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Aging—From molecules to populations

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Abstract

The mean age of the human population is steadily increasing in many areas around the globe, a phenomenon with large social, political, economic and biological/medical implications. Inevitably, this phenomenon is stimulating great interest in understanding and potentially modulating the process of human aging. To foster interactions and collaboration between diverse scientists interested in the biochemical, physiological, epidemiological and psychosocial aspects of aging, The University of Copenhagen Faculty of Health Sciences recently organized and co-sponsored a workshop entitled *Aging—From Molecules to Populations*. The following questions about human

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☆The Workshop, *Aging—From Molecules to Populations* 12–14 May, 2008 at Hotel Marienlyst, Elsinore, Denmark, was organized 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, University of Aarhus and the Danish Aging Research Center. The Workshop Steering Committee included Ulla Wewer, Dean at the Faculty of Health Sciences, University of Copenhagen, Vilhelm Bohr, National Institute on Aging, NIH, USA, Kirsten Avlund, Department of Public Health, University of Copenhagen, Martin Lauritzen, Department of Neuroscience and Pharmacology, University of Copenhagen, Tinna Stevnsner, Department of Molecular Biology, University of Aarhus and Tina Gottlieb, Faculty Secretariat, Faculty of Health Sciences, University of Copenhagen. Kirsten Avlund and Vilhelm Bohr were Co-Chairs of the Workshop.

aging were discussed at the workshop: What is the limit of human life expectancy? What are the key indicators of human aging? What are the key drivers of human aging? Which genes have the greatest impact on human aging? How similar is aging-related cognitive decline to pathological cognitive decline associated with neurological disease? Are human progeria diseases, characterized by premature aging, good models for “normal” human aging? Is delayed or “elite” aging informative about “normal” human aging? To what extent and by what mechanisms do early life environmental factors influence aging-associated physical and cognitive decline? To what extent and by what mechanism does the social environment influence life course outcomes? What physiological factors underlie the timing and extent of aging-associated physical and cognitive decline? How do cultural stereotypes and perceptions of aging influence the process and experience of aging? One of the primary outcomes of the workshop was a recognition that cross-disciplinary studies and “out-of-the-box” approaches, especially those that adopt an integrated life course perspective on human health status, are needed to expedite advances in aging research. This and other outcomes of the workshop are summarized and discussed in this report.

Keywords

Lifespan; Life course; Proteosome; Cognitive decline; Elite aging; Alzheimer’s disease

1. Executive summary

1.1. Overview

The mean age of the human population is steadily increasing in many areas around the globe, a phenomenon with large social, political, economic and biological/medical implications. Inevitably, this phenomenon is stimulating great interest in understanding and potentially modulating the process of human aging. As a consequence, aging research has become a major focus of a large number of biomedical and social scientists in universities and institutes in countries that are affected by this trend. Aging research spans many different disciplines and is likely to benefit from cross-disciplinary studies as well as “out-of-the-box” approaches, especially those that adopt an integrated life course perspective on health outcomes. To foster interactions and collaboration between diverse scientific groups who are interested in the aging process, The University of Copenhagen Faculty of Health Sciences, in conjunction with the International Alliance of Research Universities (IARU), recently organized and co-sponsored a workshop entitled *Aging—From Molecules to Populations*. The following document summarizes the highlights of this workshop.

1.2. Introduction

Human aging is a complex process influenced by multiple interacting factors including genetics, biology, and behavior as well as physical, social and cultural aspects of the human environment. Symptoms of normal aging can include a state of increased vulnerability to stress and general loss of physiological homeostasis. However, there is large inter-individual variation in the rate and nature of aging-associated disease and dysfunction. Both global and local patterns of human longevity and aging have changed dramatically over the past 400 years, and are likely to continue to change in the immediate future. Thus, patterns and

kinetics of aging observed in one population at one period in time may not be observed in a different contemporary population or at another period of time.

The following questions about human aging were discussed at this workshop: What is the limit of human life expectancy? What are the key indicators of human aging? What are the key drivers of human aging? Which genes have the greatest impact on human aging? How similar is aging-related cognitive decline to pathological cognitive decline associated with neurological disease? Are human progeria diseases, characterized by premature aging, good models for “normal” human aging? Is delayed or “elite” aging informative about “normal” human aging? How do early life environmental factors influence aging-associated physical and cognitive decline? To what extent and by what mechanism does the social environment influence life course outcomes? What physiological factors underlie the timing and extent of aging-associated physical and cognitive decline? How do cultural stereotypes and perceptions of aging influence the process and experience of aging?

These questions, as well as a few answers, were discussed over two days at the Marienlyst, Denmark workshop on *Aging—From Molecules to Populations*. The workshop was unusual, because it brought together diverse scientists with interests in biochemical, physiological, epidemiological and psychosocial aspects of aging, and this led to particularly interesting and stimulating presentations and discussions on the subject of aging.

This workshop was organized as part of a larger IARU initiative on human aging and longevity. IARU is an alliance between ten of the world's leading research universities,² whose goals are to promote “value-added” collaborative international research and to achieve research objectives that could not be achieved by any single member university alone. IARU seeks to promote globally oriented globally responsible international research and a commitment to educating future world leaders to continue a tradition of international cooperation. IARU recently established a research initiative called *Ageing, Longevity and Health* (<http://www.ageing.iaru.ku.dk/>). There are three subtopics within this initiative: Health Policy Challenges of Ageing Populations; Neurodegeneration: The Role of Oxidative Stress, Life Course Issues; and Evolutionary Medicine.

