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Plenaries

K-1

What are the main issues expected in psychogeriatrics in the future?

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The so-called three D disorders, Dementia, Depression and Delirium have always been the challenging targets in the areas of psychogeriatrics and its related disciplines. Especially, number of people with dementia has reached to about 1.8 million in 2005 and is expected to rise in the future in Japan because of its rapidly aging population. The Japanese Government revised the National Long-term Care Insurance System launched in 2000 after five years implementation in order to make adjustment. Among the changes in corporate in the revised law is an increased emphasis on the reduction of unnecessary use of services under the program and prevention of disability in old age. There is the new establishment of community comprehensive support centers with aim to promote community-based care. In 2005 the Ministry of Health, Labour and Welfare, together with various organization, started a nation-wide 10 year Campaign called 'the Campaign to understand Dementia and Build Community Network'. The program aims to train one million "dementia supporters" throughout whole nation by 2010 in order to provide community support. It is crucially important to create multidisciplinary professionals including family physicians, nurses, care workers, local government officials and volunteer citizens etc in order to facilitate early diagnosis and continuous adequate care services so that people with dementia will be able to lead a safe, comfortable and dignified life with minimum independence on institutionalization. There will be growing needs to psychogeriatrician with the leading role in the community-based strategies in the Campaign now and in the future.

K-2

A view towards the future from the prospective of the past quarter century

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Change, indeed accelerating change, is characterizing geriatric psychiatry. The demographic change in world-wide aging and the enhancement of scientific and clinical information relevant to patient care will be the subject for this keynote address as we view the past and project to our future.

For the past 25 years, knowledge about the biologic bases of psychopathology, particularly of Depression, Alzheimer's disease, Anxiety, and of Aging itself, have reshaped our thinking about clinical management. Accompanying these data, are new insights into the socio-cultural aspects of aging as well as behaviors and emotions that can accelerate or prevent maladaptation. The greater emphasis on diversity among older person's ranges from those involved in active and valued civic engagements to those in need of community and family support; indeed recognition of the impact of providing care, among caregivers has in many countries altered the clinical interaction. Once thought virtually impossible, emerging database techniques for illness prevention and functional enhancement, and the discoveries concerning neuroneogenesis and genomics promised to usher in a future for psycho-geriatric practice much enlarged in scope from where we are today and much more individualized as well as community and culturally framed.

K-3

The restoration of Confucian family principals: Toward mutualism for kinship ties of elderly

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Most of the developing countries are unprepared for the future aging of their populations. The increase of the numbers of the 'oldest old', age 85 and over, alarms nations with it's impact on social policies, institutions, pensions, and social welfare. Republic of Korea, for example, the annual medical cost for elderly, $5.200.000.000 in 2005, is about 9 times of the cost in 1995. The Census Bureau predicts that the elderly population will reach 20.0% of the total population in 2010. Concerned of such demographic and economic changes, however, we often overlook important variations and diversity of life styles and cultural behaviours of contemporary aging. The majority of people with dementia, for example, may not have to go to nursing homes if society accepts their full rights to social inclusion. In 1960's, before senility and its brain change is medicalized as Alzheimers disease, people with dementia were accepted and tolerated in families, understood as senility or a senile disease. The effect of the neurological impairment can be moderated through social inclusion, providing proper bio-psycho-social support. Furthermore, the expectation that science will be able to prevent the onset of dementia or to deliver an effective cure may risks diverting attention from the need for the support of those disabled elderly particularly of their families. Familism is a unique social character among Koreans, evolved both as a means of life and philosophy. The ideology of filial piety is originated from the filial return of parental love and sacrifice. However, the direction in the family relationship of today is toward egalitarianism and the individualism. The center of family life is being shifted to conjugal ties, and recently to children. On the other hand, old people tend to choose to be free from the family. We see dispersion of families everyday in Korea. Parents of nuclear families now devote and sacrifice their lives for the education of children, even until they reach old ages. Notwithstanding, according to a current press survey, the ideological concept of Confucianism and the spirit of filial piety are still ingrained in peoples mind, with their sense of duty taking care of elderly parents. Author stresses the transformative potential of Confucian family principles Korean people inherited; spirit of vertical family relationship to be revived and the direction of filial piety to be mutualistic and reciprocal.

K-4

Active ageing-a personal view

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The author will describe personal experiences which reflect his own views on active ageing as well as illustrating the development of psychiatry in the 15th century Ottoman Empire and its relevance to the treatment and management of psychiatric disorder today. He will draw largely on experiences gained during travels to IPA meetings and his encounters with the world of Sultan Beyazid II in 1488in Edirne (Adrianopolis) as well as visits to Cairo and Aleppo (Syria). The talk will be illustrated by pictures from the medical museum set up by the Council of Europe and Trakya University in Edirne as well as those obtained from bimarestans in Egypt and Syria. The contrast between the humanitarian approaches adopted by these institutions and those current in contemporaneous Western institutions will be noted as will the subsequent decline of these approaches.

