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Aging, longevity and health

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Abstract

The IARU Congress on *Aging, Longevity and Health*, held on 5–7 October 2010 in Copenhagen, Denmark, was hosted by Rector Ralf Hemmingsen, University of Copenhagen and Dean Ulla Wewer, Faculty of Health Sciences, University of Copenhagen and was organized by Center for Healthy Aging (CEHA) under the leadership of CEHA Managing Director Lene Juel Rasmussen and Prof. Vilhelm Bohr, National Institute on Aging, NIH, Baltimore, USA (associated to CEHA). The Congress was attended by approximately 125 researchers interested in and/or conducting research on aging and aging-related topics. The opening Congress Session included speeches by Ralf Hemmingsen, Ulla Wewer, and Lene Juel Rasmussen and Keynote Addresses by four world renowned aging researchers: Povl Riis (The Age Forum), Bernard Jeune (University of Southern Denmark), George Martin (University of Washington, USA) and Jan Vijg (Albert Einstein School of Medicine, USA) as well as a lecture discussing the art-science interface by Thomas Söderqvist (Director, Medical Museion, University of Copenhagen). The topics of the first six Sessions of the Congress were: Neuroscience and DNA damage, Aging and Stress, Life Course, Environmental Factors and Neuroscience, Muscle and Life Span and Life Span and Mechanisms. Two additional Sessions highlighted ongoing research in the recently established Center for Healthy Aging at the University of Copenhagen. This report highlights outcomes of recent research on aging-related topics, as described at the IARU Congress on *Aging, Longevity and Health*.

Keywords

Lifespan; Life course; Cognitive decline; Alzheimer's disease; Mitochondrial dysfunction; Oxidative DNA damage; Gerontology; Neurodegeneration

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1. Background

The mean age of the human population is steadily increasing, a phenomenon that will bring social, political, economic and biomedical challenges to future generations worldwide. The evolution of population age structure in urban and rural regions of more and less developed countries over the last 50 years is well documented (Fig. 1), and projections of future change in population age demographics have been modeled (Fig. 2). By 2050, 22 percent of the world population and 33 percent of the population of developed countries are predicted to be 60 years old, representing a doubling of the elderly fraction of the population worldwide. This change will challenge our understanding of and ability to manage human health and disease in the elderly population. To rise to this challenge, researchers, research institutions and multi-institutional research groups are conducting and planning extensive programs to study and better understand human aging and aging-related disease and dysfunction. One such program is being spearheaded by the International Alliance of 1 Research Universities (IARU),¹ an alliance of 10 leading research universities who are collaborating on activities and research related to challenges with global scope and implications for society. The program on Aging, Longevity and Health is a core element of the IARU vision.

To facilitate the IARU vision, the University of Copenhagen Center for Healthy Aging (CEHA) and collaborating IARU universities are conducting leading edge research in the fields of aging, DNA damage, oxidative stress, neurodegeneration and related areas. Many significant contributions in these fields were presented and discussed at the IARU Congress in Snekersten, Denmark, 5–7 October 2010². This document summarizes key outcomes of the presentations at the 2010 IARU Congress (see also Box 1/*An aging world* and Box 2/*Key discussion points and future aging research directions*).

Keynote Address by Povl Riis

(Age Forum, Denmark)

Research in Aging and Gerontology: Target Centered Methodology, Adjusted Research Ethics, and Clinical Relevance

Until the relatively recent past, medical and clinical science has focused primarily on the adult stage of human life, and given much less attention to the specialized needs or characteristics of children and the elderly. However, when they did emerge as new clinical specialities, the fields of pediatric and geriatric medical and clinical science benefited from a pre-existing large clinical knowledgebase, and were therefore established with relatively sophisticated methodology from the outset.

¹IARU member universities are Australian National University, ETH Zurich, the National University of Singapore, Peking University, the University of California, Berkeley, University of Cambridge, University of Copenhagen, University of Oxford, the University of Tokyo and Yale University. The IARU Secretariat is at National University of Singapore (NUS) and IARU is chaired by Professor Tan Chorh Chuan, President of NUS. The IARU “Aging, Longevity and Health” project was co-founded by Peking University and the University of Copenhagen.

²The Workshop, *Aging, Longevity and Health*, held 5–7 October, 2010 in Snekersten, Denmark, was organised by The Faculty of Health Sciences, University of Copenhagen in conjunction with the International Alliance of Research Universities and was sponsored by University of Copenhagen Faculty of Health Sciences and the Copenhagen Center for Healthy Aging. The Workshop Organizing Committee included Ulla M. Wewer, Dean at the Faculty of Health Sciences, University of Copenhagen, Vilhelm A. Bohr, National Institute on Aging, NIH, USA, and Lene Juel Rasmussen, Director at Center for Healthy Aging, University of Copenhagen.

Two well-established axioms are central to current clinical best practice: first, all clinical judgements rest on comparisons; and second, all biological processes vary constantly over the human life span and the human population. The relatively new disciplines of pediatrics and geriatrics are also based on the paradigm of so-called “evidence-based research.”

Within the field of clinical geriatrics, the following issues represent persistent dilemmas: (1) it can be challenging to obtain informed consent from elderly who are in declining health and suffering from dementia and other significant morbidities; (2) the therapeutic window for treating health issues such as stroke and myocardial infarction, which are common among the elderly, is very short (less than 5 h); this makes it difficult to systematically test new treatment modalities for these acute conditions; and (3) pharmaceutical companies and clinical researchers have shown minimal interest in performing clinical trials on individuals >55 years old. Nevertheless, it is important that therapeutic approaches be developed for and specifically tested in elderly populations; this will become more socially relevant and important as the proportion of elderly in the population increases in many countries over the next several decades.

Keynote Address by Bernard Jeune

(Southern Denmark University)

Are We Living Both Longer and Better?

During the twentieth and early twenty-first centuries, decreases in human mortality, especially during the first and last decades of life, led to a large increase in human life expectancy. As a consequence, octogenarians, nonagenarians, centenarians and supercentenarians (<110 yrs) are increasing in number and the probability of dying at any specific age is decreasing in many developed countries of the world (Figs. 1 and 2). Long-living centenarians include many more women than men, and super-centenarians are almost exclusively female non-obese nonsmokers. However, it is important to ask whether we (on average) are not only living longer, but whether we are also living better. Does decreased mortality come with an increased proportion of individuals or an increased proportion of late-life years living with disability and morbidity? In contrast, current data suggest that the trend is toward successful and healthy aging with somewhat decreased morbidity. For example, studies of self-reported health in Denmark show that women's lives have been extended by 3–4 morbidity-free and disability-free years and men's lives by 2–3 morbidity- and disability-free years over the last two decades, with associated decreases in the number of years living with morbidity and disability. Furthermore, self-reported health statistics also showed that Danish female centenarians born in 1905 were healthier in their late years than Danish female centenarians born in 1895: in particular, the later birth cohort included fewer disabled centenarians and more centenarians capable of independently performing activities of daily living. These encouraging findings among Danish elderly will need to be confirmed in other elderly populations in the future.

