LONG TERM CARE...
SHORT TERM CHALLENGES?
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With the aging of the world’s populations and the frailty of public insurance schemes, financing long-term care is sure to be one of our biggest challenges for the decades to come. To meet it, insurers will have an important role to play. At AXA, we believe that protecting our clients is intrinsically tied to better understanding and anticipating risks.

Long Term Care insurance requires a high degree of conceptual, pricing and management rigor. From a Risk Management perspective, dependency is quite a long-term risk, meaning that, often at least a couple of decades can elapse between a policy’s purchase date and the eventual claim or death. With the potential for unexpected future deviations, it is easy to understand how these ever longer cycles translate into greater mispricing risks. On the financial side, the current low interest rate environment also presents a challenge for the products’ sustainability.

The need for long-term care ties in with longevity and ongoing medical advances both of which are likely to decrease the probability of becoming dependent, to increase our LTC-free life expectancy and, in the meantime, to increase the actual number of seniors for which the incidence rates are the highest. Medical advances could also lengthen dependent people’s life, particularly those at very moderate levels of dependency. Insurers would therefore pay more claims in total and for a longer period than forecasted.

As an insurer, we keep a close track of these trends, and we count not only on historical data (internal and external), but also on insights from the scientific community to define our best estimation of risks: detecting deviations early is key to avoiding accumulation.

**Our long-term care modeling and monitoring keeps track(s) of each step(s) in our life**

The most comprehensive modeling is quite traditional and broadly used in the life insurance industry. It consists of estimating, for any given individual, the probability of living a healthy life, the probability of becoming dependent, and finally the probable duration of benefit payments.

This entails the use of so-called multi-state models, which are illustrated here. An individual, at any given time, can only be in one of these three states: healthy, dependent or deceased. The idea is basically to estimate the probability of remaining in a given state and the probability of moving from one state to another.
These laws of transition are estimated based on age, gender and even on the level(s) of dependency (moderate or severe). The most sophisticated models, called semi-Markovian, also add another dimension by calculating the probabilities of moving from one state to another in function of the duration of the preceding state: the probability of dying during the first year of dependency is higher than in the years that follow, in particular for individuals who are under the age of 60.

**The quality and the relevance of the data used to define these transition laws are critical**

In general, insurance data are more appropriate than public surveys, which do not necessarily use the same risk definitions and which can be based on self-disclosures—less robust by nature.

Insurance data offer the advantage of specifically and precisely identifying policy trends and developments. Since the introduction of the first policies covering severe dependency in the 1980s, we have been acquiring experience from year to year. Hence, experience for the highest ages is still rather limited, in particular for the mortality rate of dependent policyholders. Additionally, designing simple products helps to optimize the data’s availability, whereas highly segmented products with a broad array of options take far longer to generate statistically reliable findings.

The lack of data is a frequent issue faced by emerging markets, and even mature ones now willing to respond to the increasing demand for coverage of more moderate levels not formerly monitored. In these situations, we turn to experience in academic publications or in similar markets. But the dependency definitions often vary or can be interpreted differently from one country to another. All this makes the LTC risk difficult to estimate and hence to price.
In addition, the consequences of demographic aging have a direct impact on how dependency is modeled. There is no consensus on whether we gain a longer healthy or dependent life. Pricing impacts are not negligible and turn out to be quite variable depending on the various possible future trend scenarios: compression, stability or extension of the morbidity period. According to the latest surveys and data, we may also need to differentiate not only between physical and cognitive dependency, but also between low and severe dependency.

**Other insurance risks also need to be considered**

In addition to biometric risks, there are other insurance related risks that must be integrated into the model:

- **The policy lapse risk**¹: For a long-term care product, overestimating lapse rates leads to under-pricing.
- **The random element of the cost of benefits** must be taken into account for reimbursement-based products. Modeling must therefore incorporate assumptions on medical inflation and anticipate technical advances.

These two factors have generated massive losses for numerous insurance carriers in the United States, who overestimated lapse rates and underestimated future payouts.

- **The anti-selection risk**²: This additional factor is non-existent in mandatory universal coverage but does appear whenever coverage is optional. In this case, medical underwriting and the enforcement of waiting periods provide risk mitigation against cases of pre-existing conditions.

¹When the insured terminates the policy
²The anti-selection risk (or adverse selection) is the result of asymmetry of information. The insured has the possibility of using to his or her advantage undisclosed information about the level of risk he or she presents, and of which only he or she is aware.
Full and on-going monitoring is of essence if we are to enhance our knowledge and anticipate risks for the years to come.

Risk monitoring must be carried out via the various factors used to build the model: incidence and autonomous/dependent mortality rates. With this basic, it is possible to rapidly roll out corrective actions when an adverse deviation is observed, thereby making it possible to provide fairly-priced coverage over time.