1.3. What are the key drivers of aging in humans?

Speakers at this workshop proposed that protein damage, DNA damage, mitochondrial dysfunction, inflammation and oxidative stress play possible roles in driving age-related disease and dysfunction. These pathways are not mutually exclusive, and different physiological or biological events may drive different age-related processes. Social, economic and behavioral factors at all life stages also influence multiple life course outcomes.

²IARU 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 Australian National University in Canberra and IARU is chaired by Vice-Chancellor, Professor Ian Chubb of ANU.

1.4. Proteasome dysfunction and protein spatial quality control

Accumulation of damaged proteins may be a key factor in cellular senescence and cognitive dysfunction associated with aging-related dementia. Mechanisms that lead to an increased load of aberrant and/or damaged proteins include somatic mutation, proteasome dysfunction, pharmacological intervention, and oxidative stress. Barry Halliwell (National University of Singapore) suggested that proteasome overload and/or dysfunction may be a key step in the pathology of neurological diseases characterized by cognitive deficit (*i.e.*, Alzheimer's Disease (AD), Huntington's Disease, Parkinson's Disease). This may reflect increased oxidative stress and/or inflammatory processes; alternatively aberrant expression of normal or mutant proteins may lead to proteasome overload and proteasome stress (Fig. 1). Thomas Nyström (Göteborg University) suggested that accumulation of oxidized proteins may be a key factor in cellular senescence. Nyström described the process of Protein Spatial Quality Control, which is a Sir2- Hsp104-dependent process that sequesters carbonylated proteins in the mother cell during cytokinesis in *Saccharomyces cerevisiae*. When Protein Spatial Quality Control is inactivated, replicative capacity of mother and daughter cells decreases significantly. A similar process may exist in mammalian cells to protect mammalian organisms from high levels of protein damage in somatic tissue.

1.5. Protein aggregation in human neurological disease

Protein aggregates are a common feature in the brains of patients with AD, Huntington's Disease and Parkinson's Disease. However, previous studies have not clearly indicated whether protein aggregates, in the context of these diseases, are a cause or a symptom of the disease pathology, and the kinetics of appearance of protein aggregates in diseased brains has been insufficiently documented. Ole Petter Ottersen (University of Oslo) reported on recent experiments that address this question using the 3x-Tg-AD mouse model of Alzheimer's Disease. Using immunogold electron microscopy and three-dimensional image reconstruction, Ottersen showed that submicroscopic deposits of β -amyloid colocalize with and appear at approximately the same time as dystrophic neurons, and that the deposits are tightly associated with the plasma membrane domain of large caliber dendrites. This result is consistent with the possibility that deposition of β -amyloid is a trigger leading to AD pathology. Ellen Garde (University College of London), also showed that grey matter atrophy and white matter hyperintensity can be detected in pre-symptomatic patients with familial AD as early as 4 years prior to diagnosis of AD. Additional studies are needed to develop effective pre-clinical diagnostic tools for AD.

1.6. DNA damage, mutagenesis and aging

DNA damage may also drive aging-related processes. Jan Vijg (Buck Institute for Age Research) argued that somatic mutational events could at least in part account for the stochastic nature of aging, as evidenced by the high degree of inter-individual variability in aging-associated phenotypes. Importantly, while proteins are subject to turnover, genes are not, and although DNA damage can be repaired, unrepaired DNA damage frequently generates irreversible somatic mutations. In support of the role of mutagenesis in aging, Vijg showed that fruit flies raised at an elevated temperature have a shortened lifespan, and the average lifespan of fruit flies correlates inversely with mutation rate and temperature. In

addition, Vijg compared the variance in gene expression at the single cell level in young and old mouse cardiomyocytes. The results provide evidence that mutations accumulate in a stochastic manner in gene regulatory regions in mammalian cells over time. This phenomenon could lead to aging-related functional decline.

1.7. Genetic determinants of aging: To what extent is your life expectancy in your genes?

In experimental model systems such as *Caenorhabditis elegans*, it has been shown that genotype can confer up to a 10-fold increase in life expectancy. In *C. elegans*, the most potent alleles affecting lifespan are in the insulin-like growth factor 1 signaling pathway. Rudi Westendorp (Leiden University Medical Center) and others at this workshop pointed out that human lifespan has increased more than 2-fold in the last 400 years (Fig. 2A). However, because studies of mono- and dizygotic twins, centenarians, long-lived cohorts and long-lived siblings suggest that genetic factors confer no more than 30 to 40% of the human lifespan potential (*i.e.*, risk of mortality), it appears that environmental influences play a large role in determining human lifespan. Until recently, it was not possible to identify specific genes that regulate human lifespan. At this workshop, Kaare Christensen (Danish Aging Research Center) and David Melzer (Peninsula Medical School, Exeter) described recent studies that identify human genes that may influence longevity or alter risk of aging-related diseases. Christensen reported that a single nucleotide polymorphism (SNP) affecting paraoxonase 1 correlates with longevity in cross-sectional twin studies and the 1905 Danish cohort; and Melzer reported on genome-wide association studies that identify SNPs that regulate cellular senescence or confer significant risk of type 2 diabetes, myocardial infarction, obesity, age-related macular degeneration, restless leg syndrome and other aging-related diseases. Interestingly, a SNP in the cellular senescence gene *INK4a/CDKN2a* was significantly associated with aging-related decline in physical mobility. These results suggest that future studies may be able to identify specific genetic determinants of human lifespan and aging-related dysfunction.