Keynote Address by George Martin

(University of Washington, USA)

Nature, Nurture and Chance: their Relative Contributions to intra-Specific versus Inter-specific Variations in Life Span and Health Span

The relative importance of genetic and environmental influences on human life outcomes has been debated extensively, often being described as the *nature vs nurture* debate. In the context of interspecies comparisons, it is clear that species-specific genetic determinants have a much larger influence on life span than environmental determinants. For example, caloric restriction can extend the life span of a mouse by only 1.5- to 2-fold, which is characteristic of the magnitude of life span change due to an environmental factor. On the other hand, the expected life span of a mouse is 1.5–2 years, while the expected life span of a human being is 100–115 years, and this difference likely reflects many genetically encoded differences between the two species. In fact, approximately 200 genetic loci are known to modulate the life span of *Caenorhabditis elegans*, when the worms are grown in the laboratory environment. On the “nurture” side, environmental factors play a significant role in health prognosis and the rate of human aging. George Martin coined the word *gerontogen*, which he defined as a “putative environmental agent that modulates the time of onset and/or the rate of development of specific aspects of the senescent phenotype.” Putative gerontogens include smoking, exposure to UV irradiation, physical trauma, excess food intake and stress, and putative anti-gerontogens include exercise, anti-oxidants, caloric restriction and positive social experience.

Somewhat less often discussed is the stochastic nature of survival and the value and/or significance of chance as a determinant of survival at the cell, individual or population level. In *C. elegans*, the survival of individual genetically identical worms varies significantly, such that some worms carrying the pro-survival allele age-1 live less long than wild type worms lacking this gene. In addition, worms that express high levels of heat shock promoter-driven green fluorescent protein (GFP) reproducibly survive longer than genetically identical low GFP-expressing worms, but this survival advantage is 90% non-heritable. Many characteristics of genetically identical eukaryotic cells also show a range of penetrance, and this variation may have adaptive value when the cell or organism encounters adverse or novel environmental challenges. Mutagenesis in eukaryotic somatic tissue is a well-recognized example of a stochastic phenomenon in human cancer biology. Thus, with the entire genome as a mutagenic target, a mutation can occur in a gene that is essential for viability, a non-essential pseudogene, or a tumor suppressor gene that restricts uncontrolled growth, with dramatically different potential consequences for survival of the mutant cell and its host.

Comparative genomics provides an opportunity to identify species-specific or species-dependent determinants of life span as well as determinants of healthy and unhealthy aging. In this regard, one particularly useful organism is the naked mole rat (*Heterocephalus glaber*), a species that lives approximately 10 times longer than its close relative, the laboratory rat. In fact, the naked mole rat queen often lives for 32 years and continues to be fertile until very near the end of her life span. In contrast, some mutant *C. elegans* display extended longevity and reproductive potential, but only under relatively “protected” laboratory conditions. Continued systematic genomic studies of the naked mole rat, a very unusual

rodent, and other unusually long-lived species or species subpopulations might help elucidate novel mechanisms that contribute to long life span.

Keynote Address by Jan Vijg

(Albert Einstein College of Medicine, USA)

Genome Dynamics in Aging

DNA is intrinsically unstable and highly susceptible to damage from heat, reactive oxygen species and other adverse environmental conditions. In addition, errors introduced during repair of DNA damage leads to a basal rate of spontaneous mutagenesis in living cells. Although the mutability of DNA is an asset, because without the potential for change in the sequence and information content of DNA in the germline, the evolution of species would not be possible, mutations that accumulate in the DNA of somatic cells over time are a putative driver of aging-related cellular and systemic dysfunction in multicellular organisms. Furthermore, accurate assessment of the rate at which mutations accumulate in different species and tissues is important to understanding many biological processes, including aging and carcinogenesis.

Quantitative assays have been developed to measure the basal and induced mutation rates in human cells using the endogenous housekeeping gene encoding *hypoxanthine-guanine phosphoribosyltransferase* (*HGPRT*) or in various tissues in the mouse and fly using a reporter *lacZ* transgene. Using *HGPRT* as a mutation reporter, George Martin and colleagues showed that the mutation rate in proliferating human T cells is approximately 10-fold lower than the mutation rate in human kidney epithelial cells (approximately 10^{-4}). In the living mouse and fly, Vijg showed that mutations accumulate in a *lacZ* reporter transgene in an age- and tissue-dependent manner, with highest rates observed in the small intestine, liver and heart in mice ($1-3 \times 10^{-4}$) and in the abdomen and thorax in flies, and the lowest rates in mouse testis and brain ($<5 \times 10^{-5}$). The average mutation rate was approximately 3-fold higher in flies than in the mouse, and fly mutations included 5- to 6-fold more insertion/deletion events than point mutations, while mouse mutations included nearly equal numbers of insertion/deletions and point mutations. In ongoing work by Vijg and others, massively parallel DNA sequencing technology is being used to characterize genome-wide DNA sequence variation in single cells.

Special Lecture by Thomas Söderqvist

(Medical Museion, University of Copenhagen)

Healthy Aging on the Art-Science/Art-Design Interface

Museum institutions around the world are currently experimenting with modes of communication that exploit the interface between science and art/design. This approach grows out of the idea that science communication grounded in art and design may be a useful tool for increasing public engagement in science. In fact, major science funding agencies as well as scientific institutions themselves are realizing that neither scientific data *per se* nor scientific data disseminated via printed and electronic mass are sufficient

mechanisms for effective science communication. Instead, art and design are essential tools that can and must be leveraged to foster and promote scientific cultural awareness through many social strata, so that the potential of socially, culturally or economically important research findings can be realized and scientific research can flourish. Accordingly, science communication is currently evolving from a didactic to an aesthetic paradigm. The installation *An Aging World*, which welcomed Workshop participants at the opening session, is an example of *Healthy Aging* on the Art-Science-Design interface (see Box 1).

Session 1: Neuroscience and DNA damage—The Workshop session on *Neuroscience and DNA Damage* included presentations by **Jan Hoeijmakers** (Erasmus University, The Netherlands), **Linda Hildegard Bergersen** (Oslo University, Norway) and **Cynthia McMurray** (Mayo Clinic, Rochester, Minnesota, USA).

Jan Hoeijmakers described mouse models for human DNA repair deficiency diseases characterized by progressive neurological dysfunction including *Xeroderma pigmentosum* (XP), Cockayne syndrome (CS) and trichothiodystrophy (TTD). Eleven of the thirteen complementation groups for these three DNA repair deficiency diseases are associated with defects in nucleotide excision repair (NER). Hoeijmakers presented studies on ERCC1-defective mouse strains, that have a more severe phenotype than many other mouse models of XP. ERCC1 forms a heterodimer with XPF (protein corresponding to XP complementation group XPF), a structure-specific DNA endonuclease that is unusual because it plays critical roles in both NER and DNA cross-link repair. *Ercc1* null mice display a severe phenotype in which post-natal neurodegeneration is prominent. In addition, *Ercc1* null mice display kyphosis and osteoporosis, dystonia and ataxia, weight loss, muscle wasting, bone marrow failure, epidermal atrophy, decreased kidney and liver function and premature death at 4 weeks. Interestingly, mice with moderate or mild defects in ERCC1 protein have a correspondingly less severe phenotype and longer life span. Biochemical and genetic studies of other XP complementation groups confirmed the general rule that the severity of the DNA repair defect parallels the severity of the phenotype, including life span and rate of progressive neurological decline. **Hoeijmakers noted that *Ercc1*-defective mice display progressive time-dependent neurodegeneration in the absence of exposure to exogenous DNA damaging agents; this suggests that an endogenous form of DNA damage may play a causal role in pathology in *Ercc1*-deficient mice. This idea is central to one of the current views on the etiology of aging-associated cognitive and neurological decline, and the so-called “free-radical theory of aging.”**