PL1-1

Implication of sleep and circadian rhythms for aging

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Most physiological and cognitive functions are comprised of an endogenous component influenced by the circadian system and an evoked component influenced by the sleep-wake cycle. The interaction of these components leads to fundamental questions regarding the source of cycling of a given rhythm and introduces experimental challenges that need to be carefully addressed before the endogenous circadian nature of an observable rhythm can be established. This particularly relates to potential medical interventions based on the presumed sensitivity to known circadian synchronisers such as light and exogenous melatonin. The first aim of this presentation is to review the experimental approaches available to reliably investigate circadian rhythms in the elderly population. This is important since disturbed sleep and insomnia appear more frequently in the elderly than in any other age

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group and can drastically affect the overall health and quality of life. It has been suggested that some of the changes observed in sleep might be markers of the central nervous system deterioration with age. Reduced amplitude and/or earlier timing of several diurnal rhythms have been reported with age such as that of core body temperature, plasma melatonin, cortisol, and the rest/activity cycle. Contradictory results have also been observed which suggest that a selection bias in favor of uncharacteristically healthy older individuals might have prevented some investigators from observing significant differences in the circadian rhythms of their elderly population. This observation raises the possibility that subjects who maintain robust circadian rhythms growing old might also age significantly better than other individuals. Interestingly, *post mortem* studies have detected a reduction in the volume of the suprachiasmatic nuclei (SCN), the master component of circadian rhythms, with aging. These changes are more pronounced in demented patients in whom a more severe disruption of the sleep/wake cycle and a drastic reduction of melatonin secretion have been reported. The second aim of this presentation is to discuss the interventions available to alleviate these sleep-wake cycle and circadian rhythms abnormalities, with the goal to promote overall cognitive and physical functioning late in life.

PL1-2

Management of sleep disturbances in older adults: Role of light and physical activity

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It has been estimated that over 30% of older adults experience sleep disturbances. These complaints include habitually earlier bedtimes and wake times, inability to maintain sleep at night, undesired early morning awakenings and frequent daytime sleepiness. Alterations of the circadian system are also known to occur with advancing age. In humans, the aging circadian system has been observed to exhibit changes in both amplitude and phase. Additionally, the elderly have reduced exposure to external entraining agents such as light, socialization and physical activity. These age-related changes in circadian clock functions and/or reduced exposure to synchronizing agents such as light, social and physical activity may contribute to the development of sleep disturbances, such as insomnia, irregular sleep/wake patters and advanced sleep phase syndrome.

This session will provide a review of the effects of bright light exposure and structured physical and social activities on circadian activity rhythms, night-time sleep and daytime performance in older adults. Current evidence indicates that bright light exposure can improve the timing and amplitude of circadian rhythms, night-time sleep and daytime alertness in older adults with sleep disturbances associated with circadian rhythm sleep disorders, such as advanced sleep phase and irregular sleep/wake cycle disorders. In the demented elderly, Ancoli-Israel and colleagues have demonstrated that increasing exposure to morning bright light in mild to severely demented elderly living in nursing homes can normalize the timing of the activity rhythm, improve the robustness of the circadian rhythm and enhance sleep consolidation at night.

Exercise or structured physical activity has also been shown to improve sleep quality and daytime performance in older adults. For example, Zee and colleagues have shown that night-time sleep and daytime neuropsychological performance improved after only two weeks of daily sessions consisting of exercise and social activity. While more studies are needed to fully asses the positive effects of activity programs on sleep and circadian rhythms in the elderly, these early results are encouraging. Furthermore, preliminary data from our study on the effects of aerobic exercise as a treatment for chronic insomnia in older adults indicate that increasing physical activity may be an effective treatment for this population. Therefore, timed bright light exposure and physical activity are important behavioural strategies for the management of sleep disturbances in older adult populations.

PL1-3

Sleep and circadian rhythm disorders in the elderly

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Numerous epidemiological studies have consistently demonstrated that older adults are disproportionately dissatisfied with the quality of

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their sleep compared to younger individuals. As many as 40% of elderly individuals complain about sleep problems, including disturbed or "light" sleep, frequent awakenings, early morning awakenings, and undesired daytime sleepiness.

The subjective complaints of poor sleep quality by older adults have been repeatedly validated by observed objective changes in the amount, pattern and circadian timing of their various stages of sleep and wakefulness compared to younger populations.

The sleep changes typically seen in older adults include: increased time in bed, decreased total sleep time, reduced slow wave sleep, increased nighttime wakefulness, increased fragmentation of sleep by periods of wakefulness, increased daytime napping and daytime sleepiness. Both circadian and homeostatic mechanism could be involved in these characteristic changes in the elderly.

In addition to these aging processes of sleep, elderly patients with dementia frequently showed behavior disorders, such as wandering, aggressiveness agitation or night delirium as well as sleep disorders. In these patients, circadian rhythm of sleep-wake, endocrine functions and autonomic systems have been impaired. Among several important endocrine hormones, relating to biological clocks. Three-to 4-year follow-up study we recently conducted revealed that there exists a group of elderly people who showed relatively rapid decline in melatonin secretion simultaneously with sleep maintenance disturbances.

For these elderly patients, chronobiological treatments with bright light, social interactions etc. are effective. In clinical practice, however, more studies are needed to develop treatment protocols for individual patients according to their characteristic features of circadian and sleep disorders.

PL2-1

Alzheimer's disease: From neurobiology to therapy

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The deposition of brain beta-aymloid consisting of aggregated Abeta peptides is a central feature of the neuropathology of Alzheimer's disease (AD). Oligomeric assemblies of Abeta can be neurotoxic. Therefore, reducing their brain concentrations is an important goal for the development of novel therapies to cure and prevent AD. Immunotherapies targeting brain Abeta are currently tested for safety and efficacy in patients with AD. Initial attempts with active Abeta immunization were halted because of the development of meningoencephalitis in a subgroup of patients, but follow-up studies established that Abeta immunization induced chronic elevations of antibodies against beta-amyloid. These are transported across the blood brain barrier into brain tissue and cerebrospinal fluid. In patients who had developed such antibodies, cognitive decline was slowed, brain beta-amyloid load was greatly reduced, and shrinkage of hippocampus volume was prevented. These initial beneficial clinical effects were independent of the prior occurrence of meningoencephalitis. Together, these pilot data suggest that chronically elevated titers of antibodies against beta-amyloid in AD patients could be safe and potentially efficacious in reducing the decline of cognitive functions, hippocampus tissue loss and beta-amyloid-related neuropathology.

