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**Congress report: 2nd Meeting of the Egon & Ann  
Diczfalusy Foundation "Prevention in Women's Health" -  
September 30-October 1, 2008, Szeged, Hungary**

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# 2<sup>nd</sup> Meeting of the Egon & Ann Diczfalussy Foundation “Prevention in Women’s Health”\*

September 30 – October 1, 2008, Szeged, Hungary

M. Oettel

One year after its establishment, the **Diczfalussy-Foundation** organized the 2<sup>nd</sup> scientific meeting again in the old and famous Hungarian town of Szeged. The objectives of the foundation are as follows:

- Supporting scientific work conducted in the field of improving reproductive health including recognizing scientific results achieved so far.
- Launching new research programs and supporting the exchange of junior scientists.
- Promoting and supporting lectures and publications on the subject of reproductive health and organizing scientific events.
- Granting yearly the Diczfalussy Medal, to acknowledge the scientific work carried out by a basic or clinical scientist and her/his life-time scientific achievements.
- Presenting, also on a yearly basis the Diczfalussy Award to a researcher under the age of 40, working in the above-mentioned field.

This is the framework of cooperation between the Serbian, Romanian and Hungarian Gynaecological Societies, more precisely, the Departments of ObGyn at the Universities of Novi Sad (Serbia), Timisoara (Romania) and Szeged (Hungary). The aim is to disseminate the most up to date scientific information, using the yearly Symposia organized by the Egon and Ann Diczfalussy Foundation and the Diczfalussy Award and Prize Lectures for that purpose. Moreover, the Foundation would like to catalyze research work in the prevention of women’s health in this particular geographic region. For this purpose the Väsby Gård meeting was supported by the Foundation. The aim of the Väsby Gård meeting was to establish a project concerning cardiovascular disease mainly for this European region (Danube, Tisza, Maros/Mures, Köres)

with the active research support given by Italian and Swedish researchers. Last but not least, the Foundation would like to encourage young scientists from this region to actively participate in research meetings and collaborate in many ways. A good example of this lastly mentioned approach was the successful poster session of the 2<sup>nd</sup> Meeting of the Foundation. The reason for that remarkable progress is also the personal engagement of the founder **Egon Diczfalussy** and of **György Bártfai**. For the recognition of the scientific life-time work of Egon Diczfalussy and his merits see “gyne”, October 2007. The 2<sup>nd</sup> meeting „Prevention in Women’s Health“ was characterized by the presence of many internationally well known scientists from Europe, USA and Asia, often Egon’s disciples or coworkers.

The Diczfalussy-Medal of 2008 was received by **Britt-Marie Landgren** from the Karolinska Institutet, in Stockholm. The laudation of Prof. Landgren

was presented by **Salvatore Mancuso** (Rome/Italy), the recipient of the 2007-Medal. The scientific interests of the prizewinner and, as a consequence, her most significant contributions in the field of Gynecological Sciences are in several areas: the sequential steps of reproductive patho-physiology both in the male and female, the endocrinology of human reproduction, contraception and the menopause. Of special interest is the research on metabolism, pharmacokinetics and pharmacodynamics of progestational steroids and the careful evaluation of circulating levels of a number of endogenous steroids and of their metabolites throughout the human menstrual cycle. In addition, she carefully investigated the chemistry as well as physico-chemical modifications of the cervical



Britt-Marie Landgren

mucus during the fertile phase of the menstrual cycle. Britt-Marie Landgren carried out biochemical and morphometric studies of the human endometrium in different phases of the menstrual cycle. Finally, she evaluated the effects on multiple targets and the benefits of different combinations of steroids utilized in hormonal contraception and in hormonal replacement therapy during menopause. In addition, she has been Scientific Secretary of the Swedish Society of Obstetrics and Gynecology and also Member of the Executive Board and Treasurer of the International Menopause Society. During her scientific life, Britt-Marie Landgren participated in 80 clinical trials – in 30 of them as Principal Investigator – and during a period of 10 years she chaired the Swedish Expert Committee on Drug Regulation in Obstetrics and Gynecology. To this day, she works as the Editor of “Acta Obstetrica et Gynecologica Scandinavica”.