Linda Hildegard Bergersen investigated whether a defect in DNA repair impairs neural stem cell proliferation and neurogenesis in the mouse hippocampus. Previous studies demonstrated that NEIL3, one of several enzymes that carry out the first step in base excision repair (BER) of oxidative DNA damage, is selectively expressed in the subventricular zone and dentate gyrus subregions of the hippocampus, areas associated with neurogenesis and neural development. Bergersen used quantitative confocal immunofluorescence microscopy and quantitative immunogold electron microscopy to quantify neurotransmitter receptor density and synaptic density in inhibitory and excitatory synapses in young and old wild type and NEIL3 knockout mice. The data suggest age-dependent changes in synaptic morphology and function in brains of the mutant animals. In

particular, post synaptic density failed to increase, but expression of NMDA receptor subunits NR1 and NR2A/B, the AMPA receptor subunits GluR1 and GluR2/3, and the GABA_A subunits alpha1 and gamma2 was higher at excitatory and inhibitory synapses within CA1, CA3, and the dentate gyrus in mutant mouse brains. This suggests a compensatory mechanism that maintains neurological function despite synaptic loss in aged mice lacking the NEIL3 gene. Further, the results indicate that **the neural stem cell niche may be especially sensitive to persistent oxidative DNA damage.**

Huntington's disease (HD) is a human disease syndrome characterized by progressive neurodegeneration that occurs at a variable rate and age of onset. For HD patients, disease severity correlates directly with the number of CAG triplet repeats in the coding region of the gene encoding huntingtin, with a threshold for clinical symptoms beginning at 40 CAG repeats. **Cynthia McMurray** presented evidence that trafficking and subcellular localization of huntingtin, membrane-associated lipids and cholesterol are altered in patients with HD, leading to Golgi/ER induced oxidative stress. McMurray also showed that functional BER is required for expression of neuropathology in a mouse model for HD. In particular, knock-out mutation of the *OGG1* gene, encoding 8-oxoguanine glycosylase 1, rescues all disease pathology in a mouse carrying a 150-repeat disease-causing allele of huntingtin. Thus, **McMurray argued that Golgi-ER-induced oxidative stress is central to pathology in HD, but that manifestation of the pathology requires active BER. McMurray's data provides a rationale for the hypersensitivity of post-mitotic neuronal cells to the biological impact of mutant Huntingtin.**

Session 2: Aging and Stress—The Workshop session on *Aging and Stress* included presentations by **Leona Samson** (Massachusetts Institute of Technology, USA), **Tone Tonjum** (Oslo University, Norway), **Gunhild Waldemar** (Rigshospitalet, Denmark) and **Albert Gjedde** (University of Copenhagen, Denmark).

A large body of evidence based on many experimental systems demonstrates that DNA repair pathways mitigate DNA damage-induced processes that lead to cancer and other human diseases. However, as mentioned by Cynthia McMurray in the preceding Workshop session, in some cases, active DNA repair can have adverse consequences at the cellular and organismal levels. In this Workshop session, **Leona Samson** also presented evidence supporting this idea. Samson's studies focused on mammalian 3-methyladenine (Aag) glycosylase, a tumor suppressor protein that initiates BER by incising 3-methyladenine in duplex DNA. Although *Aag*-deficient mice have a normal lifespan and show no increase in susceptibility to spontaneous tumors, *Aag*-deficient mice are highly resistant to alkylating agent-induced degeneration in the retina, bone marrow, thymus and brain. While wild type mice become blind within 2 days of exposure to low dose MMS, *Aag*-deficient animals are completely immune to such damage. Partial protection against MMS-induced blindness is evident in *Aag* hemizygous mice, while 5- to 9-fold overexpression of *Aag* exacerbates MMS-induced degeneration in retinal cells and post-mitotic neurons in the mouse cerebellum. When animals were tested for motor neuron function on a rotarod 3 days after exposure to MMS, *Aag*-overexpressing mice performed significantly less well than wild type or *Aag*-deficient mice. These data show that the toxicity and pathological consequences ensuing from exposure to MMS manifests in an *Aag*-dependent manner in the eye and

cerebellum of the mouse. Interestingly, the level of human Aag and human Ape1 enzyme activity varied 20- and 50-fold, respectively, in lymphocytes from 96 human individuals. This result suggests that **polymorphic variation in expression and/or activity of human BER enzymes could significantly impact disease processes that are initiated by oxidative DNA lesions, and that SNPs in human BER genes could potentially have significant clinical implications.**

Tone Tonjum used an epidemiological approach to examine whether single nucleotide polymorphisms (SNPs) in BER genes modulate cognitive performance and/or cognitive decline during normal brain aging and/or dementia-associated cognitive decline. To test this possibility, the association between non-synonymous SNPs in selected exons in BER genes and cognitive performance was examined in a cohort of 712 normal Norwegian persons aged 20–75 years, using a combined cross-sectional and longitudinal study design. The SNPs selected for this analysis included Apoe4 (a known diagnostic marker for Alzheimer's disease), Pol β _{Pro242Arg}, hOGG1_{Ser326Cys}, MutY_{Val22Met}, MutYGln324His, Ape1_{Gln51His}, Ape1_{Glu148Asn}, XRCC1_{Lys298Asn}, XRCC1_{Leu7Arg}, Neil1_{Asn252Asp}, and Neil2_{Arg257Leu}. Highlighting selected results from this effort, hOGG1_{Ser326Cys} and Ape1_{Gln51His} showed associations with general cognitive function, reasoning, cognitive control and speed of processing in both cross-sectional and longitudinal analyses, with a moderate to large genotype by age interaction in the cross-sectional analysis, and a primary effect on longitudinal decline. Dispersed association effects involving MutY, Pol β , and Neil2 were also detected when Apoe4 or CHRNA4, which were previously proposed to modulate cognitive aging, were included in the statistical model. Comparing normal controls with a cohort of 115 AD patients, significant positive correlations between aging and cognitive performance indicators were observed for hOGG1-Ser326Cys and Ape1Gln51His. Together, **these data support the notion that some polymorphisms in BER genes are independently associated with cognitive performance and/or capacity in normal as well as dementia-affected elderly individuals.** Tonjum is continuing to explore the impact of BER SNPs on susceptibility to and severity of AD and other human dementia syndromes, and whether any BER SNPs may be useful therapeutic targets.

Alzheimer's disease (AD) and other human dementias are prevalent among the elderly and are associated with large emotional, social and financial costs to affected patients, their families and the communities in which the affected individuals live. **Gunhild Waldemar** spoke at this Workshop as an advocate for the importance and value of clinical research on these diseases. Although some treatments are available for AD, there is no cure and there are no effective preventive interventions. Furthermore, despite the availability of molecular and clinical biomarkers for AD, such as amyloid β , hyperphosphorylated tau, neurofibrillary tangles, cerebral atrophy, mild cognitive impairment (MCI), and dementia, the lack of clear diagnostic criteria remains a significant barrier to progress in understanding, treating and preventing AD. Waldemar is participating in two ongoing EU-sponsored collaborative programs designed to help develop such criteria: EDAR and PredictAD. Eleven primary and one affiliated partners are involved in EDAR, whose goal is to characterize genetic and non-genetic factors that modulate accumulation and processing of β -amyloid oligomers and evaluate their potential as clinical markers of AD. **PredictAD is collaborative effort of**

eight EU-based research and industrial partners, whose goal is two-fold: first, to develop a set of validated early diagnostic markers for AD from heterogeneous data sources including neuropsychological tests, brain imaging (MRI, PET), electrophysiological data (TMS/EEG), and protein and metabolomic biomarkers; second, to develop a software algorithm for evidence-based patient diagnosis using the newly developed AD diagnostic criteria. The study has access to four patient cohorts; two small cohorts will be used for analytical training and two larger patient cohorts (ADNI, ~800 cases; Kuopio Longitudinal Study, ~900 cases) will be used for validation of the diagnostic criteria and for evaluation of software algorithms. Waldemar also emphasized the importance of collaboration among research groups who are studying AD and related diseases, a goal that is facilitated by organizations such as the European Alzheimer's Disease Consortium (<http://www.eadc.info>) and the Danish Dementia Research Center (<http://www.videnscenterfordemens.dk>).

