all the various reactions can be studied simultaneously. The advent of cDNA microarray gene expression and proteomics where the global expression of genes and their proteins can be measured at any time (initial and late events) are making it easier to understand pathology of diseases and their progression. Recently we have employed these techniques to determine the global mechanisms involved in the death of nigro-striatal dopamine neuron of MPTP mice model of PD and compared them to substantia nigra pars compacta of idiopathic PD. Employing a Clontec Atlas microarray with 1200 genes MPTP induced alterations in expression of 51 genes at the time of dopamine neuron death associated with oxidative stress, iron metabolism, inflammatory processes, glutamate, nitric oxide, adenosine, intermediatory metabolism glucose metabolism, cell cycle, apoptosis, neurotrophic derived factors, significant transcription factors, prostoglandins and protein processing. Neuroprotection induced by pretreatment with the anti Parkinson drugs R-apomorphine and rasagiline and the green tea polyphenol antioxidant, EGCG, reversed the expression of most of these gene to those observed in controls. Our microarray studies with initial effects of MPTP (first 24 hr), prior to its neuron killing effect, have shown a time dependent expression of other genes that eventually interact with other death gene cascades to cause the death of the neurons. Preliminary analysis gene expression in substantia nigra pars compact of PD subjects as compared to matched control (n = 6 in each), employing 8000 gene Afimetric chip, have not only confirmed what we have established in the MPTP model, but a number of other newly discovered important clusters of cascade events previously not described. Our studies have clearly established that dopaminergic neurodegeneration involves a "dominio cascade" of vicious events, which could be induced initially at any point on the cascade. They also point out why single drug neuroprotective therapy was not and may not be possible. Thus, serious consideration should be given to neuroprotective drug "cocktail". These results will be discussed in term of drug induced neuroprotection and discovery.

3

Role of sympathetic nervous system in neuroimmune diseases

E. S. Vizi[1] and **A. Lajtha**[2]

[1] Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary
[2] Nathan S. Kline Institute, New York, NY, U.S.A.

It is generally accepted that the brain communicates with the immune system via two pathways: (i) the neuroendocrine humoral axis and (ii) direct innervation through autonomic neuronal efferents. Although the concepts of cellular and humoral immunity (Metchnikoff, Ehrlich), and of chemical neurotransmission (Elliott, Loewi) emerged at the beginning of the previous century, neurosciences and immunology developed for many years without serious consideration of the possibility of interactions between the brain and the immune system. Until now the emphasis has been placed on the humoral axis, in light of the role of glucocorticoids and other hormones, in the immune system. Evidence has recently been obtained that the branches of the autonomic nervous system, namely, the sympathetic and parasympathetic, regulate blood flow and cytokine production. Not only the primary (thymus, bone marrow) and secondary (spleen, tonsils, and lymph nodes) lymphoid organs, but also many other tissues are involved in immune responses and are heavily influenced by noradrenaline (NA) derived from varicose axon terminals of the sympathetic nervous system. Besides NA released from nonsynaptic varicosities of noradrenergic terminals, circulating catecholamines (adrenaline, dopamine, NA) are also able to influence immune responses, the production of pro- and anti-inflammatory cytokines by different immune cells [Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES (2000) The sympathetic nerve – an integrative interface between two supersystems: the brain and the immune system. Pharmacol Rev 52: 595–638]. In our laboratory convincing evidence has been obtained that NA released non-synaptically from sympathetic axon terminals is able to inhibit production of proinflammatory (TNF-a, IFN-g, IL-12, IL-1) and increase antiinflammatory cytokines (IL-10) in response to LPS, indicating a fine-tuning control of the production of TNF-a and other cytokines by sympathetic innervation under stressful conditions. This effects are mediated via b2-adrenoceptors expressed on immune cells and coupled to cAMP levels. The effect of sympathetic tone on autoimmune disorders, traumatic brain injury and septic shock will be discussed.