Risk monitoring is not limited to our own historical data. It equally embraces the insights that other professional disciplines can provide:

• Valuable epidemiological studies are now available and the long-term trends they provide are benchmarked to our own experience, despite the lack of homogeneity in LTC definitions from one study to another - as mentioned above – makes comparing details quite complex.
• All the research related to prevention and educational programs is also very promising. It provides evidence of the population ageing and establishes a link between habits and lifestyle notably with the prevalence of certain disease. But will this continue to be so in the future?
• There is no doubt that medical progress should affect the LTC risk. A large number of programs have flourished in the last decades with the promise of developing medicines to address cognitive diseases. Despite these efforts, there is still a lot to do in this domain in preventing, diagnosing early and curing these pathologies. a more holistic approach is now being investigated and they may contribute to the remaining challenges. The years to come will hopefully confirm their expectations.
Considering future societal models

The demographic ageing of world populations is now a common backdrop for a number of countries. At a time when many social security and welfare budgets are facing deep deficits, the public debate tends to focus on financing coverage and funding treatments. Once they have occurred, pathologies and dependency are very costly. In some countries, current policies rely principally on family care-givers, who jeopardize their own health in caring for their loved ones. To relieve this burden, some governments provide these family care-givers with the possibility of receiving an indemnity when they take an LTC-leave. Two other alternatives to supplement family care could be considered:

• The service sector: a promising but often unaffordable solution on a full-time basis. In addition, there is a lack of appetite for such a career, making it difficult to find a sufficient workforce.
• Robotics also offers fantastic opportunities in the mid-term for stimulation and monitoring.

Public policy choices will be decisive in determining tomorrow’s long-term care trends. An example is given by the models developed in Northern Europe where maintaining the autonomy of senior citizens is seen as a priority. They result in better ranking in terms of healthy life expectancy compared to Southern Europe where dependency occurs earlier. Whatever choices we make for the future, they will undoubtedly impact the life and needs of our customers and as a consequence the insurance industry.

Understanding present risks means anticipating future trends. To complement our traditional monitoring-based technical expertise we need to reap knowledge from multiple other disciplines. In our current reality with a highly complex mix of ageing populations, socio-economic and financial contexts, ever-changing innovative technologies, and evolving family structures, just to name a few, multiple disciplines and industries will have to pull together to share their knowledge to make it possible to age with dignity.

Mohamed Baccouche
AXA Group Chief Actuary
Life Savings & Health Chief Risk Officer
While increases in life expectancy are good, increases in “healthy life expectancy” are better

Unfortunately, health does not generally improve with age. Life expectancy is generally increasing around the world, which is good. But, it would be better if “healthy life expectancy” (the years we spend in good health as we get older) increased too. Carol Jagger, AXA Professor of Epidemiology of Ageing at Newcastle University in the UK is studying the factors that could help us live both longer and healthier. We have a certain amount of control over some of these factors – for example, having an upbeat attitude to life, eating better and exercising more. Some others, of course, are not always in our hands – examples here include socioeconomic factors like education and wealth.

Jagger’s research is based on analyzing data from the Cognitive Function and Ageing Studies (CFAS) project, which followed people aged 65 years or above in three centers in England (Cambridgeshire, Newcastle and Nottingham) between 1991 and 2011. There were 2500 participants in each center. This data provides prevalence estimates for three health measures: self-perceived health (defined as excellent-good, fair or poor), cognitive impairment (moderate-severe, mild or none – as assessed by the Mini-Mental State Examination score); and disability in daily living activities (defined as none, mild, or moderate-severe). She calculated health expectancies for the three regions combined using the so-called Sullivan method.
Carol Jagger answers our questions:

**Why is studying healthy life expectancy, as opposed to just life expectancy itself important?**

“The last century saw huge changes in life expectancy around the world. The result is an increasingly ageing population and particularly numbers of very old people – that is those aged 85 years and over, who are the fastest growing demographic in many countries. We know that getting older means more health problems but life expectancy is only a measure of the quantity of life lived. Healthy life expectancy (HLE) on the other hand gives us information on both the quality as well as the quantity of years lived. This measure is especially useful in answering the important question of whether those extra years of life we are seeing are good/healthy or not.”

Living healthier as we age is not only important for us as individuals, but also as a society. Ill health places a burden on families and caregivers, the social security and healthcare system of a country, as well as pension funds, both public and private.

*Participant at Tyne bridge.*
*Credit: Newcastle 85+ Study*
“In most countries, women live longer than men. However, since women’s HLE is generally on a par with that of men’s, women tend to spend a greater proportion of their remaining years unhealthy. What is more, recent research from both the UK and US suggests that, at least in terms of disability-free life expectancy, women are losing ground to men.