It is well known that energy and oxygen requirements of the human brain are high, and insufficient blood flow and/or low supply of oxygen have serious acute consequences on brain function. With regard to chronic human neurological dysfunction, it has been proposed that aging-related changes in brain energy metabolism may contribute to normal brain aging as well as to the accelerated neurological dysfunction associated with Alzheimer's disease (AD). **Albert Gjedde** examined these relationships and possible interactions by measuring blood flow and oxygen consumption in different brain regions in healthy and AD-affected individuals. Age-dependent decline in blood flow and oxygen consumption was observed consistently in the frontal and parietal, but not the occipital lobes of 70 normal individuals. However, the magnitude of this decline was negligible compared to the almost two-fold inter-individual differences in blood flow and oxygen consumption in this population sample. Gjedde proposed that a higher degree of mitochondrial uncoupling in cells in the occipital region could explain lack of age-related decline in oxygen consumption in this brain region. The oxygen extraction fraction (oxygen consumption normalized to rate of blood flow) is approximately 0.4 in all regions of young healthy human brains, increasing only slightly during normal aging. Interestingly, blood flow decreased, but oxygen consumption increased with aging in brains of 5 AD-affected patients. Consequently the oxygen extraction fraction was on average close to 0.6 in these AD patients, significantly higher than in a group of 8 normal controls. **This high oxygen extraction fraction in AD patients is likely associated with increased risk of hypoxic conditions in some brain regions, which could potentially contribute to AD pathology. Gjedde further proposed that high levels of β -amyloid and increased numbers of uncoupled mitochondria may contribute to this phenomenon in AD patients.**

Session 3: Life Course—The Workshop session on *Life Course* included presentations by **Kaare Christensen** (University of Southern Denmark, Denmark) **Boo Johansson** (University of Göteborg, Sweden), **Diana Kuh** (MRC Unit for Lifelong Health and Ageing, London, UK) and **Ian Deary** (University of Edinburgh, Scotland).

The *Life Course* approach to aging research examines the integrated impact of earlier life events on later life outcomes as well as the timing of these outcomes. Frequently examined outcomes include age at death (*i.e.*, life span/longevity), cognitive decline (normal or

disease-associated), specific morbidities (*i.e.*, obesity, high blood pressure) and physical performance indicators that are used to assess life skills in late life (*i.e.*, grip strength, walking speed, and standing balance).

At the start of his Workshop presentation, **Kaare Christensen** expressed his opinion that **the change in mean human life span, which increased from approximately 55 to 85 in Western countries during the early to late 1900s, is the greatest achievement of the twentieth century.** This increase in human longevity reflects the near eradication of infectious-disease related mortality in very early life, as well as increased number of healthy years in later life. Data supporting and consistent with this trend include the fact that the frequency of hospitalization was higher, the number of surgical procedures higher, but the length of hospital stays shorter for a Danish 1905 birth year cohort in later years than for a matched Danish 1895 birth year cohort. However, after stratifying these data by sex, it was evident that longevity increased for females in the 1905 cohort, but did not increase for males in the cohort. Furthermore, a similar sex-biased increase in longevity was observed in female American-born but not male American-born centenarians. The reason for this sex bias is not yet known, but could reflect higher tobacco-use and associated cancer deaths in males than females. Christensen also discussed studies of a large group of Danish twin pairs and long-lived Danish families, which have the potential to reveal the genetic determinants of longevity. Although genetic factors are thought to contribute no more than 25% to variation in human lifespan, it is thought that environmental factors may play a much larger role. Accordingly, Christensen observed that age-related traits such as grip strength and cognitive abilities in later years correlate not only in frequency but in approximate rate/age of decline among both monozygotic and dizygotic twins. Interestingly, Christensen's studies also show that even after data are controlled for actual chronological age, **estimates of perceived age are strong predictors of actual time-to-death.**

As a framework for understanding the large interindividual variation in rate of cognitive aging, **Boo Johansson** suggested that aging can be subdivided into primary, secondary and tertiary aging subtypes. Primary aging is characterized by decreased mental speed and loss of capacity for memory and fluid cognitive abilities, secondary aging is associated with compromised health and loss of crystallized cognitive abilities, and tertiary aging is associated with proximity to death and pervasive loss of memory as well as loss of fluid and crystallized cognitive capacity. Longitudinal analyses of markers of cognitive decline reveal inflections in the slope known as "change points," where the rate of decline in a specific function increases. These change points are predictive of future dementia from 6 to 15 years before onset of clinical disease. On the other hand, time from death is a better predictor of the overall trajectory of cognitive decline than time from birth. Neuroprotective factors that increase cognitive reserve and therefore counter-balance the risk of cognitive decline have been identified; these include education, mental-stimulating leisure activity, physical activity and social networks. Johansson reported on a study that examined the impact of high body mass index in midlife on verbal and memory cognitive functions in late life. In this study, body mass index (BMI) was measured in a cohort of 430 individuals in their '50 s and cognitive function was tested 5 times over a period of 2 years on the same non-demented individuals 30 years later, when they were in their '80 s. This study suggested that high BMI

in midlife correlated with lower mean cognitive function, but not with faster rate of cognitive decline, in late life for non-demented individuals. Johansson also found evidence for an interaction between APOEε4 and Aβ42 in individuals with mild cognitive impairment, such that a high level of Aβ42 is associated with increased risk of β-amyloid deposits and rapid memory decline in individuals with an APOEε4 genotype. In sum, Johansson indicated that **genetic factors account for a significant amount of inter-individual variability in normal cognitive function, early and late onset dementia and expected life span** (measured as predicted number of years until death). **This variability is further influenced by environmental risk and neuroprotective factors, some of which may interact with each other and/or with genetic factors.**

There is growing evidence that social and biological factors throughout the life span have a significant impact later in life on physical, cognitive and cardiovascular function. Extensive longitudinal studies described at this Workshop by **Diana Kuh** and **Ian Deary** are among the most ambitious efforts to date to analyze these relationships using large birth cohorts. Kuh is helping to develop the MRC National Survey of Health Development (NSHD) into a world class interdisciplinary life course study on aging (www.nshd.mrc.ac.uk). The NSHD is an ongoing study of 5362 men and women born in one week in March 1946. The NSHD has collected and is continuing to collect a large diverse body of data on these individuals from birth to death. Furthermore, this cohort is one of nine UK cohort studies included in a research program on healthy aging across the life course (HALCyon, www.halcyon.ac.uk). Kuh's main emphasis at present is discovery of factors that influence cardiovascular health and physical performance indicators in late life. **Ian Deary** is involved in long-term longitudinal studies of two Scottish birth cohorts, the Lothian Birth Cohorts of 1921 (550 individuals) and 1936 (1091 individuals), with a primary focus on life course effects on cognitive aging. Deary is collecting and analyzing multifactorial datasets on these large cohorts throughout the life course. Data collected include incidence of candidate genes and biomarker, brain imaging, diet and lifestyle choices, childhood intelligence, social class in all life stages, education and other social factors.