PL2-2

Molecular mechanism of nigral neuronal death in Parkinson's disease

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Parkinson disease (PD) is characterized clinically by rest tremor, rigidity, bradykinesia, and postural instability and pathologically nigral neuronal death with Lewy body formation. It has been postulated that nigral neurodegeneration is initiated by the interaction of genetic predisposition and environmental factors to induce mitochondrial dysfunction and oxidative damage. Decrease in ATP formation is likely as a consequence of mitochondrial dysfunction and this would lead to proteasome and lysosome dysfunctions. Such proteolytic dysfunctions would lead to aggregate formation of proteins such as Lewy bodies. In case of PD, oligomer formation of alpha-synuclein appears to play a crucial role in neurodegeneration. Oligomers of alpha-synuclein are toxic to proteasome as well as to membranous structures such as mitochondria, lysosome, and synaptic vesicles. Oligomers of alpha-synuclein disrupt dopamine storage vesicles to release dopamine into the cytoplasm, which

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would increase oxidative stress; oxidative stress is another inducer of alpha-synuclein oligomer formation. Thus vicious cycles are formed within nigral neurons and such molecular mechanism is believed to induce apoptotic cascades as well as disturbance of axonal follow leading to neuronal death. Recent progress in familial PD contributed to the understanding of molecular mechanisms of nigral neuronal death. For instance, in PARK1, mutant alpha-synuclein proteins have increased tendency for aggregate formation and in PARK4, increase in the amount of normal alpha-synuclein triggers aggregate formation. In PARK2, proteasome dysfunction is likely to be a main denominator of nigral neuronal death; in addition, parkin protein has a strong anti-oxidant property. In PARK 6 due to PINK1 mutations, PINK1 protein was found to be a mitochondrial protein which is essential to maintain the integrity of mitochondria. In PARK7 due to DJ-1 mutations, DJ-1 protein was found to have a very strong anti-oxidant property and DJ-1 migrates between cytoplasm and mitochondria. In PARK8 due to LRRK2 mutations, it has a protein kinase activity. Dysfunction of protein phosphorylation may be another important process of nigral neuronal death. In PARK9 due to ATP13A2 mutations, ATP13A2 protein is an ATPase expressed in the lysosomal membrane. Thus it seems likely that a common mechanism exists in the nigral neuronal death between familial PD and sporadic PD.

PL2-3

The substrates of dementia and regeneration in vascular dementia

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Vascular dementia accounts for 20% or more of dementias, but in comparison to Alzheimer's disease little progress has been made in understanding the key disease mechanisms or in developing treatments. In small case series and according to established operationalized diagnostic criteria large single infarcts, multiple infarcts, strategic infarcts, microvascular disease and hypoxic brain injury can all be an attributable cause of dementia in individual patients. However, in larger cohort studies, microvascular disease and concurrent neurodegeneration emerge as the main substrates of dementia. Experimental evidence indicates that hypoxia induces an amyloid cascade, whilst at a molecular level other vascular risk factors such as hypertension may induce pro-neurodegenerative pathways. The factors governing the progression of microvascular disease are poorly understood, but inherited conditions such as CADASIL and studies of key polymorphisms have highlighted candidate genes that may offer valuable insights. Work over the last 18 months has also suggested that alterations in key angiogenic proteins may be associated with microvascular disease in the context of Alzheimer's disease and may also be linked to neurogenesis. Exciting recent studies have also highlighted a substantial increase in neurogenesis following cerebrovascular lesions, and led to the suggestion that there may be some capacity for "regeneration" within the human brain after a stroke or other cerebrovascular lesion and that enhancing this process could potentially provide a novel treatment target in vascular dementia.

PL3-1

Models of psychogeriatric practice in immigrant ethnocultural communities

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Cultural phenomena are indisputably important in clinical care of elders. However culture is difficult to define and its impact on individual treatment is often closely intertwined with other factors, particularly the effect of immigration, earlier psychological trauma, and dramatic transitions in cultural norms caused by various natural and man-made calamities. Delivery of psychogeriatric care to elders must take into account both macro cultural influences such as stigma together with other features which may erroneously be attributed to culture such as avoidance of mainstream institutions. Cultural perspectives are particularly important in societies such as Canada, which have received large numbers of immigrant elders who are confronted with adaptation to new cultural norms and health care systems. Immigration and change poses a variety of important barriers to accessing clinical care and to its effectiveness when it is made available. This presentation will explore some of the key issues in defining cultural and culture-related barriers to access to clinical care

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and describe evidence-based models of intervention developed in Canada. Such models are most effective when they are built upon sophisticated understanding of the influence of culture on attitudes to determinants his of health, help seeking and pathways to care, acceptability of different forms of intervention, and the need to integrate traditional and well accepted interventions with less familiar Western based models. Some key strategies includes ensuring accessibility by creating programs which are geographically available, enhancing acceptance by creating clinical environments which are both familiar and destigmatized and ensuring effectiveness by integrating methods and programs with mainstream institutions and practitioners.