A good example of the broad scientific interest of Britt-Marie Landgren was her prize winning speech in Szeged: “The Swedish action plan from 2007 for combating men’s violence against women.” The basic message of the plan is that men’s violence against women is unacceptable. This also includes men’s violence and oppression in the name of honour as well as violence in same-sex relationships. All measures to combat men’s violence against women must be based on the needs of the victims. The responsibility for providing the necessary support and protection to those exposed to such violence lies with central and local government authorities. Closer cooperation among various actors is essential if efforts to contain this type of violence are to be forceful and effective. Research has shown that women with abuse/addiction problems are more prone to assault than other women. Effective measures also include higher standards and greater efficiency of the judicial system. The current situation in Sweden is far from its goal, which was

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set by the government, although a distinct improvement was seen between 1997 and 2006. As demonstrated in the presentation, some Swedish countries are pioneers in this field and could serve as good examples for others.

**Eszter Ducza** (Szeged/Hungary) was the recipient of the Diczfalussy-Prize for young scientists. The laudation was held by **Maria Natalia Cruz**



Eszter Ducza

(Stockholm/Sweden) the winner of the 2007-Prize. Ms. Ducza is working at the Department of Pharmacodynamics and Biopharmacy, Faculty of Pharmacy, University of Szeged as a senior lecturer. Her scientific interest is focused on reproductive pharmacology, specifically on the role that adrenergic and estrogen receptors have in premature labour and in the nidation phase, moreover, the "cross-talk" between adrenergic receptor subtypes and the estrogen receptors. The results of the elegantly designed studies could have great influence on the development of totally new concepts in the pharmacological treatment of *abortus imminens* and for the protection of a successful implantation. In her prize-winning-speech Eszter Ducza summarized her most important findings. Using implantation in the rat as a model she hypothesizes that the  $\alpha_{1A}$ -adrenergic receptor has a crucial role in embryonic implantation. In rats, in addition to day 5 of pregnancy (day of the implantation) the expression of the uterine  $\alpha_{1A}$ -adrenergic receptor mRNA is clearly elevated also in late pregnancy (days 18–22). However, in contrast to this, in humans the expression of  $\alpha_{1B}$  AR is significantly higher. The findings suggest that the development of a uterine-selective  $\alpha_{1B}$  AR-inhibitor may lead to a new drug for tocolysis. Finally, concerning tocolytic activity Eszter Ducza found a synergism of  $17\alpha$ -hydroxy-progesterone and the well known  $\beta$ -adrenergic mimetics.

In a narrower sense, the scientific program of the meeting started with the presentation of **Kerstin Hagenfeldt** (Stockholm/Sweden) concerning the morbidity among elderly women – facts and fancies. Doubtless, basic diseases

are the same in elderly men and women. But, rates, trends and specific types differ between men and women. One of the erroneous assumptions is that cardiovascular death rates are higher among men than women – thus CVD would mainly be a male problem.

The fact is that CVD is the main killer in both sexes. Actually CVD kills a greater number of women than men as old women outnumber old men. Another example: overall rates of psychiatric illness are almost identical for women and men but striking gender differences are found in the pattern of mental illness. Depressive disorders account for 42 % of the disability among women compared to 28 % among men. Unipolar depression, predicted to be the second leading cause of disability burden by 2020, will be twice as common in women. In summary, depression, anxiety, psychological distress, sexual violence, domestic violence and high rates of substance abuse affect women to a greater extent than men across different countries and societies. Therefore, promotion is necessary for the formulation and implementation of health policies that address women's specific concerns from childhood to old age.

**David F. Archer** (Norfolk/USA) reported about new hormonal methods for the prevention of unwanted pregnancies. Comparing Loestrin-24® with Loestrin 1/20® it is obvious that the 24-days regimen shows significantly fewer intracyclic bleedings and spottings. The duration of active +steroid use was recently extended: to 24, 84 and also 365 days allowing individualization of oral contraception. David Archer concluded that women without medical problems can use all hormonal methods. Intrauterine devices do not cause infertility and menstrual dysfunction is a common reason for discontinuation of hormonal methods. Finally, low motivational methods perform best for younger women.