Session 4: Environmental Factors & Neuroscience—The Workshop session on *Environmental Factors and Neuroscience* included presentations by **Kaarin Anstey** (Australian National University), Kenneth Howse (University of Oxford, UK), **Mats Harms-Ringdahl** (Stockholm University, Sweden) **Barry Halliwell** (National University of Singapore), **Hartwig Siebner** (Hvidovre Hospital, Denmark) and Lihua Pang (Peking University, China).

Kaarin Anstey recently proposed that subtle cognitive decline in mid-life, a period when cognitive function is usually stable or increasing, correlates with and could be used as a predictive indicator of late life dementia. Anstey is testing this idea, as well as other risk factors and indicators of late life cognitive decline, in the PATH Through Life Project, a longitudinal study of three cohorts of Australian citizens aged 20–24, 40–44, and 60–64 yrs old at the start of the study. Study participants will be monitored at 8-year intervals. Initial data is currently being processed and analyzed.

Kenneth Howse discussed the health policy and socio-political challenges associated with the increasing mean age of human populations. Howse pointed out that **the aging of the population is likely to increase overall health care need and health care cost, increase the ratio of dependent/independent individuals in a society, thus lowering economic output, change the ratio of investment/consumer spending, and change the demographics and priorities of the electorate in democratic societies.** The challenges are both technocratic (*i.e.*, how to prevent and treat age-associated disease and improve old-age quality of life) and non-technocratic (*i.e.*, prioritize spending and choose how to distribute limited resources). In order to effectively address these challenges, the goals of the health care system will need to be defined (or redefined) to fit the current social scenario. **One of the largest non-technocratic challenges could be to reach consensus on how to balance competing medical, social and economic needs and priorities in a society with new and continuously changing demographics.**

Mats Harms-Ringdahl described cell-based studies on the non-cancer biological effects of low dose/low dose rate γ -irradiation using premature senescence as an endpoint. Unfortunately, epidemiological studies lack sufficient sensitivity to document the cancer and non-cancer dose-response curves following exposures below 100 mSv. Therefore, human fibroblasts were exposed to Cs137 radiation in the range 1–15 mGy per hour, yielding exposures $\approx 10,000$ -fold higher than ambient background radiation. Under these experimental conditions, it was estimated that 1 extra DNA double-strand was induced per irradiated cell every 10 h. Proliferation rates and gene expression analyses showed that **biomarkers of cellular senescence, including senescence-associated β -galactosidase, p53, p21 and p16, were induced at earlier time points in irradiated than in unirradiated control cells.** The results showed that 29 of 40 genes were common to the gene expression signatures associated with premature and normal senescence. **Harms-Ringdahl proposed that low dose radiation induces cellular senescence by a non-genotoxic mechanism involving oxidative stress.**

Barry Halliwell's previous studies led to seminal contributions in the fields of oxygen free radical metabolism, antioxidant biology, and models of neurodegenerative disease and aging. In his presentation at the Workshop, Halliwell discussed opportunities and pitfalls in using *Caenorhabditis elegans* as a model system to study the effect of endogenous and dietary antioxidants on longevity and/or aging-related dysfunction. In this context, Halliwell pointed out that, with a few exceptions, **the rate at which aging proceeds is directly correlated with overall metabolic rate, such that animal species with a relatively fast metabolism, such as rats and flies, have a relatively short lifespan.** A corollary of this fact is that agents that interfere with or slow metabolic rate, such as cold temperature, appear to increase animal life span, an artifact that must be kept in mind when screening anti-oxidant compounds for anti-aging effects in animal model systems. Another consideration is the well-recognized fact that **dietary restriction (*i.e.*, reduced calorie intake) increases life span. While this is an interesting and significant result in and of itself, this phenomenon can confound efforts to identify orally dosed compounds that have anti-aging or anti-oxidant properties;** if a compound that tastes bad is put in animals daily food ration, the animals ad-lib food intake is likely to decrease, which could inadvertently increase longevity. Lastly,

when life span experiments are performed in the laboratory environment, statistical power, careful data collection and objective data evaluation are critical. To ensure reliability and validity of the results, experimental protocols must include blinded data collection. Using a *C. elegans* model, **Halliwell recently identified six of 35 extracts of plants used in traditional Chinese medicine that prolong life span in a dose-dependent manner and protect against paraquat-induced premature death.** However, the mechanism of the effect of these extracts on nematode life span remains unknown and is under investigation. **Hartwig Siebner** presented preliminary efforts to use functional MRI brain imaging to monitor real-time brain activity and analyze cognitive function in humans. While Halliwell's and Siebner's studies describe experimental approaches with significant potential, these approaches also present many pitfalls, and appropriate controls must be carried out to identify and correct for artifacts leading to inappropriate or unjustified conclusions.

Lihua Pang (on behalf of Xiaoying Zheng) reported on the life expectancy and probability of survival of approximately 24,000 Chinese persons with disability (PWD) during the period 2006–2010, a representative sample of the estimated 83 million PWD living in China in 2006. Data were obtained from an extensive national survey on disability conducted in 2006 as well as annual follow-up surveys in 2007–2010. Recorded death statistics were used to construct life tables and measure life expectancy of PWDs for each annual time interval. **The results showed that life expectancy was dramatically lower for disabled individuals than for the general population and was modulated by gender, urban-rural residence, disability severity and marital status. Probability of survival of PWD was modulated by type and severity of disability, but not by gender or urban/rural residence.** Notably, there was a strong negative relationship between life expectancy and disability severity: persons with mild, moderate and severe disabilities had life expectancies of 64.2, 59.8 and 40.5 years, respectively. Furthermore, PWDs have a much shorter life expectancy than the general population. Future studies will examine the influence of disability type and other risk factors on mortality of PWDs.

Session 5: Muscle and Life Span—The Workshop session on *Muscle and Life Span* included presentations by **Stefano Schiaffino** (Venetian Institute of Molecular Medicine, Padova, Italy) **K. Sreekumaran Nair** (Mayo Clinic, Minnesota, USA) and **Julia Twigg** (University of Kent, UK).

Functional decline of skeletal muscle, a central feature of normal aging, can occur as a direct result of time-dependent progressive change within the muscle itself, or can be secondary to neurodegenerative changes in the brain and spinal cord, loss of neural control, or altered musculoskeletal mechanics. Throughout the life course, muscle mass is determined by the relative rates of muscle protein synthesis and degradation (protein turnover) and the relative rates of addition and loss of myonuclei in multinucleate muscle cells (cell turnover). The master transcriptional regulatory protein FOXO3A positively regulates muscle protein degradation by both the autophagic/lysosomal and the ubiquitin/proteasomal pathways. **Stefano Schiaffino** demonstrated that muscle atrophy is induced in muscle cells transfected with constitutively active FOXO3A and that autophagy-deficient *Atg7* muscle-specific knockout mice demonstrate muscle atrophy, decreased myofiber size and reduced absolute and normalized muscle force. Schiaffino proposed that **autophagy is essential for**

maintaining muscle protein quantity and quality and muscle function in all life stages, that defects in autophagy could contribute to age-related muscle dysfunction, and that dietary restriction might enhance longevity at least in part by stimulating autophagy and muscle tissue renewal.