4

Ethics in clinical neuropharmacology

F. Gerstenbrand[1], **H. Baumgartner**[2], and **W. Struhal**[1]

[1] Department of Neurology, University of Vienna, Vienna, and
[2] Department of Neurology, University of Innsbruck, Innsbruck, Austria

In the third millennium every man who is part of the industrial society demands that all the possibilities of modern medicine have to be available to him. He aspects to be relieved of his physical and mental illness as fast as possible and at the same time wants to be certain, that all the advances of research will be used to grant him a longer life. Modern human claims his right to be treated everywhere and at any time at an advanced age, with incurable disease as well as for mental decline. Because on his presumed right to have access to all resources, which are meant for him as a member in a social welfare system. The feeling of freedom of the individual human is equalised with the presumed right for personal well being, separated from the well being of the community.

Different civilisations and various cultures developed different religious systems and special ethical and moral rules. Based on the Greco-Roman Culture a Christian dominated life form developed in Europe, a life form that generally cannot be implanted in other cultures with different religious and historical background. This demand has to be included all ethical discussions, in the connection with treatment program as well, as in research projects.

Clinical trials have become important instruments to advance medical knowledge and to fulfil regulatory requirements. The controlled trial compares the effects of interventions in groups of patients to obtain unbiased, reliable and generalized evidence. The individual trial subject carries the risk hoping for individual or collective medical benefit. Freely given informed consent is the ethical precondition for participation in clinical trials. The ethical basis of every comparative interventional trial is balancing the promising but unproven benefit of something new with its associated risks against the established benefits and risks of something known. Only if uncertainty or equipoise regarding the comparative advantages of either intervention exists can a patient be asked to enter into a trial. This ethical principle translates quite differently into research practice. Europeans favour individual equipoise, the US favours clinical equipoise or collective professional uncertainty. The primary duty of the physician, always to act in the best interest of the patient, is interpreted differently in Europe than the US reflecting prevailing cultural and social mores.

The Declaration of Helsinki has offered ethical guidance to the medical community. Everyone involved in clinical trials has to contribute to high ethical standards.

Every clinical trial has to follow the rules of Good Clinical Practice (GCP) with detailed demands GCP-EU transferred.

The current economic divide of our continent is a challenge for the development of common ethical standards for clinical trials in Europe. The current economic divide on the other side is a demand to use carefully the elected medicaments for exact diagnosed diseases under the obligation to include the economic background.

CLOSING CEREMONY

Chairmen: L. BATTISTIN (Padova, Italy)
P. RIEDERER (Würzburg)

16.00 **Closing Lecture** F. GERSTENBRAND (Wien, Austria)

F. GERSTENBRAND (Wien, Austria)
Ethics in clinical neuropharmacology

17.00 **End of the Congress**

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Contents Vol. 111 No. 5 May 2004

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Abstracted/Indexed in:
Current Contents, SCI, ASCA, and ISI/BIOMED, Biosis, Elsevier BIOBASE/Current Awareness in Biological Sciences, Reference Update, Index Medicus/MEDLINE, EMBASE/Excerpta Medica

Published May 3, 2004

Printed on acid-free and chlorine-free bleached paper

Ethics in Clinical Studies

F. Gerstenbrand[1], W.Struhal[1], H. Baumgartner[2]
[1]Ludwig Boltzmann Institute for Restorative Neurology and Neuromodulation, Vienna, Austria,

Socrates and his pupil Plato are the founder of Western ethical thinking. Aristotle developed ethics into science, Saint Augustine and Thomas Aquinas incorporated Christian ethics, Kant gave an ethical order with his categorical imperative in the demand that every human person has always to act in such a way that the maxim of his action can be regarded as an universal law of humanity. In the so called Western ethical principals the ethical rules of Buddhism and Confucianism are not included, demanding that the well being of the community as priority to the well feeling of the individual. The question to diminutive life form based on Greeco-Roman culture and its ethical rules cannot be transferred to other civilisations and to different ethnic groups. It needs a long way to find common ethical rules for the mankind in all the different attitudes of human being.

Bound by the Hippocratic laws ethics in medicine have clear basic rules. The physician is obliged to heal and to treat the disease of his patient. He has to interrupt the treatment of patient that suffer form incurable illness and those who suffer from advanced age or mental disabilities. To prolong life over hours and days with special therapeutic actions is neither morally nor ethically justicable. According to the oath the physician has the obligation to heal but although to reduce suffering.