“Over the 20 years between the two CFAS studies (CFAS I and II), we found that men’s LE at age 65 increased by 4.5 years and women’s by 3.6. However, for men, over half of this increase was in years free of disability (2.6 years) whilst women saw only a 0.5 year increase in these years.

“In a similar US study that reported changes over a 30 year time span from 1982 to 2011, men’s overall LE at age 65 increased and the proportion of life spent free of disability rose from 78% in 1982 to 81% in 2011. In contrast, women enjoyed much smaller increases in LE and the proportion of life lived without disability remained at 70% over the whole 30 years.”
“Some of this increased disability for women comes from the fact that they tend to suffer from more diseases and health conditions, particularly non-fatal ones like arthritis. Another study in Newcastle, the Newcastle 85+ Study, recruited a cohort of over 1000 men and women born in 1921, aged 85 years at first interview, and followed them up for five years. At age 85, women had on average five diseases compared to men who had four ([http://www.bmj.com/content/339/bmj.b4904](http://www.bmj.com/content/339/bmj.b4904)).”

“But it’s not all doom and gloom. For both the UK and US, however, increases in disability were, at least, in less severe form. Our study also showed positive results for mental health in that, for women, all the extra years were free of cognitive impairment.”

**Are cognitive and physical disability related as we get older?**

We generally measure disability by the degree of ability to perform daily life activities (ADLs) without difficulty or help. Basic ADLs involve personal care, such as bathing, going to the toilet, dressing and getting in and out of a bed or a chair. Activities that tap less severe disability, and known as instrumental ADLs, are those required for maintaining a household – for example, doing the shopping, laundry or making a hot meal. Many of these require both mental and physical function, but activities related to cognitive abilities are typically managing money and medications.

Someone who cannot dress unaided, for instance, might be cognitively impaired, which means they might dress inappropriately without help, or have arthritis, which means they cannot do up buttons or zips. But, cognitive and physical functions are also related because they share common risk factors. One good example is obesity, which increases the risk for both dementia and arthritis.

Importantly, cognitive disability or dementia are not inevitable as we get older. Research from the CFAS studies has shown that not only has the prevalence of dementia reduced over the last 20 years but the most recent work finds the incidence (the proportion of people developing dementia in a given time period) has fallen by 20%, albeit mostly in men rather than women ([http://www.nature.com/ncomms/2016/160419/ncomms11398/full/ncomms11398.html](http://www.nature.com/ncomms/2016/160419/ncomms11398/full/ncomms11398.html)).
Figure: Dementia incidence rates in men and women. 
(a) Incidence rate of dementia per 1,000 person years in CFAS I and CFAS II by age at baseline interview. Natural scale. (b) Incidence rate of dementia per 1,000 person years in CFAS I and CFAS II by age at baseline interview. Logarithmic scale. 
(a) Incidence rate of dementia per 1,000 person years in men for CFAS I and CFAS II by age at baseline interview. (b) Incidence rate of dementia per 1,000 person years in women for CFAS I and CFAS II by age at baseline interview.
What role does a person’s education play in their HLE?
Early life circumstances, including education and even parental education are known to influence life health and mortality. People with lower levels of education tend to have more disease and disability and die earlier and some, but not all of this comes from later life disadvantages. In CFAS I, almost 75% of participants had only a basic education (0-9 years) with just 9% going onto to higher education (12 or more years of age). At age 65, men and women with the lowest education lived on average a fewer 0.8 and 1.4 years respectively and 0.9 and 1.9 years less free from disability when compared to people with the highest level of education. Things appear to improving though, since in the CFAS II, only 27% had 9 or less years of education and 22% had benefited from higher education. But education has a long-lasting effect. In the Newcastle 85+ Study, education was the only socio-economic measure that differentiated the different disability trajectories that 85 year olds had over the next five years, those with higher education being much less likely to be in the most disabled trajectories. (http://www.aggjournal.com/article/S0167-4943(15)00036-9/abstract)

It will be interesting to see whether these inequalities in HLE continue as more data comes in.

Jean-Marie Robine, Research Director at INSERM, the French National Institute of Health and Medical Research, who also studies human longevity, is very pleased with the outcome of Jagger and colleagues’ research so far: “The CFAS study is remarkable because it spans a period of over 20 years and concerns thousands of older people. The collected data suggest that over time people older than 65 live longer with good cognitive abilities. This is very good news and obviously related to the improved education levels of successive birth cohorts.”