PL3-2

Rapid socio-cultural changes and aging in East Asia

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About one third of the world population lives in East Asia. East Asia is characterized by diverse culture, different socioeconomic condition and diverse political systems. There were steady economic development, increase of living standards and the increase of health condition of the population. Asia has emerged as economic giants. At the same time, traditional culture and community were lost in many parts of Asia. The author will review major socio-economic changes in East Asia, analyze their impacts to the elderly mental health and suggest ways and means for active aging in East Asia. The massive demographic change took place in the past 30 years. The annual increase of the population aged 65 years and above was 2.3% worldwide and 3.0% for developing countries. On the other hand, the proportion of young generation is becoming slimmer in most of East Asian countries. China adopted one child family policy and this one child family will have a long lasting impact on health and mental health of the population. In many Asian countries, the trend toward a nucleus family is common. Small number of family member is now unable to support a disabled elderly member at home. Another disturbing factor is domestic migration. Service industry, manufacturers, information industry and public industry grew mainly in large cities. The income gap between rural and urban population became enormous. Young rural population in Asia are moving to large cities seeking the job and better living condition. This has resulted in the proliferation of villages left for elderly peoples. Another factor is the change of traditional cultures. East Asian countries had several cultural values with long history. Confusianism and Buddism still form the basic frameworks of many Asian peoples. Agrarian societies in Asia have led a communal oriented society with high value to the harmony, consensus and respect to the elderly. This is being challenged by individual oriented value system. Aging in Asia is a sign of the promotion of health condition in the Region. On the other hand, aging is a challenge for public health. The author will stress the needs for new paradigm for elderly care in East Asia.

PL3-3

Ethnic minority elders and their psychiatric needs in the United Kingdom

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The proportion of elderly from Black and Minority Ethnic (BME) groups has rapidly increased over the last two decades in the United Kingdom. However, despite the prevalence of dementia and depression, the two most prevalent mental illnesses in old age, being similar to or higher than that in indigenous white British elders and high awareness of primary care services and high general practice consultation rates among BME elders, they are poorly represented in secondary care old age psychiatry services. Reasons for this include: factors pertaining to patients and their families, factors pertaining to primary care and factors pertaining to secondary care. Each will be discussed in detail. Strategies to reduce this inequity will be discussed and will include strategies to identify examples of good practice in service delivery and their replication, development of improved communication strategy, development of diagnostic and screening instruments, improving staff training in cultural sensitivity, agenda for research and development of a public health campaign.

PL4-1

Pharmacogenetics and therapeutic optimization in dementia

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Genetic factors account for 20 to 95% of variability in drug disposition and pharmacodynamics. Recent studies indicate that the therapeutic response in Alzheimer's disease (AD) is genotype-specific depending upon genes associated with AD pathogenesis and genes responsible for drug metabolism. Pharmacogenetic studies revealed that APOE-4/4 carriers are the worst responders. PS1 and PS2 polymorphic variants do not appear to influence the therapeutic response in AD; however, APP, PS1, and PS2 pathogenic mutations may drastically modify the therapeutic response to drugs. The worst responders in all genomic clusters are patients with the 441122+ genotype, indicating the powerful, deleterious effect of the APOE-4/4 genotype on therapeutics in networking activity with AD-related genes. The presence of the APOE-4 allele influences both cognitive and noncognitive therapeutic responses to conventional drugs. Cholinesterase inhibitors (AChEIs) are metabolized via CYP-related enzymes. AChEIs can interact with drugs which are substrates, inhibitors or inducers of the cytochrome P450 system, contributing to liver toxicity and adverse drug reactions. CYP2D6 enzymes are involved in the metabolism of more than 20% of CNS drugs. The distribution of the CYP2D6 genotypes differentiates 4 major categories of CYP2D6 metabolyzer types: (i) Extensive Metabolizers (EM)(*1/*1, *1/*10)(51.61%); (ii) Intermediate Metabolizers (IM)(*1/*3, *1/*4, *1/*5, *1/*6, *1/*7, *10/*10, *4/*10, *6/*10, *7/*10)(32.26%); (iii) Poor Metabolizers (PM)(*4/*4, *5/*5)(9.03%); and (iv) Ultrarapid Metabolizers (UM)(*1xN/*1, *1xN/*4, Dupl)(7.10%). PMs and UMs tend to show higher transaminase activity than EMs and IMs. EMs and IMs are the best responders, and PMs and UMs are the worst responders to pharmacological treatments in AD. At this early stage of development, it seems very plausible that the pharmacogenetic response in AD depends upon the interaction of genes involved in drug metabolism and genes associated with AD pathogenesis. The establishment of clinical protocols for the practical application of pharmacogenetic strategies in AD will foster important advances in drug development, pharmacological optimization and cost-effectiveness of drugs, and personalized treatments in dementia.

PL4-2

Metabolic and genetic rationale for rosiglitazone treatment of Alzheimer's disease and possibly other brain mitochondriopathies

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Apolipoprotein E genotypes are associated with risk and age of onset distributions of Alzheimer's Disease. Prior to 1993 there was little data regarding a role for apoE in the brain. No human immunohistologic studies had been published and, based on rodent studies, apoE was localized only to glia. Most AD researchers have [and continue] focused on protein interactions related to the amyloid cascade hypotheses, or the tau-neurofibrillary tangle interactions. The rationale for the use of PPAR γ agonists as a treatment developed from metabolic studies in transgenic and mice human subjects differentiated by their APOE genotypes. A brief history of the use of proteomics, humanized APOE transgenic mice, and PET scanning data focused attention to glucose utilization in the brain. Proteomic experiments of APOE transgenic mice clearly defined multiple protein involved in glucose metabolism. PET scanning clearly demonstrated that cognitively normal subjects exhibited differential glucose utilization at earlier ages, based on their APOE genotypes. The dogma that apoE protein was not expressed or present within human neuronal cells was demonstrated to be incorrect. Experiments performed in 1998–2000 demonstrated the dose-related enhancement of glucose metabolism *in vivo* in mouse brain and *in vitro* in mouse brain synaptosomes using several PPAR γ agonists. The results of a Phase IIB monotherapy trial will be presented.