The end of human being is accompanied with the fear of a painful form to die, to get a soft death. This opens the way to ask for a soft dying, but Eu Thanatos, the soft dying has got a certain ambiguity in the concept of Euthanasia.

In the third millennium every man who is part of Western industrial society demands that all possibilities of modern medicine have to be available to him. He expects to be relieved of his physical and mental illness as fast as possible and at the same time wants to be certain that all advances of research are being used to grant him a longer life. The modern human claims his right to be treated everywhere and at any time, at an advanced age and with incurable diseases as well as for mental decline. Modern human holds the progress in diagnoses and in therapy, he calls upon his resumed right to have access to all resources as a member in a social welfare system.

Clinical trials have become important instruments to advance medical knowledge and to fulfil regulatory requirements. The Declaration of Helsinki of 1964 with its amendments was created to regulate medical research involving human subjects. The rules of Good Clinical Practice (GCP) in its development state of EU – GCP and at least in the ICH –GCP (International Conference of Harmonisation) are the basis for the use of the Helsinki Declaration in practical research trials.

The randomised controlled trial – the current golden standard- compares the effects of interventions in group of patients to obtain unbiased, reliable and generalizable evidence. The individual trial subject carries the risk hoping for individual or collective medical benefit. The freely given informed consent is the ethical precondition for participation in clinical trial.

A complex act of prediction is the ethical basis of every comparative interventional trial, balancing the promising but unproven benefit of something new in a therapy with its associated risks against the established benefits and the risks of something

known. Only if uncertainty of equipoise regarding the comparative advantages of either intervention exists can a patient be asked to enter into a clinical trial on the basis of informed consent. However, due to cultural differences this ethical principle translates quite differently into research practice. Europeans favour individual equipoise, the US favours clinical equipoise or collective professional uncertainty. Thus the primary duty of physician, always to act in the best interest of the patient, is interpreted differently in Europe than the US reflecting prevailing cultural and social mores.

The clinical research in Europe should be based on national law and should respect the European core values of human rights and human dignity of the Biomedicine Convention of the Council of Europe. Taking part in an industry-sponsored trial usually requires that the investigator and his staff adhere to rules and regulations like the "Good Clinical Practice" (EU-GCP) guidelines of the European Union (EU) or the recent ICH-GCP (EU, USA, Japan) guidelines. Compliance with these rules will be a stringent condition of the sponsor, even if the trial takes place in countries not formally covered by these agreements.

Everyone involved in clinical trials has to contribute to high ethical standards as follows: The trail subject has to be voluntary informed consent, compliance with the protocol, from the investigators side, scientifically valid protocol, in compliance with national laws and international guidelines, high professional standards, ethical competence and regulatory knowledge, the research ethics committee has to control an independent and competent assessment of the research protocol and its intended execution at the trial side, the state authorities are responsible for professional oversight according to the law.

Obligation of ethics in clinical trials is to create and to control guidelines for experiments including human being. Independent ethics committees (IEC) help in balancing the often delegate benefit risk assessment for the patient.

Evidence Based Medicine support unbiased scientific data. The quality of these routines depends on properly designed, executed, interpreted and published trials. But studies can suffer of built-in biased, undermining internal validity in form of selection biases, information bias confounding influences. Reviewed articles, editorials, meta-analyses, consensus statements and guidelines can be helpful for interpreting trial data, however, all vulnerable to publication biased. Under reporting of negative results, no- publication of unwanted results are of commercial interests, preference for positive results by journals etc. and unprofessional salvation practice have been recognised as factors distorting evidence. An obligatory reject of an all clinical biased has to be advocated in order to come to a publication biased. The EU is introducing a register for clinical trials conducted for registration purposes.

As a sign of the time the importance of education and training for clinical investigators has to be emphasized. It is astonishing /shocking how small the group of neurologists and psychiatrist is, who is informed of the rules to organise clinical trials.

