the entry of cholesterol into the mitochondrion facilitated by the steroid acute response (StAR) protein and the conversion of androstenedione to estrone (E1) by P450arom. Others and we recently showed that StAR, P450arom and all other steroidogenic enzymes are expressed *in vivo* in endometriosis enabling this tissue to synthesize E2 from cholesterol *de novo*<sup>10,24</sup>

(and our unpublished data). Additionally, PGE<sub>2</sub> induces expression of the steroidogenic genes StAR, side chain cleavage (P450scc), 3b-hydroxysteroid dehydrogenase (HSD) type I and II, 17-hydroxylase/17-20-lyase (P450c17) and P450arom in endometriotic stromal cells. The most striking PGE<sub>2</sub>-dependent inductions are observed for StAR (2.3-fold) and P450arom (4.3-fold) genes. In contrast, normal endometrium does not biosynthesize E2. Both endometriosis and normal endometrium contain the enzyme 17b-HSD-1 that catalyzes the final step that is the conversion of E1 to E2. What separates normal endometrium from endometriosis, however, is the *in vivo* lack of StAR and P450arom. Physiologically significant levels of these steroidogenic genes are not detected in normal endometrial tissue or PGE<sub>2</sub>-stimulated endometrial stromal cells.

Until recently, we focused our investigation on P450arom expression in endometriosis and hypothesized that the substrate androstenedione for this enzyme originated primarily from the adrenal and/or ovary and arrive at the target tissue (*i.e.*, endometriosis) via circulation. Thus, the recent demonstration of StAR and a complete set of steroidogenic enzymes including P450arom within the endometriotic stromal cell implies that estrogen is synthesized *de novo* from cholesterol and that endometriotic P450arom is not dependent for substrate only on the adrenal or ovary. These new findings revised our view of the pathogenesis of estrogen biosynthesis in endometriosis and opened new avenues of research.

***Molecular mechanisms responsible for E2 biosynthesis in endometriosis.*** We uncovered a number of molecular abnormalities that are responsible for PGE<sub>2</sub>-cAMP-dependent P450arom expression in endometriosis. Now that we and others also demonstrated aberrant and PGE<sub>2</sub>-cAMP-dependent expression of StAR and other steroidogenic genes, we hypothesize that these abnormalities are regulated by common mechanisms that co-activate multiple steroidogenic genes. One general mechanism is the aberrant expression of key transcriptional enhancers (*e.g.*, SF-1) in biopsied endometriotic tissues (*in vivo*) and cultured endometriotic stromal cells (*in vitro*). A derivative (or flip-side) of this first mechanism serves as a second mechanism to suppress steroidogenic gene expression in normal eutopic endometrial stromal cells exposed to PGE<sub>2</sub> or cAMP analogs. This involves the redundant presence and steroidogenic promoter-binding activity of multiple transcriptional inhibitors (COUP-TF) and co-repressors of SF-1 (*e.g.*, WT1) serving as a fail-safe mechanism. There are also variations of these two general mechanisms. For example, C/EBPb effectively inhibits P450arom promoter and mod-

erately stimulates StAR promoter <sup>7</sup>. The primary function of readily detectable quantities of C/EBP $\beta$  in eutopic endometrium is likely to suppress P450arom expression, since C/EBP $\beta$  in endometriotic stromal cells is markedly downregulated *in vivo* <sup>7</sup>. Another variation pertains to the differential binding activity of COUP-TF. COUP-TF is present *in vivo* in comparable quantities in both endometriosis and eutopic endometrium. In the absence of SF-1, COUP-TF binds to a nuclear receptor half site (NRHS) in the P450arom promoter and inhibits its activity in normal endometrial stromal cells <sup>6</sup>. In endometriosis, however, aberrantly expressed SF-1 effectively displaces COUP-TF from this NRHS and stimulates P450arom promoter activity <sup>6</sup>. Additionally, both WT1 and DAX-1 act as corepressors of SF-1 (for both StAR and P450arom promoters) in both eutopic endometrial and endometriotic cells <sup>8</sup>. *In vivo* analysis, however, shows that only WT1 is differentially expressed and markedly downregulated in endometriotic stromal cells <sup>8</sup>. Thus, WT1 seems to be a physiologically significant corepressor for the inhibition of steroidogenesis in eutopic endometrium.

**Summary.** Endometriosis is a significant public health problem in the US and its incidence is on the rise. The diseased tissue is estrogen-dependent, and all current treatments are based on the denial of estrogen to this tissue. Our recent laboratory findings significantly altered the concept of estrogen production in women with endometriosis and focused the attention to the diseased tissue as a significant source of local estrogen production. Timely availability and successful use of efficacious third generation aromatase inhibitors supported this concept. We previously conceptualized that P450arom expression in endometriosis is the only critical abnormality responsible for estrogen production. We recently came to realize that a number of steroidogenic promoters are concomitantly activated to give rise to *de novo* estrogen biosynthesis from cholesterol. Thus, our modified direction is to investigate common mechanisms responsible for the activation of multiple steroidogenic genes in endometriosis. To this end, we will study the common mechanisms that activate or inhibit StAR and P450arom, since we demonstrated that these two particular genes among the steroidogenic genes are differentially expressed to a maximum degree (*in vivo*), induced by PGE<sub>2</sub> (*in vitro*) and catalyze the key steroidogenic steps for estrogen production. In particular, we will investigate mechanisms, whereby aberrant expression of transcriptional enhancers and downregulation of transcriptional inhibitors give rise co-activation of multiple steroidogenic promoters in endometriosis, and the redundant presence of multiple

transcriptional inhibitors silence these promoters in normal eutopic endometrium.