K. Sreekumaran Nair presented additional data in support of the hypothesis that **increased protein turnover protects human muscle and other cells against time-dependent accumulation of dysfunctional proteins, many of which could contribute to aging-related pathology.** For example, Nair showed that the rate of depletion/degradation of isotope-labeled proteins decreased progressively in humans with age, and that oxidative modifications (*i.e.*, carbonylation, allyl-lysine) accumulate in human proteins over time. Nair further proposed that an age-dependent decrease in protein turnover reflects a general decline in efficiency of energy-intensive metabolic processes, including both protein synthesis and protein degradation. Consistent with this, mitochondrial efficiency (based on ATP production) and mitochondrial DNA copy number decrease and the level of 8-oxoguanine in mtDNA increases with human age.

Julia Twigg discussed the interplay of socio-cultural and biological/physiological factors in the process of aging, drawing on a recent trend in social sciences, arts and humanities to examine the body in a conceptual rather than physical/physiological manner. These studies point to an opportunity to re-examine how we think and feel about our bodies as we age. As an example of the premise that age is socially and culturally constituted, Twigg described how clothes are the embodiment of social structure, pointing out that established age-appropriate patterns of dress reflect ideological patterning about aging within a culture. **Twigg argued that changes in perception about aging are both possible and already in progress, and that such changes could help older individuals maintain more positive, active and more colorful lives.**

Session 6: Life Span and Mechanisms—The Workshop session on *Life Span and Mechanisms* included presentations by **Rudi Westendorp** (Leiden University Medical Center, The Netherlands), **Keshav Singh** (Roswell Park Cancer Institute, NY, USA) **Niels de Wind** (Leiden University Medical Center, The Netherlands), **Vladimir Canudas-Romo** (University of Copenhagen) and **Hiroko Akiyama** (University of Tokyo, Japan).

Evolutionary theory supports the argument that biological programs for development and fertility, which have strong implications for Darwinian fitness, are under tight genetic control. In contrast, late-acting deleterious genetic traits are not associated with decreased life span, suggesting that **genetic determinants of age-related functional decline may not be disadvantageous from a fitness perspective per se.** However, there is evidence that **fertility and lifespan are competing evolutionary priorities, such that greater longevity is incompatible with greater fertility, from a biological/physiological and evolutionary perspective** (a concept originally proposed by Kirkwood in 1977). **Rudi Westendorp** presented evidence in support of this idea, showing that longevity is associated with lower insulin signaling and higher insulin sensitivity in worms and humans, and that selection for a pro-inflammatory host response in early life has strong potential to enhance aging-associated disease processes in late life.

Nuclear genetic and/or epigenetic changes are considered obligatory steps in carcinogenesis, with endogenous and exogenous DNA damage being the most commonly presumed driver of cancer-associated genetic change. **Keshav Singh** presented evidence for the hypothesis that **mitochondrial dysfunction can also act as a driver of nuclear genetic instability, leading to both cancer and premature aging**. This novel proposal for mitochondrial-nuclear cross-talk during aging and carcinogenesis was tested and confirmed in mouse models and human cell-based systems. Singh showed that mtDNA depletion is common in human breast cancers carrying mutations in mitochondrial polymerase γ , mtDNA-depleted human cells form xenograft tumors efficiently, while control cells carrying intact mtDNA do not, and cultured cells with defects in mtDNA maintenance acquire nuclear genetic and epigenetic changes. Singh also presented evidence for genetic control of this process. **These data suggest that cells may express a genetically encoded pathway for response to mitochondrial stress, for which Singh proposed the term “mito-checkpoint.”**

The DNA damage theory of aging proposes that endogenous oxidative lesions that accumulate over time in post-mitotic and proliferating cells disrupt normal cellular and physiological functions by interfering with transcription and/or DNA replication. **Niels de Wind** confirmed this hypothesis by characterizing **$Xpc^{-/-}Rev1^{-/-}$ double knockout mice, which are deficient in both nucleotide excision repair and DNA damage tolerance. In contrast to the mild phenotype of $Xpc^{-/-}$ or $Rev1^{-/-}$ single mutant mice, the double knockout mice demonstrate a stochastic premature aging phenotype as well as short life span, bone marrow atrophy, loss of subcutaneous fat, loss of B cells and high rate of latent $CD4^{+}/CD8^{+}$ lymphomas. $Xpc^{-/-}Rev1^{-/-}$ cells accumulate spontaneous γ -H2AX foci, are hypersensitive to paraquat-induced DNA damage and show increased replication stress in response to oxidative DNA damage (*i.e.*, lipid peroxidation-DNA adducts).**

Life expectancy at birth, and the median and modal ages at death are indicators of the overall longevity within a specific population sample. **Vladimir Canudas-Romo** summarized studies of these parameters in human populations over the last 150 years. The studies show that life expectancy steadily increased from 44 years in Sweden in 1840 to 82 years in Japan in 2005. Median age at death also increased steadily over the same time period. The trend in both parameters reflects dramatic decreases in infant and early childhood mortality during the first half of the twentieth century. In contrast, **the modal age at death increased slowly until approximately 1950, after which it increased somewhat more rapidly from approximately age 80 to age 90 in 2005. This trend reflects relatively recent progress in reducing adult mortality.**

Hiroko Akiyama analyzed gender-specific factors that could contribute to the difference in life expectancy of Japanese men and women, which is 79.29 and 86.44 years, respectively. Data for the analysis were obtained from the Well-being of Japanese Elderly study ($N=5715$ Japanese > 60 years old), collected by survey instruments every third year from 1987 to 2007. Outcome measures examined in the study included level of disability and survival. Diet, exercise, social economic status and access to medical care were considered to be gender neutral in this study. **Female-specific protective factors included high self-esteem and an internal locus of control, while the sole male-specific protective factor was social activity. Male-specific risk factors included loneliness, poor relationship with spouse or**

family and smoking, and the sole female-specific risk factor was depression. Akiyama recommended a life course approach to better understand gender-specific issues relevant to healthy aging.

Sessions 7 and 8: Copenhagen Center for Healthy Aging: Current

Research Highlights: CEHA, the Copenhagen Center for Healthy Aging, was established in 2009 as part of the IARU aging research initiative. CEHA is a multidisciplinary research program whose goals are to improve quality of human health and life throughout the life course through research to improve understanding of human aging. CEHA research is focused in five research programs: Molecular Aging and Neurobiology, Muscle Metabolism, Body and Life, Society and Culture and Health Promotion and Innovation. Highlights of CEHA research were described in the two final sessions of the Workshop. Questions being addressed by CEHA researchers include the following:

Lene Juel Rasmussen: Lene Juel Rasmussen is analyzing the role of mitochondria in normal and dysfunctional human aging. Her studies are examining possible cross-talk between the mitochondrial and nuclear compartments, and how ATP production, nucleotide pool balance, and BER are altered in cells lacking mitochondrial DNA. The studies show that mitochondrial dysfunction generates complex genetic instability in the nucleus, which could affect the aging process.

Lene Otto: Lene Otto is exploring the definition of physiological ‘normality’ in later human life stages and the role of cultural expectations and social provisions in human aging. Otto’s research asks: How do people’s views of their bodies and life experiences change over time; How can health promotion activities enable individuals to remain healthy, active and independent in late life; and how can innovative technology be developed and leveraged in order to enhance general well-being in the elderly population. The overall goals are to improve health and quality of life for the elderly and reduce publically supported expenditure on behalf of this population subgroup.