Interview by Bel Dumé for Scientific American - May 2016
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Links:
• https://www.axa-research.org/fr/projets/carol-jagger
• http://www.cfas.ac.uk
• http://www.nature.com/ncomms/2016/160419/ncomms11398/full/ncomms11398.html
• http://www.aggjournal.com/article/S0167-4943(15)00036-9/abstract
• http://www.bmj.com/content/339/bmj.b4904
ABILITY VERSUS DISABILITY INDICATORS IN OLDER PEOPLE
Activities for Daily Living (ADLs)

GETTING UP
- Being able to get out of bed by yourself
- Needing help to stand up

BATHING
- Being able to wash yourself without help
- Needing help with bathing

GETTING DRESSED
- Dressing appropriately
- Being unable to match clothes

MANAGING MONEY
- Managing own bank accounts and bills
- Needing help to manage money

COOKING A MEAL
- Being able to cook a hot meal
- Not being able to prepare a meal and eating correctly

GROCERY SHOPPING
- Making a shopping list and being organized
- Being confused, and not being able to buy the right groceries in the right shop

DOING THE LAUNDRY
- Being able to load a washing machine correctly, iron your clothes and put them away in a wardrobe
- Not being able to do basic household chores

TAKING MEDICINES
- Pillbox well organized and taking the right medicine at the right time/in the right dose
- Being confused as to which medicine to take and when

©Vincent Devillard / L'agence OdyC
Unlocking the secrets of longevity in Japan
Pr Manami Inoue
University of Tokyo (Japan)

Japan has the longest life expectancy at birth in the world (86.6 years for women and 79.6 years for men in 2013) and researchers would like to understand why. Manami Inoue, professor of cancer epidemiology at the University of Tokyo and Project Professor, AXA Department of Health and Human Security, is trying to find out how selected risk factors (and especially those we have some control over) and various diseases are related. Using comparable methodology and other statistical analysis techniques, she is investigating how these risks vary across the Japanese population, depending on people’s age, gender and socio-economic status.

Identifying risk factors and pathologies
Inoue and her research team are monitoring more than 100 000 Japanese residents over their lifetimes to identify the interplay between certain risk factors and pathologies in later life. “We look at whether people become ill during the study, and if so, with which disease. We also put a questionnaire to them, asking them about their general lifestyle. We obtain hazard ratios from this data using statistical techniques like Cox proportional hazard modeling.”

This study started in the 1990s and is following people who were between 40 to 69 years old at the time. They are re-contacted every 5 and 10 years for a follow-up survey and are monitored regularly for major diseases such as cancer and cardiovascular disease, and death from all causes.

“In our research, we focus primary on premature death, and which factors increase this,” explains Inoue.

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3Hazard ratio: In cancer research, hazard ratios (or relative risks at a particular moment in time) are often used in clinical trials to measure survival at any point in time in a group of patients who have been given a specific treatment compared to a control group given another treatment or a placebo. A hazard ratio of one, for example, means that there is no difference in survival between the two groups and a hazard ratio of greater than one or less than one means that survival was better in one of the groups.
Smoking, drinking, and green tea

Some of the main results from this work so far indicate that smoking pushes up the so-called hazard ratio for premature death by 1.5 times compared to not smoking.

The researchers have also found that the hazard ratio for colorectal cancer for Japanese people who drink alcohol is higher than that of their western counterparts. This is because an estimated 50% of the Japanese population lacks the enzyme to metabolize acetaldehyde. On the plus side, they found that regularly drinking green tea, and to some extent coffee, reduces the relative risks from dying from major diseases, like cardiovascular disease.

Multivariable-adjusted hazard ratios of cardiovascular disease (A), all strokes (B), cerebral infarction (C), and intracerebral hemorrhage (ICH; D) for green tea and coffee consumption. Data were expressed as multivariable-adjusted hazard ratios adjusted for age, sex, smoking, alcohol, body mass index, history of diabetes mellitus, medication for antihypercholesterolemia and antihypertension, sports, dietary intake of fruits, vegetables and fish. Credit: The Impact of Green Tea and Coffee Consumption on the Reduced Risk of Stroke Incidence in Japanese Population DOI: 10.1161/STROKEAHA.111.677500
Could lifestyle be more important than genetic factors?

“Genetic factors appear only to play a small role when it comes to life expectancy, and lifestyle seems to be much more important,” says Inoue. “For example, Japanese women live longer thanks to their healthy lifestyle, which includes a better diet – especially for those over 50. The Japanese also consume less meat and animal fats than Westerners in general and eat more fish.

“Japanese women over 50 also drink much less alcohol than their male folk, and hardly ever smoke, which means that they are half as likely to develop stomach or liver cancers compared to men. Drinking less alcohol also reduces the risk of developing colorectal and breast cancers for women.”

Obesity is still rare in Japan

In general, Inoue’s work has revealed that the incidence of cancer in Japan overall is much lower than in European countries and that obesity there is still rare since Japanese people generally have a lower body-mass index, or BMI (mass in kg/height in cm2). This is especially true for younger age groups, and in particular for women.