Taina Rantanen described a recent study, which showed that muscle cross-sectional area (CSA), strength, power, and walking speed shared a genetic effect which accounted for 7% of the variation in CSA, 51% in strength, 37% in power and 35% in walking speed, all important factors underlying functional independence in old age (Tiainen et al., 2008). Another important study found that shared and individual environmental factors explained most of the variance in maximal walking speed and endurance, while only modest portions of the variations were accounted for by genetic factors (Ortega-Alonso et al., 2006).

1.8. Inflammatory cytokines: Pro- or anti-aging?

Low grade inflammation has been associated with aging-associated chronic diseases including diabetes, obesity, atherosclerosis and cardiovascular disease. These diseases appear to be correlated, leading to the concept of an age-related diseasome, which may be linked by the process of inflammation (Fig. 3). However, as pointed out by Bente Klarlund Pedersen (University of Copenhagen) and Helle Bruunsgaard (University of Copenhagen) at this workshop, cytokines, the small molecule messengers of the inflammatory system, can play pro-inflammatory or anti-inflammatory roles (Fig. 4). Furthermore, some cytokines, such as IL-6, appear to have context-specific pro- or anti-inflammatory effects. Bruunsgaard

showed that levels of IL-6 and the pro-inflammatory cytokine TNF- α increase 2- to 4-fold with age, and risk of all-cause mortality is almost 2-fold higher in centenarians with the highest tertile of circulating TNF- α . Risk of dementia is higher in centenarians with high levels of TNF- α and performance on tests of cognitive function is lower in >85 years old from the 1914 cohort with the highest tertile of TNF- α or IL-6. Because TNF- α causes insulin resistance, dyslipidemia, and endothelial dysfunction/activation, it is possible that it drives susceptibility to metabolic syndrome, type 2 diabetes and CVD on the molecular level. However, Bruunsgaard emphasized in her presentation that it is not yet clear whether inflammation drives the process of cognitive decline or onset of dementia in older individuals. In contrast, Bente Klarlund Pedersen showed clearly that IL-6 is an exercise-inducible myokine (*i.e.*, cytokine secreted by contracting muscle) that has anti-inflammatory effects and that stimulates release of other anti-inflammatory cytokines including IL-10 (Fig. 4). In addition, IL-6 promotes lipolysis, increased glucose uptake, and protects against TNF- α induced insulin resistance. This suggests that IL-6 is involved in a feedback loop with TNF- α .

1.9. Telomere length as indicators of mortality

What are the clinical markers that indicate near-term or future risk of mortality in humans? Kaare Christensen reported that telomere length inversely correlates with risk of mortality in 273 twin pairs aged 73–94. In this study, Christensen used multiple methods to determine telomere length in circulating leukocytes in blood samples collected from twin pairs in 1997, and followed mortality in these individuals over 10 years from 1997 to 2007. The results showed that for matched twin pairs, the twin with the shorter telomere had a significantly higher risk of mortality than the twin with the longer telomere, and the bigger the difference in telomere length, the bigger the difference of age at death. It is not yet known why telomere length correlates with all-cause risk of mortality.

1.10. Lifespan and life course approaches to aging research: Taking the long view of longevity

A lifespan or life course approach to aging and cognitive function was emphasized by several workshop speakers, including Kaarin Anstey (Australian National University), Rebecca Hardy (University College London), Boo Johansson (Göteborg University), Rikke Lund (University of Copenhagen), Merete Osler (University of Copenhagen) and Marcus Richards (University College London). It has been suggested that adverse early environmental conditions can lead to poor growth and development as well as increased risk of adult chronic disease. Anstey suggested that “lifespan” includes a connotation of age-related dysfunction or pathology, while “life course” focuses on normal progression through distinct life phases. Johansson introduced the Cascade Model of Cognitive Aging (Birren and Cunningham, 1985), which defines primary aging as age-related loss of fluid abilities, episodic memory and mental speed, secondary aging as loss of crystallized cognitive abilities, and tertiary aging as pervasive loss of all types of cognitive function (Fig. 5). Tertiary aging is associated with compromised health and proximity to death. While it is common to evaluate “age” in terms of time from birth, Johansson pointed out that some functional measures may be more informative about time to death than about time from birth.

George Martin presented the Biological Theory of Aging, and argued that decay of biological homeostasis involving multiple complex physiological functions begins in “middle-aged” individuals (*i.e.*, 30-year old). Taina Rantanen (University of Jyväskylä) showed that grip strength declines approximately 1% per year from mid-life and that low grip strength at mid-life is a strong predictor of increased all-cause mortality and functional disability, as long as 25 years post-measurement. The significance of this correlation is not yet understood.