Erik Lykke Mortensen: Cognitive decline during late life represents a significant public health concern and burden. Medical and social management of individuals afflicted by cognitive decline would likely improve, if reliable mid-life predictors of late life cognitive decline were available. To address this problem, Erik Lykke Mortensen is conducting extensive longitudinal studies of cognitive performance from age 50 to 90 in the Danish Glostrup 1914 birth cohort.

Kirsten Avlund: Frailty is a symptom of aging characterized by decreased mobility, altered gait, muscle weakness, poor exercise tolerance and sarcopenia. Studies suggest that fatigue may be useful as a self-reported indicator of frailty. Kirsten Avlund is studying how social, biological and mental factors influence onset of fatigue during the life course. Avlund’s research is focused on the biological and cognitive processes underlying fatigue, and the relationship between empirical indicators and the subjective experience of fatigue.

Avlund is also leading efforts to collect and analyze data for the Copenhagen Aging and Midlife Biobank (CAMB), a biological and cognitive database for subsamples of the

Metropolit Study (born 1953), the Copenhagen Perinatal Cohort (born 1959–61) and the Danish Longitudinal Study on Work, Unemployment and Health (born 1949, 1959). The data collection phase for CAMB extended from 2009 to 2011 and included cognitive testing, administration of questionnaires and blood sampling. Physical tests include measurements of height, weight, fat percentage, blood pressure, spirometry, muscle strength, maximum muscle force, flexibility, balance, chair-rise test, and reaction time. Blood samples were analyzed immediately or were stored in the Biobank for future use.

Allan Krasnik: Allan Krasnik is interested in the role of health policy and biomedical technology in managing and promoting healthy aging. Krasnik's studies are exploring the social and moral dimensions of preventive medication. Research goals of these studies are: understanding of the role of long-term preventive medication in healthy aging; analyzing coordination of preventive interventions by health care providers and consumers; evaluating equitable and fair policy related to preventive drug interventions with an impact on healthy aging.

Flemming Dela: Flemming Dela is studying changes in muscle energy metabolism associated with aging and chronic disease. Dela's studies are exploring the hypothesis that physical inactivity causes loss of motor function, decreased muscle performance and reduced capacity for tissue regeneration, leading to metabolic and energetic dysfunction. Dela also hypothesized a link between insulin resistance and frailty. Dela's recent studies analyzed mitochondrial respiratory capacity in biopsies of skeletal muscle and insulin sensitivity in individuals with or without type 2 diabetes. The results demonstrate that mitochondrial respiration in the skeletal muscle of diabetics is normal; however, the number of mitochondria is significantly reduced in type 2 diabetics, leading to lower oxidative phosphorylation and reduced electron transport capacity. Thus, mitochondrial dysfunction is not linked to insulin resistance in type 2 diabetics.

Michael Kjaer: Collagen is a key player in adaptation of the skeletal muscle matrix to exercise. Collagen biosynthesis and/or structure may also play a role in aging-related muscle dysfunction. Michael Kjaer conducted studies on age-dependent changes in collagen biosynthesis and structure and its relationship to biomechanical properties of tendons, which have higher collagen content than muscle. The results indicate that basal and exercise-stimulated rate of collagen synthesis is similar in young and old tendon, and that old tendon has lower collagen content, but a higher number of enzymatic and non-enzymatic collagen cross-links. This high cross-link content may help maintain the mechanical properties of tendons in older individuals.

Martin Lauritzen: Martin Lauritzen is interested in regulation of oxygen metabolism in the brain during periods of cognitive function. This process is being studied in humans, by conducting neuroimaging, neurological function and odontology tests in an ongoing clinical study ($N=210$; data collection 2010–2012), and by conducting two-photon in vivo imaging of brains of normal young mice, normal old mice and mice with accelerated aging (mouse model of Cockayne syndrome). Electrophysiological and Ca^{2+} imaging techniques are being used to evaluate cerebral blood flow and oxygen metabolism. Initial data show that blockade

of Ca^{2+} signaling in neurons does not impact cerebral oxygen metabolism in the brain of normal adult mice. Future studies will use this model system to examine the possible effect of age-dependent changes in calcium homeostasis on neural function.

Ian D. Hickson: Ian Hickson recently moved his lab from the University of Oxford Cancer Center in the UK to CEHA. In the context of CEHA, Hickson will extend his research on the roles of DNA helicases and BER enzymes in preventing genetic instability in eukaryotic cells. Among other projects, Hickson intends to investigate the association between neurodegeneration and defects in putative DNA repair enzymes aprataxin and senataxin. Mutations in the genes encoding aprataxin and senataxin are linked to autosomal recessive human diseases ataxia oculomotor apraxia 1 (AOA1) and AOA2, respectively. AOA1 and AOA2 are characterized by progressive cerebellar degeneration, ataxia, peripheral neuropathy and oculomotor apraxia. Aprataxin and sentaxin are poorly characterized enzymes that may play roles in mitochondrial and/or nuclear DNA metabolism. Senataxin is a putative DNA/RNA helicase.

Vilhelm Bohr (National Institutes of Health, USA): Vilhelm Bohr and his colleagues at the National Institute of Aging (National Institutes of Health, USA) have extensive collaborative interactions with CEHA researchers. Glutamate is the major neurotransmitter in the central nervous system. Aberrant regulation of glutamate is associated with age-related neurodegenerative diseases, and synaptic glutamate plays a role in learning and the response to physical exercise. Interestingly, high physiological levels of glutamate can cause oxidative DNA damage leading to cell death, by a mechanism involving Ca^{2+} -dependent increases in mitochondrial ROS. Bohr's recent studies show that glutamate induced DNA damage is efficiently repaired in neurons, and that low levels of glutamate induce AP endonuclease, a major BER protein, but not other enzymes in the BER pathway. Furthermore, low levels of glutamate stimulate phosphorylation of the transcription factor CREB, which positively regulates expression of APE1. These results suggest a novel mechanism by which BER is regulated in neuronal tissue, which may have important consequences for understanding disease- and aging-related neurodegeneration.

Perspectives: critical future challenges in aging research: As the demographics of human populations change and the mean population age increases over time, the goals and most pressing problems for aging researchers will also change and evolve. Participants at the IARU Congress spoke of several specific future challenges and emphasized use of a multi-faceted interdisciplinary approach to address these challenges. It will be important to develop therapeutic interventions tailored for and specifically tested in elderly populations and to continue to ask whether increased longevity (on average) enhances the *quality* of a human life while increasing its length. Another important technical challenge is to continue to improve our ability to understand human biology at the level of a single human cell and to develop cost-effective efficient methods for sequencing each human being's unique genome. This is important because it will make it possible to identify loci and mutations that drive aging-related cellular and systemic dysfunction and reveal molecular mechanisms of aging and carcinogenesis. Lastly, one of the largest non-technocratic challenges of living in an aging human society could be reaching consensus on how to allocate limited resources to

meet the competing medical, social and economic needs and priorities of different age groups in the population.

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Box 1**An Aging World**

An Aging World is an installation on the *Science-Art-Design* interface that was produced for the Center for Healthy Aging, University of Copenhagen by the University of Copenhagen Medical Museion to mark the opening and ongoing activities of the IARU Congress *Aging, Longevity and Health* at the University of Copenhagen, 5–7 October 2010.