“This low BMI could also help explain future projections of diabetics in Japan,” says Inoue. “We only see a serious increase in diabetes in people over 60, even though the number of diabetic patients in Japan is increasing too and will continue to increase in the future – perhaps because people are simply living longer and because diabetes prevalence increases with age anyway?

Until now, our studies have mainly focused on people who were born in the 1920s and 1930s and we haven’t really studied those born after 1960. This population group is more familiar with fast-food, for example, and, in general, drinks more alcohol than previous generations and has a more western-style diet.”
Future research must focus on younger populations too
Hiroshi Noto, MD, Director of the Endocrinology Department at St. Luke's International Hospital in Tokyo, who was not involved with this work, says that it is crucial to distinguish between life expectancy at birth and the average age of death when interpreting data on longevity. The former means "how long people are expected to live" and the latter "how long they have actually lived".

“In addition, life expectancy at birth significantly affects the death rate in childhood and this is not always correlated with that at older ages. For instance, the life expectancy at age 80 for Japanese women was 11.3 years in 2011, which is shorter than that in some other countries. Therefore, while Inoue and colleagues’ findings are pertinent and important for elderly people, studies on younger populations would indeed be good too, as the researchers rightly mention.

“Understanding the factors that allow Japanese people to live so long will be useful for global health policies, and especially for countries struggling to improve public health”
Establishing lifestyle recommendations
Such studies are important for health policy makers to establish lifestyle recommendations, she adds. “Japan will lead the way here. Since we have the longest life expectancy in the world, the recommendations put forward by our health policy makers will be keenly followed by the global community. What is more, neighboring countries, like Korea, China and Taiwan, which have similar lifestyles to Japan’s, will also be keeping a close eye on our guidelines.”

Inoue’s team is now turning its attention, among other subjects, to the increase in the cases of observed dementia in Japan. As ageing increases, so, unfortunately, does the risk of developing neurodegenerative diseases, but the problem here is that people suffering from the condition are difficult to quantify. “It is not at all like cancer, where the illness is well diagnosed,” explains Inoue. “Using general population research, we will now try and create a good way of identifying dementia and this work will be critical for predicting what happens in future generations. Ultimately, we hope to be able to answer the question: what actions can we take now to protect ourselves from dementia in the future?”

Interview by Bel Dumé for Scientific American - May 2016
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Links
• http://www.ghp.m.u-tokyo.ac.jp/profile/staff/minoue/


• Association of green tea consumption with mortality due to all causes and major causes of death in a Japanese population: the Japan Public Health Center-based Prospective Study (JPHC Study), E Saito et al. Annals of Epidemiology 25 (2015) 512e518

Total alcohol per capita (15+ years) consumption in litres of pure alcohol among drinkers 2010

Current smoking of any tobacco product (age-standardized rate) 2013

Meat consumption in Japan is much less than in the west. It is roughly 40% of that consumed in France or the United States, for example.

MEAT CONSUMPTION 2014
kg/person/year

35.7
88.9
90.1
LE and HLE at birth 2013

Mean Body Mass Index (BMI) 2014 (18+ years)

Normal: 18.5 - 25
Overweight: 25 - 30
Obesity: + 30

This data might change as younger Japanese people have a more western-style diet. They are more familiar with fast food, and, in general, drink more alcohol than previous generations.
How can we improve healthcare for people with dementia?

Pr Adelina Comas-Herrera – LSE (UK)

Adelina Comas-Herrera is an economist and research fellow at the London School of Economics and Political Science in the UK. One of her current projects involves modelling the costs of looking after people with dementia and looking into more efficient and cost-effective ways to treat and care for them (the Modem project). She is also one of the authors on this year’s World Alzheimer Report.

An estimated 47 million people worldwide have dementia and this number looks set to increase to over 130 million by 2050 as populations age. Dementia is an expensive disease to treat and manage and is currently costing the global economy over $800 billion. It will become a trillion-dollar disease by 2018 if things continue as they are.
One of the major problems here is that the huge majority of people living with dementia have not yet been diagnosed with it, and so do not receive the relevant care and treatment. And, to make things worse, even when they have been diagnosed, the care they do receive is too fragmented, uncoordinated and ill-adapted to their needs, and to the needs of their carers and families.

“People with dementia have poor access to the right healthcare, even in the most high-income countries (HICs), where only about half the people are diagnosed,” explains Adelina Comas-Herrera. “In low and middle-income countries (LMICs) the situation is even worse and the rate of diagnosis even lower, at around 5-10%. In the future, we would like these figures to increase to 75% and 50% respectively.

“As the number of people with dementia increases, particularly in the LMICs, where the population is ageing really fast, it will be difficult for the traditional specialist-led, ‘curative’ approach to dementia care to keep up with increases in need. It will be even more difficult to increase the coverage from its current low starting point.”

