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The Fifth International Geneva/Springfield Symposium on Advances in Alzheimer Therapy. Geneva, Switzerland, April 15 – 18, 1998.

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The conference was organized by Ezio Giacobini and Jean-Pierre Michel (Dept. Geriatrics, Geneva Univ. Hospital, Geneva, Switzerland) and Robert Becker (formerly Dept. Psychiatry, Southern Illinois Univ, Springfield, IL), The World Health Organization (WHO), Geneva, Switzerland, co-sponsored the conference. Over 600 participants from 24 countries attended the conference. Companies with a major interest in Alzheimer disease (AD) were represented and Bayer, Novartis and Pfizer sponsored thematic symposia. Twenty five symposia with 113 papers were presented.

Earlier meetings have been held at two year intervals since 1988 and published as the series "Advances in Alzheimer's Disease Therapy." Selected papers from the most recent meeting will be available in a supplement to the International Journal of Geriatric Psychopharmacology.

A. Roses (Glaxo Wellcome, Research Triangle Park, NC) opened the conference with a plenary lecture on new paradigms of genomic screening methodologies to allow more rapid identification of susceptibility genes. In his introduction, **J. Knowles** (Hoffman-La Roche, Basel) identified this theme, repeatedly raised by other speakers, as medical treatment for the individual to replace the current statistical model. Roses used his work with the ApoE genotype to illustrate the susceptibility gene biology which he proposed could provide individualized profiles of the genome relevant to rational therapeutics. Roses foresaw drug prescription tailored to individual susceptibilities to adverse events, which would improve the response rate in medical practice.

In a session entitled "Neuronal Degeneration," **J. Wegiel** (NY State Institute for Basic Research in Developmental Disabilities, New York, NY) reported on the mechanism by which hyperphosphorylated tau aggregates neurofilaments into tangles and inhibits microtubular assembly, leading to cell death. Taxol stabilization of microtubules decreases cell death, suggesting that microtubule stabilizers may be a possible approach to AD therapy. **K. Iqbal** of the same institute further elaborated on the role of defects in protein phosphorylation/dephosphorylation that lead to the hyperphosphorylation of tau, and on the disassembly of microtubules by sequestering normal microtubule-associated protein. Citing evidence that tau can be dephosphorylated *in vitro*, Iqbal suggested that by promoting tau dephosphorylation in AD it might be possible to inhibit neurofibrillary degeneration.

A number of sessions addressed amyloid precursor protein (APP) and β-amyloid (β-A4) processing and modeling in animals. **R. Tanzi** (Harvard Univ., Cambridge,

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MA) discussed familial Alzheimer disease (FAD) mutations in the presenilins (PS) that increase levels of Aβ42 and render cells more susceptible to apoptosis and caspase-mediated endoproteolysis of the presenilins. He suggested that aberrant caspase activation is caused by overexpression of mutant PS2. PS2 serves as a common molecular phenotype of FAD-associated gene defects, and could be a possible target for AD prevention or therapy. **F. Checler** (IPMC du CNRS, Valbonne, France) proposed that PS1 is an intracellular modulator of βAPP maturation, demonstrating that the FAD-linked mutations produce a drastic exacerbation of the pathogenic A β42 fragment. He claimed proteasomal control of the catabolic rate of PS1, upstream to its interaction with βAPP, as a target for therapeutic interventions. **D. Schenk** (Lilly Research, Indianapolis, IN) reviewed the expression of these mutations in transgenic animals overproducing APP/Aβ- and AD-like neuropathology and reinforcing the need to identify targets in the cascade for therapeutic interventions. **D. Price** (Johns Hopkins, Baltimore, MD) discussed cDNA microinjection into YAC-ES cells to introduce APP and PS1wild type and mutant transgenes into mice. The importance of these model systems lies in the opportunities they offer to define the mechanisms of AD-related abnormalities and as a critical test for potential therapies, accelerating their introduction to the clinic. A large number of excellent papers expanded on these themes of susceptibility genetics, genetic mechanisms, and genetic-therapeutic interactions.