Medical Museion is an academic unit of the Faculty of Health Sciences at the University of Copenhagen, which curates collections and exhibitions concerned with medical history and information using a design- and art-oriented approach. As such, the Medical Museion considers the history of health and disease in a cultural perspective, with focus on the material and iconographic culture of recent biomedicine. As a contribution to the opening and ongoing IARU Congress, Thomas Söderqvist and Bente Vinge Pedersen of the Medical Museion faculty installed and opened the sculpture entitled *An Aging World* at the Panum Building (pictured below), University of Copenhagen, where the opening session of the IARU Congress was held. This installation is an example of the work of the Medical Museion, which has established its prominence in leading thought and activity at the Art-Science Art-Design Interface. The exhibit grew out of a successful 2007–2008 exhibit entitled *Oldetopia* at the Medical Museion, which was in turn inspired by the late 1920s *Vienna Method of Pictorial Statistics* pioneered by Otto Neurath, founding Director of the Social and Economic Museum of Vienna.

An Aging World is based on charts and data from *World Population Ageing: 1950–2050* (United Nations 2002; www.un.org/esa/population/publications/worldageing19502050), a report prepared by the United Nations Population Division of the Economic and Social Affairs Department as a contribution to the 2002 World Assembly on Aging. The report describes global population trends, and includes a section focused on age demographics. Comparable data from the current release of the UN report (*World Population Ageing: 1950–2050*; United Nations 2009) is summarized in Figs. 1 and 2 of this report (reprinted with permission from the United Nations). Credits for *An Aging World* are as follows: Concept development: Thomas Söderqvist and Bente Vinge Pedersen, Medical Museion, University of Copenhagen; Architect: Mikael Thorsted, Studio 8; Graphics: Lars Møller Nielsen, Studio 8; Production: Exponent Stougaard A/S; © Medical Museion 2010.

Box 2**Key Discussion Points and Future Aging Research Directions****Neurobiology, Brain Pathology and Aging-associated Degenerative Disease**

- ERCC1-defective mice display progressive time-dependent neurodegeneration in the absence of exposure to exogenous DNA damaging agents, suggesting that an endogenous form of DNA damage may play a causal role in aging-related neuropathology in this model system.
- A compensatory mechanism maintains neurological function despite synaptic loss in aged mice lacking the NEIL3 gene, and the neural stem cell niche may be especially sensitive to persistent oxidative DNA damage in these animals.
- Xpc^{-/-} Rev1^{-/-} double knockout mice demonstrate stochastic premature aging phenotype as well as short life span, bone marrow atrophy, loss of subcutaneous fat, loss of B cells and high rate of latent CD4⁺/CD8⁺ lymphomas.
- PredictAD is collaborative effort of eight EU-based research and industrial partners, whose goal is two-fold: to develop a set of validated early diagnostic biomarkers for AD from heterogeneous data sources; and to develop a software algorithm based on validated biomarkers for evidence-based patient diagnosis.
- High oxygen extraction fraction in brains of patients with AD could increase risk of hypoxic conditions in some brain regions, which could potentially contribute to AD pathology.

DNA Repair, Aging and Stress

- Polymorphic variation in expression and/or activity of human BER enzymes could significantly impact disease processes that are initiated by oxidative DNA lesions, suggesting that SNPs in human BER genes could have significant clinical implications.
- Polymorphisms in BER genes are associated with cognitive performance/capacity in normal & dementia-affected elderly individuals.
- *Caenorhabditis elegans* is a useful model system for analyzing the effect of endogenous and dietary anti-oxidants on longevity and/or aging-related dysfunction, if applied with appropriate controls.
- Low dose radiation induces cellular senescence by a non-genotoxic mechanism involving oxidative stress.

- Golgi-ER-induced oxidative stress may promote neuropathology in Huntington's disease, but manifestation of the pathology requires a functional and active BER pathway.
- Interspecies comparisons suggest that species-specific genetic determinants have a larger influence on lifespan than environmental determinants. Nevertheless, smoking, UV irradiation, physical trauma, excess food intake and stress are probable pro-aging "gerontogens", while exercise, antioxidants, caloric restriction & positive social experience are probable "anti-gerontogens."

Muscles, Mitochondria and Bioenergetics

- Autophagy is essential for maintaining muscle protein quantity and quality and muscle function in all life stages, and defects in autophagy could contribute to age-related muscle dysfunction.
- Increased protein turnover protects human muscle and other cells against time-dependent accumulation of dysfunctional proteins, many of which could contribute to aging-related pathology.
- Mitochondrial dysfunction can act as a driver of nuclear genetic instability, leading to both cancer and premature aging.

Life Course/Life Style/Sociocultural Aspects of Aging

- Mean human life span increased from approximately 55 to 85 years in Western countries during the 1900s, one of the great achievements of the twentieth century.
- The modal age at death increased slowly until approximately 1950, after which it increased somewhat more rapidly from approximately age 80 to age 90 in 2005. This trend reflects relatively recent progress in reducing adult mortality.
- Fertility and lifespan are competing evolutionary priorities in many mammalian species, such that greater longevity is incompatible with greater fertility, from a biological, physiological and evolutionary perspective.
- Perceived age is a strong predictor of time to death, even after chronological age is taken into account.
- Changes in perception about aging are both possible and already in progress, and such changes could help older individuals maintain more positive, active and more colorful lives.
- Genetic factors account for a significant amount of inter-individual variability in normal cognitive function, early and late onset dementia and predicted longevity (*i.e.*, estimated years until death). This variability is further influenced by environmental risk, stochastic events

- and neuroprotective factors, some of which may interact with each other and/or with genetic factors.
- Preliminary results suggest that cancer, diabetes, and stroke (poorly modifiable medical conditions) and low exercise (a readily modifiable life style factor) had small, non-pervasive but statistically reliable effects on cognitive performance in mid-life.

Future Directions in Aging Research

- Therapeutic approaches specifically designed for & tested in elderly populations are urgently needed, and will become more socially relevant and important as the proportion of elderly in the population increases in many countries over the next several decades.
- It is important to ask whether we (on average) are not only living longer, but whether we are also living better. Does decreased mortality come with an increased proportion of individuals or an increased proportion of late-life years living with disability and morbidity?
- One of the largest non-technocratic challenges of an aging society could be deciding how to allocate limited resources to meet the competing medical, social and economic needs and priorities of different age groups in the population.
- Mutations that accumulate in the DNA of somatic cells over time are a putative driver of aging-related cellular and systemic dysfunction in multicellular organisms, and accurate assessment of the rate at which mutations accumulate in different species and tissues is important to understanding many biological processes, including aging and carcinogenesis. To this end, massively parallel DNA sequencing technology is being used to characterize genome-wide DNA sequence variation at single cell resolution.

Fig. 1. Population age demographics in rural and urban populations in 1975 and 2005

Age diagrams provide a pictorial description of population age demographics. Here, data is stratified by urban/rural social structure (upper/lower panels), country economic development status (left/right panels), sex (left/right category axis), and age bracket (value axis) at two snapshots in time, 1975 and 2005. Graphs are based on data collected and reported by the United Nations Population Division in 2009.

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Fig. 2. Past and projected percentage of the world population 60 years old

Percent total population 60 years old at 3 past and 2 projected future dates in world, more developed or less developed countries. See cited reference for list of countries stratified by development status.

Adapted with permission from United Nations *World Population Ageing 2009*; <<http://www.un.org/esa/population/publications/WPA2009/WPA2009-report.pdf>>.