**Elisabeth Johannisson** (Geneva/Switzerland) using as an example the progestin chlormadinone acetate (CMA) gave a review on the history of oral contraception focusing on the hurdles by translating results of animal experiments to what has happened in women. The metabolism of CMA in beagle dogs, rhesus monkeys and rabbits is significantly dif-

ferent from that in man, leading e.g. to errors in the interpretation of mammary tumors in beagle bitches induced by CMA. Today highly sophisticated analytical methods and a special steroid toxicology based on the cellular and molecular-biological level incl. electron-microscopical pictures can limit misinterpretations. An interesting challenge is researching on the influence of steroids on stem cells.

The long way for the development of effective methods for preventing HIV/AIDS was illustrated by **Henry Gabelnick** (Arlington/USA). The attempts to date are behavioral change, male condoms, female condoms, diaphragms, local microbicides, and male circumcision. Today, the best results are coming from the reliable use of male condoms. Male circumcision reduces the infection risk significantly (prevalence in some African countries would decline from 23 % to 14 %). Unfortunately, the spermicide and microbicide nonoxonyl-9 seems to enhance the infection risk. An original approach is an intravaginal dual principle for preventing HIV/AIDS and for contraception. This method was explained more in detail by **Régine Sitruk-Ware** (New York/USA). The progestin Levonorgestrel known to be absorbed from the vagina and used in a ovulation inhibiting dosage is combined with a microbicide. A gel serves as a vehicle. This dual principle should be used prior to intercourse. Unfortunately, the Phase III trial did not demonstrate efficacy of the microbicide (Carraguard®) for HIV prevention. However, there are continued efforts in progress by the Population Council supported by several governments and NGOs to identify a suitable locally acting virostatic agent enabling the development of a dual principle for contraception and for the prevention of STI.

**Kristina Gemzell-Danielsson** (Stockholm/Sweden) demonstrated that at present HPV-vaccination can not replace a suitable screening program for prevention of cervical cancer. The Nordic countries have played a leading role towards successful cancer prevention and control. Since the late 1960ies screening programs are established in all Swedish counties. This resulted in a 60 % reduction in the number of cervical cancer cases. All Swedish women between 23



and 50 years of age are invited every 3<sup>rd</sup> year to a midwife for a PAP-smear and women between 50 and 60 years are invited for screening every 5<sup>th</sup> year. Almost one million of PAP-smears are done annually in Sweden and 2 to 4 % show any form of atypic cells. Only a minor fraction of these approx. 30,000 women/year develop into CIN II/III and cancer. HPV-DNA test is now proposed in all ASCUS/LSIL cases (atypical squamous cells of undetermined significance) and colposcopy is now referable for only HPV positive cases. In a Swedish study conventional cytology was compared to liquid based cytology samples. PAP-smear had a sensitivity to detect CIN III of 47 %, compared to 66 % for liquid based cytology. **József Kovács** (GlaxoSmithKline) compared the two registered prophylactic vaccines: HPV 16/18 and HPV 6/11/16/18. Vaccination alongside screening will reduce the risk of cervical cancer further than screening alone, and will also reduce the number of abnormal screening results. It is important that screening continues to co-exist with vaccination for many years. There are many different types of HPV that are oncogenic and vaccination targets only few of these oncogenic types. In countries with screening programs the vaccines are expected to have a positive impact on both cervical cancer and its precursors. In countries without organized screening programs the vaccines are expected to have a great impact on the number of cervical cancer cases prevented.

Coming to the topic of breast cancer, **Marius Raica** (Timisoara/Romania) compared the conventional morphological methods with the modern molecular classification for the diagnosis of mammary cancer. Why does the oral contraceptive pill not protect against breast cancer although ovarian function is suppressed? On the other hand, pregnancy protects against breast cancer but estrogen levels are very high during pregnancy and estrogens are considered to increase the risk of breast cancer. **Herjan Coelingh Bennink** (Zeist/The Netherlands) addressed this question explaining that during pregnancy the threefold hydroxylated estriol is excessively increased. Additionally, the fourfold hydroxylated fetal estrogen estetrol is detected during pregnancy (first description of estetrol by Egon Diczfalussy).