C. Cotman (UCI, Irvine) continued his tradition of reporting at these conferences on apoptosis in AD. Caspases appear to mediate neuronal sensitivity to apoptosis. β-Amyloid induced apoptosis depends on a Fas-like mechanism that allows β-amyloid to activate apoptosis independent of nuclear control, accounting for localized pruning of neuronal processes. In later stages of AD, inflammatory mechanisms and induction of complement factors may increase neuronal loss by apoptosis as anti-apoptotic mechanisms, bcl-2 induction, DNA repair enzyme induction, are outpaced.

A session on vascular dementia (VD) focused on problems of differential diagnosis and the possible involvement of cholinergic mechanisms. **G. Gold** (Univ. Hospitals of Geneva, Switzerland) reviewed clinicopathological evaluation of 113 cases to establish clinical criteria for VD. It was not possible to use criteria of VD to classify accurately mixed dementia, documenting the problems of low sensitivity that plague clinical research in this area, **T. Lee** (Southern Illinois Univ., Springfield, IL) reported that vasodilatory effects of nitric oxide colocalized with acetylcholine may possibly explain the observed weak effects of sympathetic stimulation on cerebral blood flow as compared with the stronger cholinergic vasodilatation. Nicotinic receptors on adrenergic nerves release norepinephrine, which in turn releases nitric oxide, canceling vasoconstriction effects.

In a special lecture, **C. Phelps** (NIA, Bethesda, MO) reviewed the American experience creating Alzheimer research and clinical centers in universities and **R. Nitsch** (Univ. Hamburg, Germany) discussed neurotransmitter-induced genes. Using muscarinic receptor type 1 (M_1) stimulation, Nitsch induced growth response genes that interact with promoters of target genes, including the gene for acetylcholinesterase (AChE). He concluded that M_1 receptor stimulants will induce AChE and many other target genes. His evidence supports the study of drugs with effects on G-protein-mediated receptors to identify possible induced genes. **A. Nordberg** (Karolinska Institute, Stockholm) found a 50% increase in cerebrospinal fluid AChE activity in the face of

25% inhibition in RBCs after 12 months treatment with tacrine. **H. Soreq** (Hebrew Univ., Jerusalem), in an archetypical analysis of clinical observation, generated a study of the convergence of neuropsychological outcomes from stress and inhibition of acetylcholinesterase. She found muscarinic mediation of cFos gene induction, which in turn regulates genes involved in acetylcholine metabolism. This reduces brain activity following stress but could promote long-term cognitive and neuroanatomical pathologies by the overexpression of AChE.

The first day of the conference continued at an evening session jointly sponsored with the International Drug Harmonization committee meeting with representatives of WHO to focus on problems in developing countries. **P. Whitehouse** (Case Western Reserve, Cleveland, OH) described the harmonization effort, intending to further the opportunities for dialogue of regulators, industry, and academics. **P. Leber** (FDA, Bethesda, MD) reviewed the experience developing dementia guidelines as a basis for discussion by a panel of representatives from China and WHO.

The second and third days of the conference focused on the evaluation of current and emerging therapies in AD. The majority of attention turned to the cholinesterase inhibitors (ChEI) which comprise the core of current treatment. **M. Mesulam** (Northwestern Univ., Chicago, IL) reemphasized the possible importance of butyrylcholinesterase (BuChE) in transformation of benign diffuse to malignant neuritic plaques. He cited the recent report by D. Smith that the K variant of BuChE may be a susceptibility factor in AD. The relative appropriateness and safety of AChE and BuChE inhibition were hotly debated among participants in view of commercial claims for the advantages of selective over non-selective inhibitors. No evidence emerged demonstrating a reduction of adverse events when peripheral ChE was spared, suggesting that this is not a factor that distinguishes among the various ChEI.

New and important data relevant to the clinical use of each of the ChEIs was presented. **S. Gracon** (Parke-Davis, Ann Arbor, MI) reported clinical trial evidence that a once-daily formulation of tacrine allowed the drug to be tolerated by a large percentage of patients, unlike the multiple daily dosing formulation, and achieved statistically significant differences on all three primary outcome measures. His report set a theme repeated for other ChEIs, that their effect was dose related, and that the effect of the highest dose increased throughout the duration of the trial. **R. Doody** (Baylor Univ., Houston, TX) and **S. Rogers** (Eisai, Tokyo) both presented data from the already published trials of donepezil.