**Task-shifted’ and task-sharing strategies**

“In this year’s [World Alzheimer Report](#), we propose ‘task-shifted’ and ‘task-sharing’ strategies for improving this situation,” she says. “Here, less-specialised, but appropriately-trained, primary-care practitioners, together with nursing and care staff, would take over or share the day-to-day tasks of highly-trained dementia specialists (such as neurologists, geriatricians and psychiatrists).

“The unit costs of such task-shifted and shared options are lower but the evidence suggests that the quality of care and outcomes are similar. Another advantage of this approach is that less-specialised staff can be found or hired more easily, and can be trained more quickly. The result is that the dementia healthcare workforce could be rapidly scaled up to meet the increased demand for care.
“Such task-shifted and shared strategies could work in low, middle- and high-income countries,” adds Adelina Comas-Herrera. “In our report, we estimated the costs of implementing these pathways (which involve increased use of services, tests, therapies and medication as more people are identified and diagnosed) in Canada, Indonesia, Mexico, South Africa, South Korea and Switzerland. We calculated that the costs are relatively low compared to overall healthcare spending and can so be considered to be affordable. Indeed, the costs of implementing the pathways ranged from $39 per person per year in Mexico to $2113 in South Korea.

**Prescription vs generic medicines**

“The project also showed that there are very big differences in the prescription costs of anti-dementia drugs, which are very high in some countries, such as South Africa, China, Indonesia and South Korea. This is because many drugs remain under patent, are not bought in bulk and because there is a reluctance to use generic medicines. These very high costs, particularly in countries where the cost of services is relatively low, raise questions about the degree to which anti-dementia drugs offer good value in these countries, until it is possible to purchase the drugs at lower prices.

“We calculated that if generic medicines became the norm by 2030, the task-shifted and task-share-care pathways would cost 40% less than that of the current, specialist-care pathway in all three of the high-income countries we studied.”
Cost of the pathways in 2030, with current local drug prices vs. England drug prices (in US$), assuming we reach 50% diagnostic rate in HIC and 75% in LMC

<table>
<thead>
<tr>
<th>Current drug prices, uprated</th>
<th>Canada</th>
<th>China</th>
<th>Indonesia</th>
<th>Mexico</th>
<th>South Africa</th>
<th>South Korea</th>
<th>Switzerland</th>
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<tr>
<td>2030</td>
<td>Specialist</td>
<td>Task-shifted</td>
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<td>Specialist</td>
<td>Task-shifted</td>
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<tr>
<td>Cost of pathways (millions)</td>
<td>756</td>
<td>438</td>
<td>2,660</td>
<td>384</td>
<td>48</td>
<td>26</td>
<td>1,652</td>
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<td>Cost per person with dementia</td>
<td>914</td>
<td>530</td>
<td>164</td>
<td>169</td>
<td>30</td>
<td>93</td>
<td>1,641</td>
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<th>If all countries had the same drug prices as England’s prices today (uprated)</th>
<th>Canada</th>
<th>China</th>
<th>Indonesia</th>
<th>Mexico</th>
<th>South Africa</th>
<th>South Korea</th>
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<td>2030</td>
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<tr>
<td>Cost of pathways (millions)</td>
<td>629</td>
<td>311</td>
<td>260</td>
<td>24</td>
<td>27</td>
<td>5</td>
<td>213</td>
</tr>
<tr>
<td>Cost per person with dementia</td>
<td>761</td>
<td>377</td>
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<td>11</td>
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“Many countries throughout the world are now stating their aspirations to improve lives of people with dementia and their families through National Dementia Plans. The World Alzheimer Report 2016 starts to address how we can realistically move from the policy aspirations behind those Plans into more practical ways of improving service coverage, while considering the health and social care systems, workforce and financial constraints faced by different countries.”
The MODEM project

The Modem project (a comprehensive approach to modelling outcome and costs impacts of interventions for dementia) aims to find out how to make more efficient use of society’s scarce resources when treating and caring for people with dementia in the future. “In short, MODEM is reviewing effective and (potentially) cost-effective interventions being put in place around the world and then using these findings to model the impacts of making these interventions more widely available,” says Adelina Comas-Herrera. “The MODEM project uses mathematical modelling as a canvas to describe these impacts in England over the period to 2040.

“Throughout all this work there is much mention of the lack of evidence on what works well in dementia care and treatment. In this context, and as part of an effort to make the evidence that there is more easily available, we have developed the MODEM Dementia Evidence Toolkit, which is a free-to-access website providing access to a database of articles on evaluations of care and treatment interventions for people with dementia. This toolkit also contains ‘plain language summaries’ of the evidence for particular interventions and is available here: https://toolkit.modem-dementia.org.uk/”.

