Summary of FEAM Madrid conference on Ageing

4 May 2012, Spanish Royal National Academy of Medicine

Introduction

Professor Jesus A.F. Tresguerres, President of FEAM; member of the Spanish Royal National Academy of Medicine; Professor of Physiology at Complutense University in Madrid

Prof. J. A.F. Tresguerres summarised the objectives of the meeting – to discuss the evidence and its use in addressing the problems associated with ageing in Europe. In particular, to review advances in understanding of biological pathways, their current relevance to medical intervention and the new opportunities for research now coming into range. Action in reducing age-related health problems has to be combined with attention to the societal consequences and this has important implications for EU strategy. The present meeting is intended to serve as a basis for FEAM's further provision of knowledge-based advice to EU policy-makers.

Demographic perspective in Europe and its implications

Professor Kay Tee Khaw, Professor of Clinical Gerontology at University of Cambridge and Fellow of the UK Academy of Medical Sciences

In order to identify and clarify what are the current challenges and their determinants, what is changing and what is the prospect for further change, it should first be recognised that ageing in Europe is a great success story in terms of declining mortality rate. The declining mortality, together with declining birth rate, is resulting, and will continue to result, in big changes in the ageing population – a doubling of the numbers older than 65 years in the EU-27 by 2060 compared with 2007. The age dependency ratio (65+/15-64) also doubles by 2060. Although these changes reflect improved population health, they present significant challenges for society in further understanding and influencing the biological, environmental and societal determinants of health during ageing, with the objective to maintain optimal health throughout the lifespan while, at the same time, preventing health care costs from escalating out of control.

The large socio economic variations in healthy life expectancy indicate large potential for improvement. Healthy life expectancy is largely determined by a relatively limited number of chronic conditions: cardiovascular disease, cancer and neurological, musculoskeletal and respiratory disorders. Data from the European longitudinal study, EPIC, have been very useful in helping to understand what influences age-related changes in health and disability. For example, physiological changes associated with ageing such as impairment in vascular function, decline in muscle strength, decline in lung function and loss of bone increase risk of conditions such as strokes, dementia, osteoporotic fracture and frailty. However, many of these physiological changes can be influenced by environmental in particular, lifestyle factors. Understanding what we can do to mitigate some of these changes may help reduce disability in later life. For example, in the UK cohort of EPIC:
(i) Good lung function predicts good self-reported physical function over the age span 42-82 years, and predicts lower hip fracture risk as well as total mortality. Smoking is a major determinant of lung function.
(ii) Higher levels of education in early life is associated with better cognitive function in later life. Seeking further understanding of this correlation is of crucial importance for identifying interventions for sustained impact on dementia.

There is already room for optimism based on the current reductions in age-specific disability rates. The interpretation of the EPIC data provides further encouragement in demonstrating that a relatively small change in lifestyle for the individual, when aggregated, has large population impact in postponing and reducing disability and societal costs. The data also confirm that public health targets are attainable by combining relatively simple behavioural changes (smoking cessation, moderate alcohol intake, moderate physical activity and diet). It is vital that these emerging results are taken fully into account in devising the research and public policy agendas.

Subsequent wide-ranging discussion explored the extent to which health data for one Member State can be generalised to others – the strength of the EPIC study is that it is a collaboration between 10 EU countries and, therefore, a great opportunity to map and compare cohorts. Another point raised in the discussion of this and subsequent presentations related to the design of models for testing the efficacy of early interventions that may induce later positive effects. How should cost-effectiveness be measured? It was also emphasised that the consideration of health issues must be part of the broader policy agenda. For example, the healthy ageing population will stay longer in employment with implications for the next generation of workers – it is imperative to change work structures to make better use of older workers without negative impact on the careers of younger workers.

Impact of ageing on public health policy in Europe
Professor Rose Anne Kenny, Professor of Geriatric Medicine, Medical Gerontology, Trinity College Dublin

There are big differences across Europe in attitudes to the ageing population and in expenditure on services for the elderly. There is also great disparity in the data collected across the EU-27 for example by the EU Task Force on Health Expectancies (www.tf-he.eu) for quantifying healthy life years (after age 65). Currently, there appears to be a four-fold difference in healthy life years between EU countries and this has major implications for national strategies and health care expenditure. In order to inform public policy, it is essential to have reliable data collected consistently but there is the concern that national estimates and projections have often been inaccurate. It has been postulated that discrepancies can partly be attributed to the systems of data collection, from which estimates are derived of variable reliability, because such data are mainly self-reported. Age-related cognitive decline may affect the recollection of health status. Various national and international longitudinal studies are now incorporating the standardised, objective (clinical) assessment of health as well as the collection of information on self-reported status. Collating generalisable data is important in allowing harmonised statistical analysis of datasets and cross-cultural inquiry.