More recent genetic experiments have begun to focus on the association of specific genes related to mitochondrial functions. **Genome-wide SNP scanning** [i.e., whole genome scans] of AD patient and control groups identified several regions along the genome with statistically significant gene and linkage disequilibrium block associations. These analyses provide a hypothesis-free opportunity to examine various existing theories of disease pathogenesis. Data will be presented that support

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the role of apoE and mitochondrial function, and provide a link to subsequent phenotypic amyloid and neurofibrillary cascades that form the pathologic landmarks of AD.

PL4-3

Alzheimer's disease: Clues to therapeutics from genetics

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Alzheimer's disease (AD) is the most common form of dementia and a genetically complex disease. Our laboratory has been involved with the discovery of the three genes, APP, PSEN1, and PSEN2, in which ~200 mutations are known to cause early-onset familial AD (FAD). Meanwhile, the epsilon4 variant of the gene encoding apolipoprotein E (APOE) is the best-established risk factor for late-onset AD. All four AD genes harbor gene defects that enhance the accumulation of beta-amyloid and its chief component, the Abeta peptide, in the brain. While APP serves as the precursor for Abeta, the presenilins play a role in the enzymatic release of the Abeta peptide from APP. Most mutations in the three early-onset FAD genes increase the ratio of Abeta42:Abeta40. Abeta42 is much more prone to driving the formation of Abeta oligomers that have been shown to interfere with neurotransmission at glutamatergic synaptic terminals. Meanwhile, APOE affects the clearance of Abeta from brain. These findings have prompted clinical trials targeted at either the production or clearance of Abeta. We have co-founded two companies currently developing AD therapeutics. TorreyPines Therapeutics, Inc., is developing gamma-secretase modulators aimed at selectively lowering Abeta42 or reversing the Abeta42:Abeta40 ratio. Prana Biotechnology, LTD, is developing (non-chelator) small molecules that strip zinc and copper away from Abeta, which prevents oligomerization and toxicity. This approach is based on our earlier findings that these metals are required for Abeta oligomerization. While, the four known AD genes have provided us with most of what we know about the etiology and pathogenesis of AD, 70% of the genetic variance of AD remains unexplained. Numerous candidate genes have been proposed over the past decade leading to a significant degree of confusion regarding which are true AD genes. To address this problem, we created AlzGene, which summarizes the data from genetic tests of more than 400 AD candidate genes, and provides meta-analyses to determine the most promising AD candidate genes. We have also employed whole genome association screens of over 1400 late-onset AD families to identify the remaining late-onset AD genes. Ultimately, the identification and characterization of novel AD genes should accelerate prediction, diagnosis, prevention, and treatment of AD.

PL5-1

New treatments for dementia

Serge Gauthier

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Drugs acting on cholinergic and glutamatergic neurotransmission have been found useful for symptoms associated with Alzheimer's disease (AD) at different stages of severity. Some of these drugs are also effective in Parkinson disease dementia and AD with vascular components.

A number of potential disease-modifying drugs (DMD) are under testing in patients with mild to early moderate AD. The favored design is parallel groups received a high or a low doses of the new drug, or a placebo, added to standard treatment (a cholinesterase inhibitor with or without memantine). Most studies are 18 months in duration to allow for separation of groups over time for the main clinical outcomes, a cognitive scale (ADAS-cog) and a global impression of change (CDR-SB). Secondary analysis include ADL and behavior. Time to progress from CDR 1 to CDR 2, e.g. from mild to moderate stage AD, may offer additional face validity to these outcomes. Alterations in the rate of brain atrophy using MRI and in levels of CSF peptides may help in proving a disease-modifying action rather than a sustained symptomatic benefit. Drugs with various modes of actions are being tested simultaneously, including neurotrophic actions, amyloid suppression, improved glucose or cholesterol transport. Responder analysis may show that different patients respond differentially to drugs with different modes of action based on genotypes, age of onset and stage of disease.

If DMD are effective in mild AD, it is possible to plan for 3-year placebo-controlled randomized clinical trials in amnestic MCI, looking at rate of progression to clinically diagnosable dementia

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as primary endpoint. Regulatory authorities may recognize amnestic MCI as "predementia AD" if the clinical and neuropsychological abnormalities are supported by one or more structural or metabolic abnormality associated with early AD (hippocampal atrophy, hypometabolism on glucose PET scan, abnormal PIB PET scan, abnormal β-amyloid or *tau* CSF levels).

Asymptomatic persons at higher risk of AD could be enrolled in 5-year placebo-controlled study with the safest of the DMD, looking at incident dementia as primary endpoint. High risk may be based on family history of late onset (>70) AD and carrier status for apoE and other genotypes. Subjects from families with early onset (<55) AD could be screened for presenilin and APP mutations, and carriers with preclinical AD could be enrolled in shorter studies. Asymptomatic persons with only the age-associated risk of AD could be enrolled in 5 to 7 years population studies where non pharmacologic interventions are compared, such as diet enriched with antioxidants, physical exercise, cognitive training.

A comprehensive symptomatic and preventive approach to AD and related disorders may thus be possible within the next decade.

PL5-2

Psychosocial intervention for dementia

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In Japan, seven years have passed after the implementation of the long-term care insurance with aiming to provide unified health, medical and welfare services for the disabled elderly persons as well as to offer the interventional programs to slowing down the functional capacities of them. In 2003, the Ministry of Health, Labor and Welfare disclosed that approximately half of the eligible persons for the long-term care insurance were suspected of dementia in the report entitled "Care for the Elderly in Japan in 2015" indicating the plan should be implemented by 2015, the year in which the tail end of the postwar Japanese baby-boom generation will become 65 years old. At present, the number of the eligible persons is 4,600,000 and it is estimated that 2,200,000 persons are suffering from dementia. However, the most serious issue is that a proportion of persons who are appropriately diagnosed and treated are not known. This is the major reason why early detection of dementia should be encouraged nation-widely in Japan. The implications of the programs to detect dementia involving health professionals in the community will be described from a view point of psychosocial intervention for dementia.