Both estrogens are so-called “impeded” estrogens showing anti-proliferative activities. The expected advantages of exogenously administered estetrol in comparison to ethinyl estradiol are: no effect on body weight, better “typical use” contraceptive efficacy due to slow elimination, less subjective side effects, less or no increased VTE-risk, less gall bladder disease and – last but not least – estetrol is an anti-estrogen in the breast. Therefore, the use of estetrol for a new generation of hormonal contraceptives and for hormone replacement could be very promising.

Multiple pregnancy is the single most important cause of adverse neonatal outcomes of pregnancies resulting from assisted reproduction. After Robert G. Edwards’ (1997) work the elevated risk of twins and high order multiple pregnancies should no longer be tolerated. **Piergiorgio Crosignani** (Milan/Italy) reviewed the state of the art in this field. 50 I.U. rFSH is a safe and effective treatment for IUI cycles leading to 57–66 % mono-ovulations of the cycles. The result is few twins and no triplets. The pregnancy rates are unchanged despite the fact that the appearance of the eggs suggests better quality of the oocytes. In IVF, single embryo transfer should be used in the majority of cycles (plus embryo freezing). At present, there seems to be no way to stop the increase in risk of natural twinning related to maternal aging. Based on her own experience and comparing with the relevant literature data **Kay Elder** (Cambridge/UK) reported about the medical and socio-economic burden of multifetal pregnancies for the family and also for society. Finally, the speaker mentioned that the UK issued four stamps to celebrate the most noteworthy British advances in clinical medicine over the last 1000 years. Those honored were: Edward Jenner for vaccination against smallpox (1796), Florence Nightingale for founding the field of nursing (1890), Alexander Fleming for penicillin (1928), and Robert Edwards for developing IVF (1978).

**Takeshi Aso** (Tokyo/Japan) discussed the prevention of and new therapeutic approaches to osteoporosis in elderly women. The main point of his presentation was the soy isoflavone daidzein and his metabolite equol formed by intestinal

bacteria. Equol is a selective estrogen receptor modulator (SERM) showing estrogenic as well as anti-estrogenic effects. It is also a selective androgen receptor modulator (SARM) and possesses antioxidant activities. 20.4 % of Japanese women aged  $20.1 \pm 0.5$  years, 51.6 % of women aged  $49.7 \pm 6.7$  years and 29.3 % of Japanese men aged  $34.5 \pm 6.8$  years are equol producers ( $> 5 \mu\text{mol}/24 \text{ hr}$  urine). The amount of excreted equol is significantly reduced in women with severe menopausal symptoms. Preventive and therapeutic effects under treatment with soy isoflavones are only seen in equol producers as demonstrated in a controlled clinical study.

The direct etiopathological role of age-related increased gonadotropin secretion especially for the CNS (e.g. Alzheimer’s disease) is at present in the focus of studies by several groups of investigators worldwide. As a model in mice, **Gyula Telegdy** (Szeged/Hungary) used the decapeptide cetrorelix, an LHRH antagonist which inhibits gonadotropin and sex-steroid secretion. Little is known about the effects of cetrorelix on brain function. The influence of the LHRH antagonist was studied following its administration into the lateral brain ventricle in mice. In passive avoidance tests, beta-amyloid 25–35 administered immediately after the learning trial impaired the consolidation of passive avoidance learning. Cetrorelix given icv fully blocked the impairment of the consolidation of passive avoidance learning when given 30 min following beta-amyloid 25–35 administration. Blocking the LH action in this model, cetrorelix elicited anxiolytic activities in the plus-maze, depending on the dose used. In the forced swimming and tail suspension tests, cetrorelix demonstrated antidepressive action.