There is now some evidence to document variability in self-reported data. For example, in one longitudinal Irish study (http://www.tcd.ie/tilda), many elderly subjects were unaware of their hypertension, atrial fibrillation or osteoporosis. While detailed epidemiological research is expensive, it is a good investment if it resolves discrepancies in current datasets and provides a sound statistical basis for strategy development and priority-setting. Projects such as the Irish TILDA require significant technological infrastructure to support national mapping and biological sample collection in a well-characterised cohort. Such data are, however, increasingly needed to inform coherent public health policy, and equivalent research initiatives merit expansion across the EU. The issue of "unreported disease" has wider ramifications for the health and morbidity of ageing populations and more work is required to establish if under-diagnosis is widespread across the EU and its implications for under-treatment.

European Innovation Partnership in Active and Healthy Ageing

Dr. Inés García Sánchez, Innovation for Health and Consumers Unit at DG Sanco of the European Commission

The changing demographics in the EU present a challenge for public and private health spending at a time when the work force in the care sector is projected to decline, opening-up new gaps in care provision. From the perspective of the European Commission (and others), confronting this challenge requires a paradigm shift in thinking and empowerment: perceiving the ageing population as a major asset and opportunity rather than societal burden, moving from passive to pro-active care and from a focus on curing disease to one that also includes improving functioning.

The ambitious European Commission target is for an average increase of two healthy life years in the EU by 2020 and this requires collaboration and innovation, bringing together the public and private sectors and all the Directorates-General. The European Commission's process to consult stakeholders, select targets and develop implementation

plans to improve active and healthy ageing started in 2010 and has now established the strategic actions. The broad scope of the first phase of priorities includes action to ensure better adherence to treatment, prevent functional decline, develop integrated care models for chronic disease, implement remote monitoring and novel ICT solutions and promote innovation in the built environment (https://webgate.ec.europa.eu/eipaha). During 2012, stakeholders are being encouraged to facilitate joint work in these areas, with goals to develop the evidence base, increase efficiency in collective activity, strengthen the potential for winning project funding, and expand the opportunities for industry in new consumer markets. The European Commission has several key roles in coordinating and supporting these stakeholder efforts: to introduce partners, monitor and evaluate progress, ensure the appropriate regulatory environment and provision of standards, and align the effective use of funding instruments.

In discussion, it was emphasised how FEAM has an important role in facilitating interaction among the biomedical community and with other stakeholders to continue to articulate the challenges and opportunities, to identify both the research needed to tackle the priority tasks and the implementation effort needed to translate research into practice.

Leopoldina memorandum on ageing

Professor Ursula Staudinger, Vice-President of the German National Academy of Sciences Leopoldina; Vice-President and Academic Dean of Jacobs University Bremen

In 2010 the German National Academy of Sciences Leopoldina together with the German Academy of Science and Engineering published its recommendations from joint academy work on ageing[1]. This multidisciplinary initiative was particularly wide-ranging, across medicine, neurosciences, psychology, economics and other social sciences, law, history, regional studies and engineering science, covering issues broadly for health and also for technology, work, education and other attributes of civil society. The analysis confirms that the multiple impacts of an ageing society will be profound, for example, in much of the EU the recent decline in labour force participation by older workers is now reversing and will likely continue to reverse, with significant impact on economic development as well as the career structures described previously.

During the past century, industrialized nations experienced an average gain in life expectancy of about 30 years – this is unprecedented in human history. The academies' initiative takes a whole lifespan view of ageing, rather than merely focusing on the period from retirement, because of the importance of the earlier antecedents of health outcomes reviewed by other speakers. In exploring what is possible in addressing the current opportunities and challenges facing society, the concept of plasticity in ageing was reinforced, "*ageing will be what we make of it*" (within biological limits). From this perspective, there are particular implications for:
(i) Planning for further increase in life expectancy – an important consideration for social policy.

[1] *More years, more life*, Nova Acta Leopoldina Neue Folge Band 108, Nummer 372.