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## Invited Editorial Article (continued)

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## More Endometriosis News

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A paper by YG Liu, RS Schenken won the second place poster award at the 2004 ASRM meeting in Philadelphia. "Tumor Necrosis Factor-alpha Induces Peritoneal Mesothelial, Endometrial Epithelial and Endometrial Stromal Cell Expression of Genes Involved in Invasion and Metastasis". The authors conclude that TNF alpha effects gene transcription in PMCs, EM42, EECs and ESCs in a

dose-dependent fashion. They hypothesize that TNF alpha contributes to the pathogenesis of new and established endometriotic lesions by inducing expression of genes involved in cell adhesion and invasion. An understanding of the effect of TNF alpha on specific genes may lead to novel approaches to the treatment of endometriosis.

# Message from Australia

## *Ignorance of electrosurgery/diathermy amongst gynaecologists*

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Before you read more journal articles about cytokines, promoters, co-factors and other subtle possible pathogenetic agents causing endometriosis, a recent publication from Australia in the British Journal of Obstetrics and Gynaecology (December 2004, Vol. 111: 1413-1418) might make you stop and ponder your own operating theatre and hospital electrosurgery/diathermy practice, next time you operate on endometriosis

As you know electrosurgery units have become a necessity in operating theatres. Stray current resulting from insulation failure, direct coupling, capacitive coupling and other malfunction of electrosurgical units may compromise patient safety. At the 1993 meeting of the American College of Surgeons, 54% of the 506 surgeons surveyed reported they knew of a colleague who had encountered electrosurgery complications. These types of incidents are prevalent in laparoendoscopic procedures, where a surgeon's field of view restricts the visibility of an electrosurgical instrument to only its tip. Injuries to non-targeted tissues are therefore unnoticed as they occur along the shaft of the instrument and are unrecognised. They are often diagnosed post-operatively if the patient presents with peritonitis, haemorrhage, organ or vessel perforation or infection.

Electrosurgical incidents arising from stray currents can be minimised with the use of appropriate technology such as return electrode monitoring systems, active electrode monitoring units and tissue response generators. These measures will not, however, prevent all electrosurgical burns. Additional contributors to electrosurgical incidents are poor technique and inadequate knowledge of the principles of electrosurgery. Surgeons must therefore be provided with adequate training in electrosurgery.

Surgeons must be aware of the type and age of the electrosurgical unit used, its safety mechanisms, the operative environment and the type of tissue cauterised as they are legally responsible. Oxygen-enriched atmospheres in otolaryngology, for instance, require minimal power settings and sparing use of supplemental oxygen in an effort to prevent flash fires. In open surgery, non-hazardous operating environments are essential. A patient treated for appendicitis was set on fire caused by the heat from the electrosurgical instrument which ignited a skin cleaning solution. The flames were doused by a couple of buckets of water. This incident occurred not long after a similar case where the electrosurgical instrument ignited a sterilising solution during a caesarean section.

We therefore designed a prospective study testing electrosurgical skill and theoretical diathermy knowledge.

We tested 20 specialists in Obstetrics and Gynaecology. Twelve candidates were specialists with 9-28 years of practice in operative laparoscopy. Eight were Trainee Fellows/Registrars/Senior Registrars with up to six years of practice in operative laparoscopy. Seven Consultants and one Fellow/Registrar/Senior Registrar were from rural centres.

Each of the 20 candidates were asked to complete a practical diathermy station and written tests of electrosurgical knowledge. The candidates were marked with checklist criteria resulting in a pass/fail score. We re-tested 11 of the candidates one year later with the same stations.

We found that no candidates successfully completed the written electrosurgery station in the initial test. Although candidates were aware of the basic differences between monopolar and bipolar electrosurgery, they demonstrated very poor knowledge of electrosurgery safety and hazard prevention. Even more frighteningly, no improvement occurred in one year as shown by the retest of 11 of the candidates. Furthermore, performance did not correlate with the number of years experience as a specialist gynaecologist.

We found that 95% of candidates reported using monopolar diathermy. However, their pass rates were 56% and 36% in the initial test and the retest respectively. There seemed considerable inconsistency between what the candidates believe they knew about monopolar diathermy and what they actually could demonstrate.

This study found ignorance of electrosurgery/diathermy amongst gynaecologists. One year later, the skills were no better.

In laparoscopic surgery, where 85% of surgeons use electrosurgical instruments, the incidence of electrosurgical complications, have been reported to have risen over the last 20 years. In some areas, this has prompted the formation of laparoscopic litigation groups. This has particular importance for endometriosis surgery. When performed by the world's best gynaecologists, these procedures are elegant and result in considerable improvements to the life of our patients.

However, this article suggests that the average diathermy performance by typical specialists is well below best gynaecological surgeons in each country and yet it is the

## Message from Australia

### *Ignorance of electrosurgery/diathermy amongst gynaecologists*

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typical gynaecologist who is most likely to operate on the typical woman with endometriosis and major symptoms. This study shows that a major problem is the lack of fundamental knowledge of electrosurgery / diathermy amongst typical gynaecologists.

This article suggests some recommendations to improve electrosurgery/diathermy knowledge and practice. Does your specialist training program include a formal course on electrosurgery? Are your surgeons credentialed every six months for their knowledge in electrosurgery/diathermy? Do all gynaecologists at your hospital practice basic and

advanced electrosurgery/diathermy tasks on surgical simulators? What does happen at your hospital regarding electrosurgery/diathermy?

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