**Michael Oettel** (Jena/Germany) addressed the following question: Is hormone replacement (HRT) in a blind alley or at the crossroads? Today we can see many new approaches like isoflavones, specific and selective CNS-acting drugs for the treatment of hot flushes, the utilization of pharmacogenomics for the individualization of the classical therapy, new dissociated estrogens and ER $\beta$ -agonists, progesterone receptor modulators. Also the investigations about the relationships between stem cells and the en-

doctrine systems allows new insights. In summary, HRT is at a very important crossroad today, representing a great challenge for researchers as well as for gynecologists. Paradoxically, hormone *displacement* (the limitation of the age-related hypercortisolism) instead of hormone *replacement* does not receive sufficient attention.

Four papers about cardiovascular diseases in women were presented by investigators from the University of Szeged and the co-operating international partner groups.

**Dan Gaita** (Timisoara/Romania) presented selected results from the Euro-Aspire III-Study (**E**uropean **A**ction on **S**econdary and **P**rimary **P**revention of **C**oronary **H**eart **D**isease in **O**rders to **R**educe **E**vents). The study is focused on lifestyle and risk factor management and use of drug therapies in high risk patients from 12 European countries. Medical reports were evaluated. 3230 women and 2457 men (18.4 % < 50 yrs) were studied. The following diagnoses were found (men vs women): smoker 22.6 vs 12.7 %, obesity 39.2 vs 46.7 %, diagnosed and non-diagnosed diabetes mellitus 43.1 vs 35.3 %, high blood pressure 65.2 vs 63.2 %. The obvious conclusions are by now widely known: No smoking, control of systolic BP, total and LDL-cholesterol, 3 km walking/jogging or 30 min moderate exercise/day and 5 portions/day of fruits and vegetables counteract obesity and diabetes.

**Tamás Forster** and **Márta Katona** (Szeged/Hungary) gave detailed reports about the prevention of cardiovascular complications in elderly women and in late pregnancy and early infancy. **Iván Valastyán** (Debrecen/Hungary) presented Cardiotom™ – a tomographic mobile gamma camera system for the diagnosis of acute myocardial infarction (width 62 cm, length 135 cm, height 140 cm, weight 320 kg). This system is easy to position close to the heart of the patient at bedside examination. This allows much faster and cheaper diagnosis of myocardial infarction.

The title of the presentation of **Günter Stock**, President Berlin-Brandenburg Academy of Sciences (Berlin/Germany) was a somewhat provocative: “*Primum non nocere*: Is the remedy sometimes

worse than the disease?” Taking oral contraceptives and hormone replacement as examples the manifold aspects of the benefit/risk ratios in pharmacotherapy were demonstrated. Today the physician is confronted with exponentially increasing knowledge also in the field of medication. Therefore the “human factor” will be more and more important for preventing unwanted drug effects. As an example for the very different possibilities to interpret and to communicate equal scientific results Günter Stock presented the outcome of the Women’s Health Initiative Study (WHI):

- Increase of breast cancer risk by 26 %.
- Increased breast cancer risk of 1.26 (relative risk).
- Increase of breast cancer rate from 30 to 38 cases per 10,000 women-years (absolute risk).
- In 8 of 10,000 women under HRT (~0.08 %) there is a risk of breast cancer diagnosis.
- In 9992 of 10,000 women under HRT (~ 99.92 %), there is no risk of breast cancer associated with HRT.

**Miguel Oliveira da Silva** (Lisbon/Portugal) succeeded the difficult journey on the crest to discuss the ethics of medicine and of society in the fields of contraception, IVF, and stem cell research. The chosen topics and open questions, like political correctness, political establishment, NGO’s, churches (e.g. *Humanae Vitae*), do ethical human values change with time(?), sexual pleasure apart from procreation, technology and research as part of the human nature, the role of self-nominated bioethical opinion generators, mixed interests and conflicts of scientists, politicians, industry and church. However, with all its abuses, frauds and malpractices, science is self-correcting and all misconceptions are subject to revision and correction, sooner or later. No other human activity on earth has these characteristics, even when we do need to replace an old paradigm by a new one. Miguel Oliveira da Silva concluded as follows: Convictions of faith have no place in questions of science and medicine. Nature (human nature included) has to be investigated without philosophical or theological reservations. Never give up hope, science and empathy.