(ii) Increasing healthy life years as a proportion of total lifespan. There is significant potential for improving functional capacity even at very high ages although more may need to be done to differentiate between healthy ageing and better medical care as the driver of longevity. This distinction has implications for public health policy to plan for the compression of morbidity and to build the robust physical and mental resources for the individual to draw upon for healthy ageing, as discussed by Khaw.
(iii) Improving cognition in old age – by education, training, adjusting the work environment and career structures. These changes require that policy-makers stop equating chronobiological age with cognitive age of the population.
(iv) Understanding that the "negative ageing" stereotype is self-fulfilling – evidence from longitudinal studies demonstrates that a negative image of one's own old age correlates with reduced survival, but there is also emerging experimental evidence that communicating positive information about old age induces a more positive outlook. It is important to take account of the societal as well as personal influences on the image of old age, and this too has implications for national policy.
(v) Re-thinking society's use of end-of-life terminology so that this is no longer a forbidden topic.

Many of these points pervaded discussion throughout the conference. FEAM acknowledges its responsibility to consider further how this German academies' initiative to generate evidence and commit to sustain debate provides a model for expanding the work by other academies internationally.

Biology of ageing
Professor Michael Klentze, President and Chief Medical Officer at Klentze Institut of Anti-ageing Medicine

Human ageing is associated with a wide range of physiological changes that increase susceptibility to death and limit normal functions. There is controversy both about whether ageing derives from changes occurring in parallel in different tissues or whether changes in one tissue are dominant, and about the relative influences of intrinsic and extrinsic determinants (and their interplay).

Insight into the processes of ageing has been gained by a wide variety of scientific approaches including: characterisation of disease-associated genes, such as the apoE subtypes; comparison of longevity between animal species; elucidation of cell biology, for example the mechanism of cellular senescence implicating inflammatory changes; and many other studies in molecular biology, gerontology and immunology. Identification of the Hayflick limit (the number of times a normal cell population divides before senescence) stimulated the search for a genomic basis of ageing, subsequently interpreted in terms of telomere shortening and complex regulatory pathways, including the involvement of the transcription factor p53 and the cyclin-dependent kinase inhibitor p16INK4a. One major finding in the experimental study of ageing was the observation that caloric restriction is associated with longevity in mice. This also stimulated the search for key genes, implicating those responsible for insulin effects through IGF-1

signalling and resistance to oxidative stress. In supportive evidence drawn from various experimental approaches, it was found that mice lacking the adipose tissue insulin receptor lived longer and that mitochondrial DNA damage by reactive oxygen species (ROS) is a major apoptosis pathway. Many of the experimental issues for identifying mechanisms of intrinsic ageing were reviewed in greater detail in subsequent presentations. In discussion, it was noted that the biological evidence also indicates that ageing has more plasticity than previously assumed, supporting the messages from the Leopoldina report.

Genetics and epigenetics of human ageing and longevity
Professor Claudio Franceschi, Department of Experimental Pathology at University of Bologna

Human centenarians may represent a good model for the study of key functions in healthy ageing in different settings. The extreme phenotype is a mixture of adaptive robustness and accumulating frailty. Inflammatory biomarkers are elevated as part of a complex balance manifested between inflammatory and anti-inflammatory molecules, possibly associated with re-modelling. Circulating levels of IGF-1 are low, supporting the animal model data presented by Klentze and thyroid hypofunction is another common biological characteristic of the centenarian.

Centenarians do possess genetic risk factors for disease, documented in the sixth Framework Programme GEHA study of 11 European countries (www.geha.unibo.it). Genotyping methodologies included:
(i) Genome wide analysis of the association with longevity. Results appeared to vary in different European populations, but one linkage region for longevity is apoE4.
(ii) Study of the association of mitochondrial DNA, again found as a population-specific association with longevity, for example in the mtDNA haplotype J.

In terms of the epigenotype, ageing is found correlated with changes in DNA methylation in the Italian centenarian study and work is continuing to clarify the reduction in genome methylation. Detailed analysis of Alu and CpG sites, linked to ageing, provides potential insight on new longevity genes. Epigenetic changes were also postulated to be associated with the status of gut microbiota (in turn, influenced by diet), leading to the notion that nutritional reprogramming of the ageing process might be possible. This is being studied currently in the seventh Framework Programme project Nu-AGE (www.nu-age.eu), assessing dietary intervention in those over 65 years using 'omics technologies'.