Rikke Lund, Rebecca Hardy and Marcus Richards emphasized the complex interplay of social, biological and environmental factors at all life stages (Fig. 6). Rikke Lund reviewed growing evidence that adult function and age-related chronic diseases have their origins in early life experience and share common risk factors (Kuh, 2007). A life course approach highlights the need to study long-term changes in cognitive, behavioral and social factors. Early life factors may influence both the development of biological strength and the timing and rate of decline. So-called “critical” exposures coincide temporally with critical aspects of biological development. Alternatively, the effect of an exposure can be magnified during a “sensitive” developmental period. Furthermore, the effects of some exposures are cumulative over the entire life course. The sequence or trajectory of multiple exposures may also be important. Rebecca Hardy indicated that physical capability increases rapidly in early life stages, reaches a peak or plateau in adult life, and then declines with age. She also demonstrated that physical capability of an older individual depends both on peak capability and rate of decline (Kuh, 2007). Merete Osler demonstrated that socioeconomic factors in childhood influence functional limitations and dental status in midlife, while fatigue and poor self-reported health in midlife were more influenced by low adult social class during adulthood.

1.11. Cultural stereotypes of aging: Perception influences outcome

Becca Levy (Yale University) proposed that internalized expectations of aging (*i.e.*, cultural stereotypes of older individuals) influence measurable outcomes in performance tests, as well as the health of older individuals. To test this idea, Levy identified two cultures with very positive stereotypes of aging, the American Deaf culture and the mainland Chinese culture, and compared them with the American non-Deaf culture, which is characterized by a relatively negative stereotype of older individuals. Levy showed significant differences in average memory performance in similarly aged individuals from these cultures. Levy also showed that subliminal messages that convey positive or negative stereotypes of aging can alter memory performance in older individuals (*i.e.*, positive subliminal messaging increased memory performance and negative subliminal messages decreased memory performance). These and other studies suggest that social and cultural factors can strongly influence aging trajectories, and that there is significant culture-to-culture variation in aging stereotypes.

1.12. When and where you live: Cohort effects and period effects

The average human life expectancy has increased more than 2-fold in the last 400 years (Fig. 2A), indicating that environmental factors have a dramatic effect on health and disease on a worldwide level. Furthermore, country-to-country and period-to-period average life expectancy shows very significant variability (Fig. 2B). Rudi Westendorp (Leiden

University Medical Center) suggested that social and economic status (SES) is a primary determinant of the risk of mortality, which supports the view that environmental factors have a large impact on human longevity. Nevertheless, David Melzer (Peninsula Medical School) pointed out that even among individuals of high social class in the most affluent societies, the variance in human life span remains large, and a portion of this variance is can be attributed to genetic factors.

1.13. Cohorts and collaborations

One of the goals of IARU, which was specifically promoted by this workshop, is to bring together an international group of researchers with different strengths, areas of expertise and resources, to promote research on human aging and longevity. Importantly, the IARU universities and countries represented at this workshop maintain country-specific databases as well as country- or region-specific cohorts, which are excellent resources for aging research. Collaborations involving more than one of these cohorts have been encouraged. Three such collaborative efforts were described at this workshop.

DARC—Three major health science universities in Denmark have recently joined together to form the Danish Aging Research Center (DARC). Formation of DARC was made possible by the support of the Velux Foundation. The DARC member universities include The Section of Social Medicine, Department of Public Health at the University of Copenhagen, the Danish Centre for Molecular Gerontology at the University of Aarhus, and the Aging Research Center at the University of Southern Denmark. DARC will exploit the distinct strengths of these research programs, which span from molecular biology to epidemiology, demography and social sciences. In particular, Aarhus University has strong expertise in molecular gerontology, University of Copenhagen has strong expertise in social epidemiology, and Southern Denmark University has strong expertise in genetic epidemiology. DARC will perform studies primarily using five existing Danish cohorts: The Danish Twin Registry, The Danish 1905 Cohort; Danish Centenarian Studies (1985 and 1905), The Metropolit Study 1953, and The 1914 Glostrup Cohort. At this workshop, Kaare Christensen (University of Southern Denmark) reported on recent collaborative research projects carried out by DARC.

CAMB—The Copenhagen Aging and Midlife Biobank (CAMB) is a new initiative, whose goal is to establish a midlife biobank in order to study biological, cognitive and social variables that influence aging over the entire life course. CAMB will establish a biological and cognitive data base for subsamples of the Metropolit Study (born 1953) (Osler et al., 2004), the Copenhagen Perinatal Cohort (born 1959–1961) (Zachau-Christiansen, 1972) and The Danish Longitudinal Study on Work, Unemployment and Health (born 1949born 1959) (Christensen et al., 2004). Each of these cohorts has unique advantages as well as specific limitations. By using all three study groups, CAMB will provide the opportunity to link biological and neuropsychological data with existing data from registers and questionnaires. Data collection for CAMB will take place 2009–2011. Kirsten Avlund (University of Copenhagen) presented a progress report on this project.

The Medical Research Council (MRC) National Survey of Health and Development 1946 Birth Cohort is a database of information on the health and development of 5362 British men and women, all born in one week in March 1946. The individuals in this cohort have been followed-up 21 times since birth. Collection of clinical data on this cohort is now underway. Initial clinical studies will focus on cardiovascular disease and musculoskeletal function. Marcus Richards presented an update on this initiative.