R. Anand (Novartis, East Hanover, NJ) reported from one multicenter trial of rivastigmine as representative of their experience with over 2200 patients followed for up to 3 years. His was the first report at this conference to draw attention to the duration of effects from ChE inhibition and the increasing effect size with time. The acceptance of this reorientation from immediate to long-term symptomatic effect by other presenters shows that the focus of ChEI research has changed dramatically from the conference two years earlier, when only one paper addressed the issue of the longitudinal vs. immediate effects of ChEI administration. Adverse events did not interfere with clinical efficacy and were associated with induction of inhibition.

Similar relationships were reported for other inhibitors, meaning that slow induction of effects in the clinic will occur with all the available inhibitors. In an interesting study involving 6-month placebo treatment, the drug response was replicated and

the persistence of a benefit from treatment documented as the originally treated group completed one year of treatment.

Demonstrating an impressive command over his data, **P. de Jongh** (Bayer, Wuppertal) presented the results from one phase II study and three multicenter clinical trials with metrifonate, leaving the details of the most recent trial for presentation by **I. McKeith** (Newcastle General Hospital, Newcastle-upon-Tyne). There are now five clinical trials with metrifonate in which the drug effects have been maintained for the duration of the trials. No clinically significant adverse events have emerged. de Jongh claimed that all of the clinical trial data will be available in publications prior to the availability of metrifonate for prescription.

In an interesting new perspective on the possible effect of the ChEIs, **D. Kaufer** (Univ. Pittsburgh, PA) reported improvements in depression, apathy, hallucinations, and motor behavioral aberrations in a 26-week clinical trial with 408 subjects, 135 placebo- and 273 metrifonate-treated. de Jongh reported similar findings in a second multicenter trial in which neurobehavioral pathology was evaluated. The strength of the findings with each of these ChEIs sparked vigorous debate over their possible relative advantages and disadvantages and promises that new applications will be explored in time for the sixth conference, scheduled to be held in Stockholm in 2000.

Papers in dedicated sessions updated progress on antioxidants, anti-inflammatory drugs, and estrogen replacement strategies in AD. **C. Kawas** (Johns Hopkins Univ., Baltimore, MO) reported a statistically significantly reduced relative risk (0.46) for patients treated with estrogen over the 16-year follow-up of 514 women in the Baltimore Longitudinal Study of Aging. **M. Sano** (Columbia Univ., New York) discussed the already published evidence of an effect of vitamin E and selegiline on negative outcomes in AD. Unfortunately cognitive decline was not changed. **P. Aisen** (Mount Sinai Medical Center, New York) discussed three trials with anti-inflammatory drugs currently in progress: prednisone-placebo; hydroxychloroquine-placebo; and colchicine-placebo.

E. Giacobini (HUG, Geneva) discussed the potential of ChEIs and direct receptor acting compounds in AD. He observed that muscarinic and nicotinic approaches have been unable to keep pace with ChEI development even though the comparative efficacy and long-term efficacy remain open questions. The many reports on nicotinic and muscarinic agents cannot be included in this discussion because of lack of space.

The Reagan Institute of the Alzheimer Association cosponsored a session on the Design and Conduct of Clinical Trials for Prevention in AD with presentations by **L. Thal** (UCSD, San Diego, CA), **S. Gauthier** (McGill Univ., Montreal, Canada), **R. Cacabelos** (Institute for CNS Disorders, La Coruna, Spain), **M. Sano** (Columbia Univ., New York), and **P. Leber** (FDA, Bethesda, MD). Sessions on methods of assessment, behavioral treatment, biochemical topics, and other important and well-treated issues were also held. An inconclusive debate as to the contributions of Alzheimer and Perusini to the identification of Auguste D. disease entertained the participants and closed the meeting, requiring discussion at the Sixth Symposium, scheduled for April 5 – 8, 2000, in Stockholm, Sweden to settle this issue and prevent the re-emergence of earlier European rivalries.