Interview by Bel Dumé

Links

Research funded by AXA Research Fund: http://www.pssru.ac.uk/axa/
(Research described in this article)
Could there be some simple ways to reduce dementia risks? The answer is Yes

As the number of older people increases worldwide, so unfortunately does the number of people suffering from Alzheimer’s and other dementias. Based on current trends, the number of individuals with dementia is expected to nearly double every 20 years, with nearly 60% of those affected living in low and middle income nations. By 2050, dementia could affect over 130 million people worldwide and could become a trillion dollar disease by the end of this decade.

A great deal of funding has been invested in developing medications that could prevent the progress of neurodegenerative diseases, but this is proving more difficult than first thought since these diseases are so complex and depend on a multitude of factors. But are there some simple ways to reduce cognitive decline in older people?

Miia Kivipelto, professor at the Department of Neurobiology, Care Sciences and Society of the Karolinska Institutet in Sweden certainly thinks so. Kivipelto is also an AXA research fellow and one of the researchers to have authored the recent Lancet Neurology report “Defeating Alzheimer’s diseases and other dementias: a priority of European science and society”. She and her colleagues are developing models to assess a person’s risk for developing dementia, which mechanisms drive the disease and how these can perhaps be mitigated through a range of simple measures such as changes in lifestyle. Such changes include a healthier diet (to normalize blood pressure and blood lipids, for example), physical exercise and mental training.
Putting the finger on important risk factors for late-onset dementia

Kivipelto led the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), which assessed the effects of some of the most important risk factors for late-onset dementia (such as high body mass index, BMI, and cardiovascular health) on how the brain functions. FINGER was the first ever large multi-domain randomized controlled trial of its kind in the world and we assessed several risk factors simultaneously to determine the optimal preventive effect, explains Kivipelto. We studied 1260 individuals from across Finland aged 60-77 over a period of two years. Half of these individuals were randomly allocated to an active study group and the other half to a control group.

All of the study participants were judged to be at increased risk of dementia, that is, they scored more than 6 on the Dementia Risk Score and had a cognition level that was equal to or slightly lower than the mean expected for their age.

CERAD=Consortium to Establish a Registry for Alzheimer’s Disease. mITT=modified intention-to-treat.
Credit: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)60461-5/abstract
Healthy Eating

The control group only received “regular” health advice while the active study group benefited from a comprehensive program of healthy eating, muscular and cardiovascular training and brain training exercises. For example, healthy eating advice was based on the Finnish Nutrition Recommendations (which are happily very similar to the Mediterranean diet) – see table.

<table>
<thead>
<tr>
<th>Daily</th>
<th>Finnish Diet Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10-20% from proteins</td>
</tr>
<tr>
<td></td>
<td>&lt;10% from saturated and trans fatty acids</td>
</tr>
<tr>
<td>Energy</td>
<td>25-35% from fat</td>
</tr>
<tr>
<td></td>
<td>10-20% from monounsaturated fatty acids</td>
</tr>
<tr>
<td></td>
<td>&lt;10% from polyunsaturated fats including 2.5-3 g/day of omega-3 fatty acids</td>
</tr>
<tr>
<td></td>
<td>&lt; 5% from alcohol</td>
</tr>
<tr>
<td>Carbohydrate intake</td>
<td>&lt; 55% from Carbohydrate food group with &lt; 10% refined sugar</td>
</tr>
<tr>
<td>Dietary fiber</td>
<td>25g-35g</td>
</tr>
<tr>
<td>Salt</td>
<td>&lt; 5g</td>
</tr>
</tbody>
</table>

If participants were deemed to be overweight at the start of the study, they were advised to lose between 5 and 10% of their body weight by reducing the number of calories consumed. All subjects were also told to eat lots of fruit and vegetables and chose wholegrain cereal products over refined ones, low-fat milk and meat products. They were also advised to limit their sugar intake to no more than 50g/day and use vegetable margarine and rapeseed oil instead of butter. Fish was to be consumed at least twice a week.
Physical and mental exercise

As for physical exercise, participants followed a modified version of the Dose Responses to Exercise Training (DRs EXTRA) regime (another large randomized controlled trial in Finland that focused on the effects of exercise) and were monitored by physiotherapists in the gym. The exercise included progressive muscle strength training (1-3 times a week) and aerobic exercise (2-5 times a week). The strength training exercise focused on the main muscle groups (knee, abdomen and back, upper back and arm muscles and lower extremity muscles).

Cognitive exercises, led by psychologists, focused on addressing age-related intellectual changes - that is, memory and reasoning applied to everyday activities. Individual sessions included computer-based training at home or at a study site, conducted in two periods of six months with each period comprising 72 training sessions (three times a week with each session lasting around a quarter of an hour). “Executive” functioning (how the brain organizes and regulates thought processes) was also assessed and tests here included mathematical and verbal, working memory (maintenance tasks), episodic memory (relational and spatial tasks) and mental speed (participants were asked to match shapes, for instance).
The main results

Doctors, nurses and other health professionals met regularly with the study participants over the two years. At the end of this period, their mental abilities were measured using the Neuropsychological Test Battery – a standard test for testing various cognitive domains. Their blood pressure, weight and BMI, and hip and waist circumferences were also measured.