Wednesday, May 5

TEACHING COURSE

CLINICAL TRIALS

Chairmen: **F. GERSTENBRAND (Wien, Austria)**
O. RASCOL (Toulouse, France)
C. SAMPAIO (Lisbon, Portugal)

Session 1 : General methodology		
14.00	F. GERSTENBRAND (Wien, Austria)	Ethics of clinical studies
14.15	C. SAMPAIO (Lisbon, Portugal) & O. RASCOL (Toulouse, France)	Clinical studies and their bottlenecks
14.40	J. FERREIRA (Lisbon, Portugal)	Critical appraisal of CT
15.00	Session discussion	
15.20	Coffee break	
Session 2: Practical application to neurological disorders		
15.40	M. EMRE (Istanbuk, Turkey)	Bottleneck in clinical trials in Dementia disorders (MCT, vascular, other)
16.00	O. BLIN (France)	Bottleneck in clinical trials in ALS
16.20	K. SEPPI (Innsbruck, Austria)	Bottleneck in clinical trials in atypical Parkinsonism
16.40	BAUMGARTNER (Vienna, Austria)	European clinical trials directive
17.00	Discussion	

Ethics in Clinical Studies

F. Gerstenbrand[1], W.Struhal[1], H. Baumgartner[2]
[1]Ludwig Boltzmann Institute for Restorative Neurology and Neuromodulation, Vienna, Austria,

Socrates and his pupil Plato are the founder of Western ethical thinking. Aristotle developed ethics into science, Saint Augustine and Thomas Aquinas incorporated Christian ethics, Kant gave an ethical order with his categorical imperative. Ethical rules of Buddhism and Confucianism with the demand well being of the community a priority to the well feeling of the individual are not included. Western ethical principals cannot be transferred. A long way will be necessary to find common ethical rules for the mankind.

By the Hippocratic law ethics in medicine have as basic rules that the physician is obliged to treat the disease of his patient, but he has to interrupt the treatment in incurable illness and in advanced age or in mental disabilities. According to the oath the physician has the obligation to heal and to reduce suffering.

Every man who is part of Western industrial society demands for the availability of all possibilities of modern medicine in the expectance to be relieved of his physical and mental illness as fast as possible. He wants to obtain all advances of research to grant him a longer life and to be treated everywhere and at any time, as well as in advanced age, with incurable diseases and for mental decline. The modern human calls upon his resumed right to have access to all resources.

Clinical trials have become important instruments to advance medical knowledge. The Declaration of Helsinki of 1964 with its different amendments regulates medical research including human subjects. The rules of Good Clinical Practice (GCP) in its last development state the ICH –GCP (International Conference of Harmonisation) are the basis for every clinical trial. The randomised controlled trial as the current golden standard compares the effects of interventions in a group of patients to obtain unbiased, reliable and generalizable evidence. The individual trial subject carries the risk hoping for individual or collective medical benefit. The freely given informed consent is the ethical precondition for participation in clinical trial.

The ethical basis of every comparative interventional trial acts on the balance of the promising but unproven benefit of something new in a therapy with its associated risks against the established benefits and the risks of something known. Only on the basis of informed consent a patient can be asked to enter into a clinical trial. For the trial subjects a scientifically valid protocol, in compliance with national laws and international guidelines in high professional standards, ethical competence and regulatory knowledge for the investigator has to exist under the advice of independent ethics committee (IEC).

Evidence Based Medicine supports unbiased scientific data. The quality of these routines depends on properly designed, executed, interpreted and published trials. Studies can suffer of built-in biased, undermining internal validity in form of selection biases and information bias . Reviewed articles, editorials, meta-analyses, consensus statements and guidelines can be helpful for interpreting trial data, however, all vulnerable to publication biased. Under no-publication of unwanted results (commercial interests), preference for positive results by journals etc. and unprofessional salvation practice are factors distorting evidence

TEACHING COURSE (Room B)

CLINICAL TRIALS

Chairmen: **F. GERSTENBRAND (Wien, Austria)**
O. RASCOL (Toulouse, France)
C. SAMPAIO (Lisbon, Portugal)

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15.55	O. BLIN (France)	Bottleneck in clinical trials in ALS
16.15	K. SEPPI (Innsbruck, Austria)	Bottleneck in clinical trials in atypical Parkinsonism
16.35	H. BAUMGARTNER (Vienna, Austria)	European clinical trials directives
16.50	Discussion	
17.00	End of the Session	

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Published May 3, 2004

Printed on acid-free and chlorine-free bleached paper