Impact of ageing on vaccination
Professor Beatrix Grubeck-Loebenstein, Director of the Institute for Biomedical Ageing Research of the Austrian Academy of Sciences

As previous speakers described, the immune system deteriorates with age. Regarding the effects of ageing on innate immunity and the vaccine response, the key finding is that the threshold for the innate immune system to induce a danger signal is higher on ageing,

resulting in impairment of antigen uptake and transport. Ageing progressively reduces thymus size and there is no new generation of T cells, so that the body is dependent on the reservoir of T cells generated earlier in life. In consequence, the repertoire changes in ageing, with a decline in young, naïve T cells, increase in memory T cells and larger increase in effector T cells. This changing balance may be problematic when the elderly are exposed to neoantigens such as travel vaccines or during pandemic influenza, with attenuated induction of protective antibodies. There may also be declining protection against tetanus, for example, related to the time since last vaccination. The larger number of effector T cells may additionally contribute to inflammatory status. B cells are less affected but there is some reduction in naïve cells on ageing and an increase in memory cells.

In translating from research findings to improved clinical practice, it was advised that vaccination status in the elderly could be enhanced by a combination of strategies: ensuring primary immunisation of younger age groups; providing regular booster vaccines; adopting shorter intervals between vaccination; monitoring (and controlling) antibody titres; and developing new vaccines and adjuncts adjusted to the requirements of the ageing immune system.

Re-evaluation of the free radical theory of ageing
Professor José Viña Ribes, Department of Physiology at University of Valencia

The theory for a role of free radicals in ageing was first formulated in 1956 but in the last decade has attracted controversy both with regard to the fundamental principle and the likely mechanism of oxidative damage. This uncertainty was stimulated in part by inconsistent evidence from animal models including, most recently, genetically modified animals with altered levels of oxidative damage. As well as the contradictory animal evidence for free radicals, it has become apparent that the exogenous administration of antioxidants (to humans and experimental animals) has not necessarily resulted in improved health; indeed some deleterious effects have been seen. However, it may be important to distinguish between exogenous antioxidants and the up-regulation of endogenous antioxidants. In discussion, it was also cautioned inadvisable to generalise about exogenous supplements because the net effect may depend on the type of antioxidant and its administration regimen.

There is some evidence for the association of free radicals with age-associated specific disease, for example from studies on the intracellular toxicity of beta-amyloid, relevant to Alzheimer's disease. Therefore, while it was concluded that free radicals are not the cause of ageing, they seem to be implicated in age-associated damage to macromolecules and, by causing derangement in signalling pathways, may induce cellular stress. In discussion, the need for further research on the pathology of other diseases where oxidative stress may be important, such as diabetes and Parkinson's disease, was also highlighted.

Melatonin and ageing
Professor Darío Acuña Castroviejo, Department of Physiology at University of Valencia

Two of the biological features of ageing, the blunting of the circadian rhythm and alteration of mitochondrial function associated with oxidative stress, might be explicable in terms of a role for melatonin. The pineal phased production of melatonin mediates the circadian rhythm and synchronises endocrine and non-endocrine rhythms. Melatonin also has an extra-pineal source in a variety of tissues, where production is not rhythmic and the effects have been associated with cytoprotection and mitochondrial homeostasis. Experimental models, for example using a senescent mouse strain, show less melatonin than in control mice and the age-related changes in senescent mice include mitochondrial oxidative stress, ATP deficiency and cell death. Long-term melatonin administration prevents the biochemical and phenotypic signs of ageing in these mice, and their longevity now matches control animals. Melatonin was also demonstrated to decrease oxidative stress in a mouse model of Parkinson's disease, increasing both ATP production and locomotor activity. Thus, low dose melatonin has chronobiological properties whereas high doses demonstrate anti-oxidative and, perhaps, anti-inflammatory properties. In discussion, it was noted that, while melatonin might be advocated to have potential therapeutic utility, the very high doses used in experimental studies would be expected to saturate the biochemical pathways postulated to be involved, and more work is needed to establish mechanisms.

Dietary polyphenols against brain ageing
Professor Vittorio Calabrese, Section of Biochemistry and Molecular Biology, Faculty of Medicine at University of Catania