PL5-3

Mastery over dementia: Online counselling for family caregivers of people with dementia

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The problems of family caregivers of people with dementia have been studied extensively. The results show a negative impact on mental health, varying from feelings of burden to psychiatric disorders including depression. Results on the treatment of caregivers' psychological problems are less clear-cut. They show no or only modest benefits. This presentation will be focused on an innovative intervention, i.e. 'Mastery over dementia', for family caregivers of people with dementia. The website treatment is primarily focused on decreasing burden in stead of depression in the first place as in other treatments. In addition, it is an adaptive treatment, that can be varied in scope and intensity to fit the person and his/her needs. In this way, it tries to overcome some of the shortcomings of existing treatments (Zarit and Femia, 2007). The three components of the treatment (information, self-help and counselling), the rationale, and some of the innovative technological aspects will be discussed. 'Mastery over dementia' is a product of the Netherlands Institute of mental Health and Addiction in collaboration with Geriant, providing outpatient mental health care for people with dementia and their family caregivers, and the patient organisation Alzheimer Netherlands.

PL6-1

Silent strokes: The eloquent realm of neuropsychiatry

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In the elderly, changes in behavior or mood, such as apathy, aggressiveness, depression, evoke an organic etiology, particularly when alterations of gait, urinary incontinence, or primitive reflexes are present. In patients with late-onset depression, incongruence of subjective objective components of mood and affect (looking sad or having crying spells without sadness) may indicate involuntary emotional expression disorder resulting from dysfunction of emotional networks linking frontal subcortical thalamic pathways and pontocerebellar networks. Apathy, a quantitative reduction of voluntary, goal-directed behaviors may result from prefrontal subcortical disruptions (limbic lesions with akinetic mutism, Parkinson disease, vascular dementia (VaD) and vascular depression).

Neuropsychiatric abnormalities of behavior, cognition, and mood in the elderly may result from lesions of prefrontal subcortical circuits due to degenerative conditions (frontotemporal dementias) and ischemic cerebrovascular disease (CVD) including silent lacunar strokes and white matter lesions (WML) in the absence of a clinical stroke syndrome. Physicians are often unaware of these eloquent behavioral and cognitive manifestations of ischemic CVD and fail to recognize these symptoms as organic. Silent lacunes, particularly in the thalamus, double the risk of dementia. Periventricular WML cause decline in information processing speed, executive function, and memory. Vataja et al (2005) classified post-stroke patients into four groups: (1) depression executive dysfunction (DED), (2) PSD without ED, (3) ED without post-stroke depression (PSD), and (4) no depression and normal executive function. In patients with DED, the number of infarcts affecting anatomic components of the left frontal subcortical circuits was statistically significant in the logistic regression model. Therefore, interruption of prefrontal subcortical circuits originating in dorsolateral prefrontal cortex, orbitofrontal cortex, or anterior cingulate cortex, by ischemic CVD at the level of caudate, pallidum, thalamus, or their subcortical cortical loops in the white matter, produce a significant increase in risk of PSD and ED, the depression executive dysfunction syndrome of late life described by Alexopoulos. Modern imaging techniques such as tractography by diffusion tensor imaging promise to define anatomically these so-called silent lesions.

PL6-2

Vascular cognitive impairment and Alzheimer's disease: Time for a concerted approach

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One in three of us will end up with stroke, dementia or both, unless we do something about it. Risk factors for stroke are also risk factors for dementia, and the two conditions may co-exist and interact, suggesting that these diseases should be treated and prevented together. Only 13% of patients with a first stroke ever have a warning and by the time that patients with Alzheimer's disease develop the first symptoms, it is already too late. Consequently, we must shift the emphases to early individual risk identification and prevention. Consensus in using the same standards and minimal common data elements is crucial, but consensus of opinion is not desirable, because every opinion contains a sizable proportion of ignorance that hides within a consensus. If the same standards in assessing cognitive impairment are used (Hachinski et al. Stroke. 2006; 37:2220–2241) then a number of provisional criteria, can be applied to the same patients, thus identifying key components of the best criteria simultaneously and saving considerable time, effort and confusion. Common data elements would allow the creation of large databases that could be subjected to data mining and other advanced informatics techniques. These could generate hypotheses based on one dataset that could be validated on another set without additional research (Hachinski. Stroke. 2007;38:1396–1403). It is time for standardized assessments and a trial in the prevention or delay of vascular cognitive impairment, stroke and Alzheimer's disease together.