2. Featured presentations

Chronic diseases with focus on inflammation and the role of exercise

Bente Klarlund Pedersen, University of Copenhagen—Bente Klarlund (University of Copenhagen) tested the hypothesis that exercise directly alters energy and fat metabolism. The results of her study provide a possible explanation for the positive health benefits of an active lifestyle and the negative health effects of a sedentary lifestyle. The hypothesis was tested by carrying out a unique intervention, in which a 14-day period of exercise-deprivation was imposed on active young males. During the exercise-deprivation period, the subjects decreased their activity level from 10,000 steps/day to 1500 steps/day, and physiological and metabolic functions were assessed before and after the exercise-deprivation. Klarlund showed that a cluster of physiological abnormalities, similar to metabolic syndrome, was induced by lack of exercise in these subjects. The physiological effects of exercise-deprivation included insulin resistance, impaired glucose uptake and hyperlipidemia. Previous studies also indicated that exercise alters muscle gene expression significantly. Thus, it has been proposed that active muscle might secrete one or more factors that mediate changes in gene expression, as well as downstream effects on physiological functions. One such factor could be IL-6. Klarlund tested this idea, and presented evidence that IL-6 mediates the beneficial effects of exercise on longevity. In particular, muscle contraction directly stimulates release of IL-6, which in turn stimulates sequential release of IL-1 α and IL-10 (Fig. 4), and trained muscle (*i.e.*, muscle with low glycogen content) releases more IL-6 than untrained muscle (Pedersen and Fischer, 2007). In this model, it is clear that IL-6 is an anti-inflammatory signaling molecule, leading to increased lipolysis, increased glucose uptake and decreased inflammatory response (Pedersen, 2007). In addition, circulating IL-6 stimulates both autocrine and paracrine responses in muscle and other tissues, respectively, and is involved in cross-talk and a possible feedback loop with TNF- α (Fig. 4). Because IL-6 has previously been reported to mediate pro-inflammatory responses and a high resting level of IL-6 has previously been associated with diabetes and inactivity, Klarlund's result is somewhat controversial. One possible explanation for this discrepancy is that sedentary individuals with a high resting level of IL-6 could display IL-6-resistance due to a dysfunction downstream in the IL-6 signaling pathway. Although IL-6 apparently mediates some of the physiological effects of exercise, other factors are likely to play a role in this process. These may include TNF- α , IL-18 and/or brain-derived neurotrophic factor (BDNF).

Recent plasticity of human mortality rates in old age

Rudi Westendorp, Leiden University Medical Center—Rudi Westendorp discussed factors that modulate human birth phenotype, adult phenotype, disease risk and longevity.

Genetic factors clearly influence human life history and longevity; however, it appears that genetic determinants may have less dramatic effects on life span in humans than in experimental model systems. For example, in *C. elegans* cultured *in vitro*, mutations in the insulin/IGF1 pathway, such as Daf-2, can alter average life span by 6- to 10-fold. In contrast, studies of long-lived human siblings, and other studies of long-lived human cohorts, suggest that genetic factors have the capacity to extend human life span as much as, but not more than 30–40%. Many studies indicate that the environment in which humans live can have a dramatic effect on life expectancy. In this context, environment is a highly complex variable that includes physical, social, cultural, political and economic components. Thus, very strong period and cohort effects on human life span have been observed. In fact, over the last 400 years, human life expectancy on a global level has more than doubled (Fig. 2A). Furthermore, the local environment, as evidenced by period effects and cohort effects, can dramatically influence the life expectancy for individuals of a specific age in a specific country at a specific point-in-time (Oeppen and Vaupel, 2002) (Fig. 2B). To explain fluctuations in life expectancy associated with rapid economic growth and social change, it has been proposed that economic prosperity (on a population-wide level) is a strong driver of human health, disease risk and life span. When examined on a country-by-country basis, females from the Netherlands had a higher life expectancy at birth in 1980 than females from most other EU countries. However, from 1987 to 1999, females from France had a significantly higher life expectancy than females from the Netherlands or most other EU countries. Strikingly, the pattern of change in life expectancy varies significantly from one country to the next. Although mortality due to myocardial infarction and stroke has decreased over the last 15 years in the Netherlands, all-cause mortality has not decreased. The exact causes for these changes in life expectancy in specific populations are not currently known and remains a matter of debate.

An immodest proposal for a research on mechanisms underlying elite aging

George Martin, University of Washington—Referring to the fact that the performance of elite athletes such as marathon runners begins to decline at approximately age 30, George Martin (University of Washington) emphasized that the process of human aging actually begins in so-called “middle-age”. This is consistent with the Biological Theory of Aging, which proposes that the process of aging reflects a time-dependent loss of homeostasis involving multiple integrated physiological systems (Martin, 2002). Martin argued that if aging-related functional decline begins in human middle-age, then it could be advantageous to define indicators of aging in this population, by carrying out longitudinal studies of middle-aged sib-pairs. This approach has many advantages, including the low expected frequency of co-morbidities in this population, a large pool of available subjects, high expected compliance, availability of subjects for long-term follow-up and access to pedigrees with three or four generations. Martin proposed carrying out extensive genome-wide association studies (GWAS) of middle-aged sib-pairs using sensitive, cost-effective, highly specific assays for well-defined phenotypes (*i.e.*, bone mineral density). Ultimately, such assays should also be fast and non-invasive. Such studies are likely to be less successful for more polygenic traits, and more successful for less polygenic traits. Nevertheless, such studies offer the possibility of identifying valuable markers of both normal and accelerated aging in diverse human subpopulations.