Previous presentations had discussed how an increasing incidence of degenerative disorders associated with the increasing human lifespan may be related to over-production of free radicals and to mitochondrial apoptosis. Protein oxidation is also implicated. Under optimal conditions, long-term health protection is dependent on protein homeostasis, balancing protein biosynthesis, folding, translocation, assembly/disassembly and clearance. Efficient functioning of maintenance and repair processes is accomplished by a complex network of inducible cytoprotective proteins coded by the vitagenes. The vitagene family is composed of the heat shock proteins, the thioredoxin system and the sirtuin system. Dietary antioxidants such as polyphenols and N-acetyl-carnitine have recently been demonstrated in vitro to be neuroprotective through the activation of hormetic (biphasic) pathways, including the redox-sensitive vitagene network. In applying proteomic methodologies to the study of brain protein ageing in senescent animals, many of the proteins identified are involved with energy metabolism and associated with increased expression of the heat shock proteins. Significant changes in both cytosolic and mitochondrial redox status were found in all brain regions analysed. The observation of the link between cellular stress response and neuroprotection provides further impetus to attempts to select pharmacological agents capable of mediating the response and to the extension of studies to other disorders such as diabetes and cancer. In discussion, the point was raised more generally that the impact of stress on the individual

is complex – without any stress there would be little development but too much stress is deleterious.

Mitochondrial physiology and ageing

Professor Erich Gnaiger, Department of Visceral, Transplant and Thoracic Surgery at Medical University of Innsbruck

The inverse relationship between lifespan and basal metabolic rate across animal species, noted by previous speakers, is complex. Explanations are controversial and the evidence that the relationship is mediated in part by production of ROS is uncertain. Mitochondrial density is correlated with metabolic rate and, as observed by previous speakers, mitochondrial function may change on ageing and in age-associated diseases. An effect of physical training on mitochondrial density has been examined in wide-ranging studies in animals and humans. In one study, mitochondrial respiratory capacity and control was compared in muscle biopsies from obese, sedentary, active and athletic humans. Both mitochondrial quantity and quality (for example, fatty acid oxidation) declined in the sedentary/obese lifestyle and this slow aerobic capacity was denominated by the term "mitochondrial fever". This notion of a critical lower limit of mitochondrial performance provides an early marker for potential tissue damage which, if ignored, has consequences for the onset of oxidative stress and inflammation. Thus, a new risk factor for cardiovascular disease, diabetes, degenerative disorders and lowered quality-of-life can be conceived. At the other extreme, top athletes (including athletic horses) may also demonstrate a loss of mitochondrial capacity, suggesting that treatment of the mitochondrial changes in the "fever" phase associated with the sedentary lifestyle might be advised to avoid extended high exercise levels and severe caloric restriction. These findings and their implications require further substantiation. Mitochondrial physiology and competence is becoming a major research topic in the effort to find novel solutions for the challenges in the ageing population but the terminology "mitochondrial fever" is controversial in implying a transient acute state for what may be a cumulative lack of capacity. In discussion, research was recommended to determine whether similar mitochondrial changes are present in tissues other than muscle and to explore the aetiology.

General discussion

In addition to specific points addressed to individual presentations, some more general, strategic, issues were raised regarding the identification and clarification of priorities for future investment in the research agenda, for the translation of research outputs into innovation and to inform the policy options for support of healthy and active ageing. Among these general points were:

- In assessing the current epidemiological evidence base, it is prudent to be sceptical about projections for future life expectancy when these are extrapolated linearly from present experience. In assessing biological evidence, it is desirable

for researchers to agree consistent use of a common terminology, for example, the term inflammation may describe different things when used in different contexts.

- When public policy-makers are considering the best use of scarce resources, is it better to invest in acting on the evidence already accumulated – "the science of intervention" – or to seek deeper understanding at the fundamental, molecular level? In reality, both are vital. Society needs to invest more in health and education in areas where interventions are known to be effective but must also continue to pursue the search for fundamental understanding. This also requires new interaction between the biological and social sciences.
- How then best to capitalise on the resources accruing from research advances already achieved? There is a problem of regulatory obstacles in the pathways for translating research into clinical practice, for example incurred with the current operation of the EU Clinical Trials Directive and the plans for the EU Physical Agents Directive[2]. Some also are sceptical about the involvement of industry in the collaborative processes initiated by the European Commission's European Innovation Partnership, but the Commission emphasises that it is not seeking to constrain basic research, rather to make the most of what has already been achieved.
- There is increasing need to cover the issues of geriatric medicine in the medical curriculum. This priority needs to be taken into account in the ongoing FEAM work on EU medical education and training.
- Ageing is global and was the theme of World Health Day earlier in 2012. There are global opportunities to challenge outdated public perceptions, political priorities and policy models[3] and further thought should be given to how FEAM might assist IAMP to tackle these global opportunities and challenges.

Dr. Robin Fears, FEAM, 31 May 2012

[2] FEAM Statements on the options for reform of these Directives are on www.feam.eu.com.
[3] P. Lloyd-Sherlock et al. 2012 *Population ageing and health* Lancet **379**, 1295-1296