PL6-3

Vascular cognitive impairment and apathy

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Vascular cognitive impairment (VCI) is different from mild cognitive impairment (MCI) which is mostly early stage of Alzheimer's disease (DAT). Vascular dementia (VD) which is progressing stage of VCI usually shows decrease of prefrontal regional cerebral blood flow (rCBF) but parietotemporal region in DAT. Memory disturbance is main symptom in MCI, while executive dysfunction is more prominent in VCI. In our study, frontal assessment battery was more impaired in VD than in DAT. In addition, it is well known that apathy is commonly observed in VD. Apathy is one of the most important post-stroke neuropsychiatric disorders as well as post-stroke depression (PSD). PSD also involves a significant factor of apathy. We investigated the incidence of apathy and depressive state in 245 post-stroke patients using apathy scale (Starkstein) and Zung self-rating depression scale (SDS). Apathy without depressive state was observed in 21% and combined cases in 23%. Depressive state without apathy was observed in only 12%. Apathy is not only symptom of VD but also one of the important causes of VD, because one of the main mechanisms of VD with multiple lacunar infarction or severe white matter lesions (Binswanger type of VD) may be considered disuse brain dysfunction. We studied the relationship between rCBF and apathy using Xenon 133 inhalation method in 40 post stroke patients. The rCBFs of the bilateral hemisphere were significantly lower in the apathetic group than in the nonapathetic group. The apathetic group showed a significantly reduced rCBF in the right dorsolateral frontal and left fronto-temporal regions. Even in silent stroke, such as silent multiple lacuna and significant white matter lesions, are also related to apathy score, but not to SDS. Cognitive functions also correlated with apathy score but not with SDS after adjusted of age. In our 6-year follow-up study in aged residents, apathy tendency developed only in silent stroke group. We also examined the relationship between apathy score and evoked potential (novelty P300) which reflects prefrontal function. Amplitude of novelty P300 negatively related to apathy score. It means that apathy is closely related to prefrontal dysfunction.

Conclusion: Apathy is not only relatively common post-stroke neuropsychiatric disorders, but also one of the important causes of VCI and VD. Therefore, early detection and treatment of apathy is important to prevent VD.

PL7-1

Serotonin modulation of neural circuitry in geriatric depression

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Monoaminergic dysfunction has been implicated in depressive disorders. Understanding serotonin dysfunction in geriatric depression may be especially important given the evidence from animal and human studies suggesting a role of the serotonin system in neurodegeneration, neurogenesis and compensatory responses. A measure of dynamic serotonin function has been developed and has been evaluated in normal aging (n = 14) and geriatric depression (n = 16) Cerebral glucose metabolism was measured with positron emission tomography after administration of saline placebo and after the selective serotonin reuptake inhibitor, citalopram (40 mg, IV). Neuropsychological testing was performed at baseline and after eight weeks of treatment. The patients were treated with oral citalopram for 8 weeks and underwent repeated PET scanning at that time. In the geriatric depression patients, a blunted right hemisphere cortical response and a greater response in the left hemisphere was observed in the patients compared to controls. After chronic treatment, the patients demonstrated significant improvement in depression and anxiety symptoms. Chronic treatment was associated with decreases in right anterior cingulate and frontal cortices and increases in right putamen and left occipital cortex. The circuitry related to improvements in depressive and anxiety symptoms will be evaluated using principal components analyses. Understanding the neural circuitry underlying depression and anxiety symptoms and modulation by serotonin will inform the design of subsequent studies to further understand the specific neurochemical substrates underlying differential response to antidepressant interventions.

PL7-2

The role of brain-derived neurotrophic factor in the treatment of major depression in the elderly

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Objectives: It has been suggested that low brain-derived neurotrophic factor(BDNF)levels are associated with major depressive disorder(MDD). There are several lines of evidence that the expression of BDNF is the downstream target of a variety of antidepressants; BDNF might therefore be an important agent for therapeutic recovery from depression. This study examines the association between the BDNF level or genetic polymorphism and depression susceptibility or antidepressant response according to the age.
Method: Patients with MDD and normal control were assessed for serum BDNF contents. BDNF were assayed with enzyme-linked immunosorbent assay methods, and severity of depression was evaluated with 21-items Hamilton Depression Rating (HAMD-21)Scale. BDNF(Val66Met) genetic polymorphism was examined using a polymerase chain reaction(PCR) method. Patients were treated with citalopram or mirtazapine. We defined the elderly as age greater than or equal to 60.
Results: Serum BDNF level was significantly lower in MDD than normal control and frequency of the Val66 was higher in patients group compared with normal control. In citalopram treated group, frequency of Met66 allele carrier was higher in response group compared with non-response group but we could no detect an alteration of serum BDNF level after antidepressant treatment.
Conclusions: Our results suggest that the BDNF Val66Met polymorphism play role in a possible susceptibility candidate for with MDD and affect antidepressant response for MDD with in the elderly. Although we could not detect the correlated with the increase BDNF level and the response to antidepressant in the elderly, BDNF level and genetic polymorphism which can predicts antidepressant response especially in the elderly.

PL7-3

Anxiety and depression in late life – challenges to assessment and treatment

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The question of whether psychiatric disorders decline or increase with age is complex. Current knowledge on the phenomenology of psychopathology in late life is limited, but the data available do suggest that distinctive features of depression and anxiety may become less pronounced with rising age. Older adults are not less likely to suffer from these disorders compared to younger adults, but they are often more likely to express psychological mood or behavioural symptoms in somatic terms. Delineating risk factors is crucial to the development of focused interventions aimed at emotional problems in late life. Epidemiological studies have demonstrated that late-life anxiety and depressive symptoms often arise in the context of medical disorders. These symptoms often go undetected in primary care, even when symptoms are clinically significant. Multiple studies have found a high prevalence of anxiety and depression in patients with chronic obstructive pulmonary disease (COPD), a disease that develops from middle age and onwards. A randomized, controlled trial of 61 adults (mean age 61.0) with COPD and co-morbid anxiety and depression was conducted to examine the efficacy of cognitive behavioural therapy (CBT) in groups on anxiety and depression. CBT was compared with a minimal telephone contact (MC). Participants in the CBT condition received seven weekly group sessions according to a treatment manual, whereas participants in the MC condition were phoned every other week during the intervention period of seven weeks. Participants in both conditions were followed up at six months. Main outcome measures were Beck Anxiety Inventory and Beck Depression Inventory-II. CBT resulted in an immediate improvement for symptoms of anxiety and depression, an improvement maintained at the six-month follow-up. Participants in the MC condition did not improve significantly over time. The results suggest that CBT in group format may be a viable treatment strategy for older COPD patients with co-morbid anxiety and depression. At present, CBT-based interventions focusing on emotional health symptoms are not widely available for COPD patients, and the potential of CBT for producing clinically meaningful improvement in emotional well-being is not systematically considered in existing treatment alternatives. For medically ill older adults with markedly high levels of anxiety or depression, targeted evidence-based interventions focusing on mental health distress are warranted.