Common neurodegenerative diseases have common features

Barry Halliwell, National University of Singapore—Barry Halliwell (National University of Singapore) pointed out that common aging-associated neurodegenerative diseases including AD, Huntington's Disease and Parkinson's Disease share similar features, despite having distinct pathologies. These common features include mitochondrial dysfunction, accumulation of abnormal proteins, increased free radical damage and altered iron deposition. Based on these and other observations, Halliwell proposed that proteasome dysfunction could be a critical causal factor (and/or marker) for neurodegenerative disease (Halliwell, 2006). This is consistent with the observation that defects in the ubiquitin-proteasome system (*i.e.*, parkin and ubiquitin carboxyterminal hydrolase 1) are linked to familial Parkinson's Disease. Proteasome dysfunction or overload can also be linked to oxidative stress, which has been proposed as a causal factor in aging-related disease and dysfunction. At the cellular level, proteasome inhibitors decreased cell survival and caused oxidative stress *in vitro*, and the toxic effects of proteasome inhibition can be ameliorated by overexpressing protein chaperones such as HSP22. This suggests that pharmacological use of proteasome inhibitors for cancer chemotherapy could have a risk of neurotoxic side-effects. On the other hand, agents that stimulate the proteasome could have neuroprotective effects. Because the genetic component of the common neurodegenerative diseases appears to be relatively small, future approaches to reduce incidence of neurodegenerative disease should focus on identifying potent environmental neurotoxins, developing improved methods for early diagnosis, and identifying neuroprotective approaches involving diet, lifestyle or novel pharmacological agents.

Multilevel imaging in the aged brain

Ole Petter Ottersen, University of Oslo—Ole Petter Ottersen (University of Oslo) demonstrated age and region-specific expression of DNA repair glycosylases in the mouse brain. Total DNA glycosylase activity for the oxidized pyrimidine lesion FAPY increased with age in all tested regions of the mouse brain; however, mOGG1, a glycosylase for 8-oxoguanine, showed a biphasic pattern of expression and expression of mNEIL3 decreased in the brains of older mice. These results suggest that base excision repair may be upregulated in brains of older mice as a neuroprotective mechanism. Deposition of β -amyloid was also examined by immunogold electron microscopy in the brains of 3X-Tg AD mice, a well-established mouse model for AD. Using three-dimensional reconstructions generated from immunogold-labeled brain sections, it was revealed that submicroscopic deposits of β -amyloid colocalize with and appear at approximately the same time as dystrophic neurons. Furthermore, β -amyloid deposits are tightly associated with plasma membrane domains of large caliber dendrites. Similar results were observed in the aged canine model for AD, suggesting that they are not an artifact of the transgenic mouse model. These results suggest that β -amyloid deposits have an intimate spatial relationship with large caliber dendrites, and that specific membrane domains of neural dendrites may facilitate amyloid deposition. This study reveals that high resolution immunogold electron microscopic analysis of pathology in transgenic mice can provide important insights into the pathological mechanisms of AD.

Segregation of protein aggregates during cytokinesis—Implications in aging and age-related disorders

Thomas Nyström, Göteborg University—Thomas Nyström (Göteborg University) used the budding yeast *Saccharomyces cerevisiae* as a model system to study cellular senescence and rejuvenation. Nyström described a Sir2- Hsp104-dependent mechanism by which damaged proteins segregate asymmetrically to the mother cell (Erjavec et al., 2007). This allows the daughter cell to have maximal replicative potential, and causes the replicative potential of the mother cell to decrease with each cell cycle. Nyström termed the process of sequestering damaged proteins in the mother cell “spatial protein quality control.” During cytokinesis, carbonylated proteins form aggregates that interact tightly with the actin cytoskeleton. Spatial protein quality control is defective in mutants lacking Sir2 or the protein chaperone, Hsp104. This suggests that Hsp104 binds and facilitates aggregation and association of oxidized proteins with the cytoskeleton. As expected, when spatial protein quality control is inhibited, the replicative potential of the mother cell decreases significantly (accelerated aging). Genetic screens for synthetic lethals with Sir2 identified protein components of the cytoskeleton and the polarisome. The process of spatial quality control is not unique to yeast, since similar observations were made in fission yeast *Schizosaccharomyces pombe* and in rat and *Drosophila* neural cells. Important future research questions include whether higher organisms utilize spatial protein quality control to dispose of damaged proteins in designated cellular “waste bins”; whether spatial protein quality control decreases with age in mammals; whether loss of spatial protein quality control plays a role in human neurodegenerative disease; and whether it is possible to promote spatial protein quality control in mammalian cells for therapeutic purposes by calorie restriction or with pharmacological agents.

Stochastic aspects of aging

Jan Vijg, Buck Institute for Age Research—Jan Vijg (Buck Institute for Aging Research) argued that aging has a large stochastic component, and that random spontaneous somatic mutation and epimutation are likely to play a role in aging and aging-related functional decline. Somatic mutation can be induced by DNA damage, a possible driver of aging, or it can accumulate spontaneously. Although DNA damage is reversible, mutations that are fixed at sites of DNA lesions are irreversible. Vijg showed tissue and age-dependent variation in spontaneous mutation frequencies in a reporter gene in the mouse. The mutation frequency increases significantly with age in small intestine, liver and heart, but remains fairly constant with age in spleen, testis and brain. In addition, the life span of fruit flies correlates inversely with spontaneous mutation rate, which varies as a function of ambient temperature in fly cages. Because a large proportion of the mouse genome is non-coding DNA, it was predicted that older mice would accumulate a significant load of mutations in gene regulatory regions. This prediction was tested by measuring the variance in expression of specific genes at the single cell level in young and old cardiomyocytes. The results indicate a significant increase in the variance of gene expression level in cells from older mice ($p = 0.01$) (Bahar et al., 2006).