From the point of view of the commentator **Sir Brian Heap’s** (Cambridge/UK)

excellent contribution about ethical demands and economic decisions was one of the highlights of the Meeting. Prevention in women’s health presents a classical example of the importance of international cooperation to achieve ethical demands in the face of economic decisions. To cooperate effectively we need to think more deeply about how to interpolate value systems based on humanitarian beliefs often informed by religious values because they have a significant role in producing results by defining fruitful scenarios for cooperation. Based on Jared Diamond (2005) Brian Heap reviewed the historical reasons why some societies succeeded but others failed and attributed the collapse of some former societies to one or more, and in some instances, all of the following five elements – climate change, galloping long term reproductive growth rates, human environmental impacts and resource depletion, unstable trading relationships, and socio-religious factors. All these elements are very closely joined. It makes no sense, to look only at one isolated factor, e.g. climate change. As Thoroya Ahmed Obaid, the Executive Director of UNFPA stated: “... five years after the Millennium Declaration (meaning the United Nations Millennium Development Goals 2000) the world has reaffirmed the need to keep gender equality, HIV/AIDS and reproductive health at the top of its agenda”. No doubt – in this frame – the Diczfalussy- Foundation serves this goal.

After these presentations, the time was for a the round table discussion “The medicine today and the ethics of tomorrow” directed by **Jürgen Mittelstrass** (Konstanz/Germany). The participants were **Giuseppe Benagiano** (Geneva/Switzerland), **Sir Brian Heap** (Cambridge/UK), **Miguel Oliveira da Silva** (Lisbon/Portugal), **Günter Stock** (Berlin/Germany) and – as a video presentation – **Robert Edwards** (Cambridge/UK). Unfortunately, there is no place here to refer to all the interesting and controversial aspects of this debate. Therefore, only some key points of the contribution of the philosopher Jürgen Mittelstrass will be cited. The great topics of tomorrow’s medicine will be prevention, optimal therapy, and regeneration. Together with the growing efficiency of high-tech medicine, they lead to ethical problems which are not just of

a medical but of a general nature – as ethical problems in science. There are, first of all, ethical problems that arise when scientific results are applied in the non-scientific world. One example is nuclear research and the bomb. Secondly, there are ethical problems arising within research itself, when investigating the nature of things, particularly when this investigation includes experimental techniques. Stem cell research and reproductive medicine are of this kind. Thirdly, as in other areas of human practice, falsehood and deceit also have their place in science (see the cloning experiments in South Korea). These principles and these problems are often interrelated, as there is no such thing as an ethics of science which is a special ethics for scientists. Ethics is always an ethics of the *citizen*, it cannot be divided along social lines, that is to say into a

scientific ethics which is the ethics of the respective scientist, and into a non-scientific ethics which is the standard ethics of society as a whole. And the same holds for morals in the common sense. There are, strictly speaking, no closed ethical or moral worlds, in each of which a single ethics or set of morals sway.

The traditional Dinner Speech was presented by **Thomas Rabe** (Heidelberg/Germany). His humorous but in a thoughtful mood special lecture “The secret of anti-aging” was concentrated on better aging and the role of living in happy and harmonic pair relationships, healthy life-style by avoiding non-validated so-called anti-aging medicine, and laughing and dreaming is wholesome.

Look into the past and work for the future! This is the summary of the 2<sup>nd</sup>

Meeting of the Egon & Ann Diczfalussy-Foundation which was dominated by the friends, students and coworkers of Egon Diczfalussy, most of this people worldwide known with high reputation and gray-haired. As the president of the Foundation Attila Pál (Szeged/Hungary) announced, the next meeting will be mainly the meeting of the scientific grandchildren underlining once more Egon Diczfalussy’s question: What is past and what is future? But: *De nihilo nihil!* Many thanks to Egon and his Foundation!

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