PL8-1

Personality disorders in older age: Constancy, special challenges and implications for treatment

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While valid assessment measures of older adults with personality disorders remain methodologically elusive, we are usually able to recognize these individuals, and they are among our most challenging patients. To the extent that we are able to describe and understand their clinical presentation, we are in better position to select from among treatment options. The robust features of personality disorders, which remain throughout sentient life, include a reliance on primitive defenses, core vulnerabilities, restricted resilience, and the effect these individuals have on others. Frequently occurring stressors in older age can overwhelm the individual's ability to cope. Older adults with personality disorders have difficulty accommodating these stressors, and typically respond maladaptively, incurring distress in themselves and others who are responding to their needs and providing care. Central to a dimensional model of personality disorders is the premise that the personality traits themselves are not inherently pathological. When pathology is expressed, this reflects a limited response repertoire and an inappropriate application of traits. A goodness of fit model is presented as a means to understand the way an individual's personality traits mesh with what is being asked of him. A distinction between personality style and personality disorder is central to this model. Evidence based treatments for older adults with personality disorders address co-morbidity with Axis I disorders; a prevalent clinical presentation. Studies mainly report that those individuals with co-morbid Axis I and II disorders have a more complicated course and more frequently relapse than those without an Axis II disorder. Psychopharmacology is used to treat specific symptoms. All psychotherapies are more challenging because those with a personality disorder have difficulty establishing and maintaining an alliance, and are less compliant and less able to change cognitions and behaviours. Treatment of choice appears to be a combination of psychopharmacology, psychotherapy, and environmental modifications.

PL8-2

A new view of psychological growth and development in the second half of life

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Remarkably limited research has been conducted on psychological growth and development in the second half of life, and few major figures in the field saw psychological development continuing with aging. Freud and Piaget, for example, saw development as predominantly a first quarter of the life cycle phenomenon. Erik Erikson was the major exception, describing eight stages of psychosocial development in his classic work Identity and the Life Cycle. But even Erikson conceded that what he wrote about aging was thin, with only three pages of the fifty in *Identity and the Life Cycle* addressing development past adolescence; only one page addressed all of later life and half of middle age. Moreover, the major theories on psychological development emphasized psychosexual obstacles that must be overcome (repression with Freud), psychosocial crises that must be resolved (with Erikson), or developmental tasks that must be accomplished (with Vaillant) for psychological growth and health to proceed unencumbered.

A new theory of psychological growth and development in the second half of life will be presented based on more than 35 years of predominantly qualitative research with more than 3000 clinical and research subjects in middle age and later life. The research has consisted of individual interviews, utilizing structured and open-ended questions, conducted longitudinally for varying time periods, by the primary investigator (PI). The most recent work in this area by the PI has focused on Baby Boomers in the United States; it is the first longitudinal, individual interview based study of Boomers-in contrast to the wide range of survey studies conducted on Boomers.

This new theory does not assert that earlier work in this area is incorrect-instead, incomplete. The new theory adds a further layer of understanding to psychological development as we age. The new theory is characterized not by tasks, obstacles, or crises to surmount, but by an inherent positive inner push-a collection of built-in drives-pushing us throughout life toward psychological growth and creative expression, not stopping as we move through the life cycle. The inner push remains constant, but its expression becomes altered in response to accumulating life experience and positive brain changes with aging. In the second half

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of life, the inner push is expressed as four phases of psychological growth that continue to foster creative expression; the phases will be delineated and illustrated.

PL8-3

Diagnosing personality disorders in older adults: Bottlenecks and dilemmas

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Reliability and validity of psychological assessment instruments are frequently studied because they can be used as reliable diagnostic tools. They ensure a systematical approach and simplify communication. However there is a lack of specific tools for the assessment of personality disorders in older adults. In this oral, diagnostically aspects of personality disorders in older adults are discussed. On a descriptive level, the Diagnostic and Statistical Manual of Mental Disorders 4th edition Textual Revision (DSM-IV-TR) (APA, 2000) is the most used diagnostic system in old age psychiatry. This a-theoretical system offers advantages in the communication between clinicians. Besides that, by using the DSM scientific as well as diagnostic study results are comparable. Moreover in the future DSM-V it is recommended that the current categorical classification will be completed by a dimensional classification, providing more detailed information about the seriousness of the pathology. More information about pathological personality traits will remain intact. Unfortunately older adults are no subject on the DSM-V personality disorders research agenda yet. This is a main bottleneck because the present DSM-personality-disorders-criteria are difficult to apply to the elderly. The manifestation of personality pathology in older adults differs from younger adults on several points. This can be explained by the so-called heterotypical continuity. This means that personality constructs will remain the same during the course of life, but that the resulting behavioral patterns can vary related to the phase of life and situational context. Heterotypical continuity has its consequences for the current axis-II criteria, as these are mainly based on the behavioral conduct of younger adults. In older adults, certain axis-II-criteria will be of more or less importance as a result from aging processes or changes related to the environment. The lack of age-related weighing coefficients in the current axis-II-criteria is not only a diagnostic obstacle in daily practice of clinicians, but also from an scientific point of view it is the most important bottleneck with regard to the criterion validity of an axis-II assessment instrument for older adults. To use the current axis-II criteria on older adults or not is a difficult dilemma.

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