The importance of lifespan, contextual approaches to cognitive epidemiology and dementia

Kaarin Anstey, Australian National University—Kaarin Anstey (Australian National University) emphasized a lifespan approach to understanding cognition and dementia, in which the entire life course is considered in a multigenerational and multi-faceted context. This approach recognizes that cognitive development over the life course is influenced by genetics, environment, culture, education, injury and disease, and that a normal life course includes both periods of cognitive growth and cognitive decline. Anstey reviewed common perceptions and misperceptions about three environmental factors that may influence cognitive function: smoking, alcohol and cholesterol. For smoking, laboratory and case–control studies document a short-term positive impact of smoking on cognitive function and potential protection from dementia. While these results were controversial, until recently, the long-term effects of smoking on cognitive function were not clearly documented. To address this question, Anstey and colleagues performed a meta-analysis of data from multiple prospective cohort studies on the impact on smoking on risk of vascular dementia and AD. The results showed that smoking correlates with increased risk of vascular dementia and AD (Relative risk = 1.78 and 1.79, respectively) (Anstey et al., 2007). While a number of studies document an “inverse U-” or “J”-shaped relationship between alcohol consumption and performance on short-term tests of cognitive function, the long-term effects of alcohol on cognitive function are not yet well-documented. Furthermore, although alcohol abstainers generally score lower on short-term measures of cognitive function than moderate drinkers, it is not clear whether this is due to a selection effect. Lastly, a systematic review was carried out of 18 prospective cohort studies on the influence of cholesterol on risk of dementia and AD. The results suggest no correlation between late-life total cholesterol and any dementia or cognitive decline; however, total cholesterol at mid-life increased risk of AD but not of vascular dementia or cognitive decline. Thus, total cholesterol may have a non-linear relationship with age and dementia risk and may differentially influence progression of different types of dementia (Anstey et al., 2008).

The Danish Aging Research Center

Kaare Christensen, University of Southern Denmark—Kaare Christensen (University of Southern Denmark) reported on recent studies carried out by the newly formed Danish Aging Research Center (DARC). One study examined the potential of leukocyte telomere length as a biomarker for risk of mortality. Previous studies reported that leukocyte telomere length decreases with age, is shorter in men than in women of a similar age, and is inversely correlated with risk of aging-associated disease. However, the relationship between telomere length and mortality was not well characterized. Here, leukocyte telomere length was measured in 273 twin pairs aged 73–94. Blood samples were collected in 1997, and mortality was studied through 2007. Deaths were reported in 204 twin pairs. The mean age at death was 78 for males and 79 for females. The study showed that the twin with the shorter telomere had a significantly higher risk of mortality than the twin with the longer telomere. Furthermore, the bigger the difference in telomere length, the bigger the difference of age at death. It is not yet known why telomere length correlates with mortality risk.

What matters for cognitive outcomes in later life: Time-related changes and pathology?

Boo Johansson, Göteborg University—Boo Johansson (Göteborg University) examined late-life memory and cognitive function within the framework of the Cascade Model of Cognitive Aging. This model suggests that aging can be subdivided into primary, secondary and tertiary aging subtypes (Birren and Cunningham, 1985). Primary aging is “normal” aging; secondary aging is associated with compromised health; and tertiary aging is associated with proximity to death. In normal aging, cognitive decline is limited to loss of fluid abilities, episodic memory and mental speed. Secondary aging involves loss of crystallized cognitive abilities, while tertiary aging involves pervasive loss of all cognitive functions (Fig. 5). There is substantial inter-individual variability in cognitive decline over the lifespan, where certain individuals remain high-functioning very late in life. Studies of non-demented mono- and di-zygotic twin pairs at 80 years old suggest that retention of cognitive function in late-life has a significant genetic component, possibly as high as 60%. Nevertheless, clinically diagnosed dementia occurs in approximately 50% of all individuals over the age of 95. Recent studies show that longitudinal analysis of performance on cognitive tests identify so-called “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. Additional longitudinal studies of patterns of cognitive decline are needed to distinguish the effects of normal (primary aging) and pathological processes (secondary and tertiary aging) that impact cognitive decline in late-life and to identify possible neuroprotective factors and their mechanisms of action.

Life course influences on biomarkers in midlife? The Copenhagen Aging and Midlife Biobank

Kirsten Avlund, University of Copenhagen—Kirsten Avlund (University of Copenhagen) described progress on establishing and collecting data for the Copenhagen Aging and Midlife Biobank (CAMB), whose goal is to understand the impact of biological, cognitive and social variables on aging over the entire life course. This study will include subjects from subsets of the Metropolit Study (born 1953), the Copenhagen Perinatal Cohort (born 1959–1961) and The Danish Longitudinal Study on Work, Unemployment and Health (born 1949, 1959). Existing data on these cohorts is considered to be of high quality (*i.e.*, valid, accurate, reproducible) and the value of CAMB will be increased by selecting participants from all three cohorts. To expand the existing data on these cohort subsets, CAMB seeks to enroll at least 10,000 participants, from whom blood and DNA samples will be obtained, and who will be evaluated clinically. Clinical tests will include physical exam (*i.e.*, height, weight, waist size, blood pressure, grip strength, physical performance), cognitive testing and a questionnaire on health, health behavior, depression and social factors. An oral examination (number of teeth, caries, saliva, periodontitis) will be conducted on at least 3000 participants. Inflammatory and genetic markers will be evaluated in blood and DNA samples. Data collection will take place in 2009–2011. Particular

emphasis has been placed on using standardized measurements of factors that are relevant to early signs of aging in middle-aged individuals. CAMB provides an outstanding opportunity to analyze the early life factors that influence aging in midlife. Further, the data set will support future studies on the importance of biological, cognitive and environmental factors on the rate and progression of aging-related functional and/or cognitive decline.

Impact of the death of spouse on the lives of Japanese men and women: Findings from a 20-year panel survey

Hiroko Akiyama, University of Tokyo—The marital relationship is one of the most influential and intricate dyadic relationships over the life course. The loss of spouse at old age after being married for many years affects every aspect of older persons' lives. To understand the impact of spousal loss latent class analysis was performed on a 20-year panel survey from a national probability sample of 4869 Japanese aged 60+. This analysis identified long-term trajectories in four major domains of QOL (health, economic status, social relations and subjective well-being) before and after the death of spouse. Major findings were: (1) There were plural trajectories indicating differential impacts and adaptation among individuals; (2) the dominant pattern showed little impact of the loss; (3) most of the individuals who were affected by the loss, recovered to the pre-loss level within 3–5 years; (4) men, those who lost their spouses at late old age, and those who lived alone after the death of spouse, were more likely to experience negative impact; and (5) for men, negative impact was observed in subjective indicators (satisfaction with health, difficulty making ends meet, and life satisfaction) rather than objective indicators of QOL.

A life course approach to biological function

Rebecca Hardy, University College London—Epidemiological studies of aging increasingly include measures of function as well as disease status. Continuous and normally distributed measures of biological function, repeated over time, provide dynamic tools for studying the biological imprint of physical and social exposures. They allow comparative study of low- to high-functioning states, instead of exclusive study of diseased and/or disease-free states. Partial loss of function may be a sign of an underlying disease process, developmental defect, or premature aging. “Physical capability” is increasingly used to describe an individual's ability to perform the physical tasks of everyday living. Functional measures (such as grip strength and standing balance) that assess these capabilities often involve several body systems. Physical capability increases rapidly in early life stages, reach a peak or plateau in adult life, and then declines with age. The physical capability of an older individual depends both his/her peak capability and his/her rate of decline. Developmental factors influence the growth phase, while both developmental and late-life risk factors influence the rate of decline. Cardiovascular function (as indicated by such measures as blood pressure and carotid intima media thickness) strongly influences physical function, and is a marker of development, aging and disease processes. There is increasing evidence that arterial function reaches a peak around puberty and that clinically relevant atherosclerosis begins to appear after puberty.

The impact of childhood and adult socioeconomic position on indicators of incipient ageing in middle-aged men

Merete Osler, University of Copenhagen—Merete Osler (University of Copenhagen) analyzed the effect of social class in early and adult life on health and physical function in adult life. In particular, the influence of adult social class was examined using data from the Metropolit cohort (males born in Copenhagen in 1953) and a random sample of middle-aged Danish twins. In both cohorts, childhood and adult social class were associated with adult physical characteristics, including physical fitness (100 m run), dental health, self-rated health and fatigue. Although marital status, BMI and smoking also co-related with these outcomes, controlling for these variable did not eliminate the effect of social class. In male twin pairs, the twin with the lower social class had significantly poorer self-rated health and a higher level of fatigue. Interestingly, social class was the only statistically significant factor that appeared to influence ageing-related health outcomes in twin pairs concordant or discordant with respect to adult social class.

3. List of senior participants

Kaarin Anstey, Hiroko Akiyama, Kirsten Avlund, Vilhelm Bohr, Helle Bruunsgaard, Kirsten Caesar, Kåre Christensen, Ellen Garde, Tina Gottlieb, Barry Halliwell, Rebecca Hardy, Boo Johansson, Michael Kjær, Bente Klarlund, Hans Krokan, Martin Lauritzen, Becca Levy, Rikke Lund, George M. Martin, David Melzer, Erik Lykke Mortensen, Thomas Nyström, Merete Osler, Ole Petter Ottersen, Taina Rantanen, Marcus Richards, Miriam Sander, Tinna Stevnsner, Jan Vijg, Rudi Westendorp, Ulla Wewer.

Abbreviations

AD	Alzheimer's disease
SNP	single nucleotide polymorphism

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Fig. 1.

The proteasome overload model of neurological disease. Reprinted with permission from *Antioxidants & Redox Signaling*.

Fig. 2.

(A) Average human life expectancy 1600–2000. Reprinted with permission from Dr. James Vaupel (Max Planck Institute for Demographic Research, Rostock, Germany). (B) Country-specific human life expectancy 1840–2000. From “Oeppen, J. and Vaupel, J.W. Broken, Limits to life expectancy, *Science* 296 (2002), 1029–1031.” Reprinted with permission from AAAS.

Fig. 3.
Aging-related diseasome.

Fig. 4.
Cross-talk and interaction between pro- and anti-inflammatory cytokines.

The Cascade Model of Cognitive Aging

Fig. 5.
The cascade model of cognitive aging.

Fig. 6.
The life course approach to aging research.