Overall test scores showed an impressive 25% higher improvement in global cognition as compared to the control one, report the researchers, and for some parts of the test, the difference was even more dramatic. For example, executive functioning scores were a staggering 83% higher for the intervention group and thought processing speed was 150% higher. The researchers also saw improvements in participants’ blood pressure and BMI.

The figure shows estimated mean change in cognitive performance from start (or baseline) until 12 and 24 months (higher scores suggest better performance) in the participant population. NTB=neuropsychiatric test battery.

Credit: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)60461-5/abstract
**Risk factors are different in midlife and older age groups**

Carol Brayne of Cambridge Neuroscience at the University of Cambridge in the UK, who was not involved in these studies, says that quite a few of the risk factors for developing dementia appear to be most important in midlife, with changing patterns of risk as people enter the older age groups. “Modeling studies, which attempt to analyze the top risk factors and their interrelationship suggest that 30% of clinically diagnosed Alzheimer’s disease could be accounted for by the top seven risks that recently emerged from a large systematic review. We also have empirical evidence that the prevalence and incidence is decreasing in some age groups in certain countries, but the reasons for this decrease have not yet been directly explained by research. The only way to test at what life stage and in what way risk and protective measures are important for developing (or not developing) dementia is to bite the bullet and have a go at trials.

“These trials might be individualized traditional trials as in Kivipelto’s group’s work, or they could be whole populations/communities looking at changing the behavioral environment. Trials in later life, like the ones described in this article, can be done within reasonable timeframes and can look at proximal risk profiles and then dementia progression with a little longer follow-up. A range of experimental designs is needed and Kivipelto and colleagues, along with those in the European Consortium for Prevention of Dementia, have been pioneers here. It is not easy: the studies can be criticized, and their findings challenging to fully interpret (as there are still relatively few yet), but they are really important for the future.

I would also like to add that the differences across generations in some countries' patterns of dementia might also be related to earlier life investment in factors such as maternal health, improved nutrition and health care throughout early life in combination with increased educational levels. These factors are much more difficult to research and we have to look for comparison across geography, time and cultures to see how we can get a handle on these.”

Michael Valenzuela of the Regenerative Neuroscience Group at the Brain & Mind Centre & Sydney Medical School adds: “The FINGER trial was important because it showed that lifestyle modifications can, in principle, slow the rate of cognitive decline in those at risk for dementia. However, that is not the same as preventing or delaying dementia, and longer term follow up and results from other trials will help clarify this key issue. Interestingly, FINGER outcomes were much weaker than anticipated from studies of individual lifestyle interventions, and so it also begs questions about how to best combine different lifestyle interventions in a way that harnesses their benefits."
Going further

Kivipelto and colleagues, who reported on their FINGER study in The Lancet, are now following up the participants (and will do so for at least another six years) to see whether reduced cognitive decline actually leads to fewer of the participants being diagnosed with dementia and Alzheimer’s. They say that they are also looking into the various mechanisms behind the observed improvements in brain function.

The researchers have also developed the first dementia risk App based on the results of a previous study known as CAIDE (Cardiovascular Risk Factors, Aging, and Incidence of Dementia). The App, which calculates the risk of getting dementia within the next 20 years based on a person’s weight, cholesterol level, blood pressure, physical activity and years of education, can be downloaded for free for use on an iPhone or iPad. It comes in two versions: one for physicians and one for individuals. It is available in five languages: German, French, Spanish, Russian, and English as default. Other languages will be available soon.

“The biggest risk factor for developing dementia is advanced age. Large epidemiological studies have demonstrated that what is good for the heart is good for the brain,” says Kivipelto. “In other words a healthy lifestyle with physical activity, low blood cholesterol levels, not being obese, and having normal blood pressure at midlife protect not only against cardiac disease, but also against dementia.”
Awards for Miia Kivipelto

Kivipelto has received numerous prestigious awards, including the Waijlit and Eric Forsgren’s award for outstanding dementia research (2015), Best PI at KI award in collaboration with Nature (2014) and the AXA Research Award (2014). In 2016 she received the Alzheimerfonden’s award for excellent research.

*Interview by Bel Dumé for Scientific American - May 2016*

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Links

- [The CAIDE Dementia Risk Score App](#): The development of an evidence-based mobile application to predict the risk of dementia

- [A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial](#)

- [Defeating Alzheimer’s diseases and other dementias: a priority of European science and society](#)

- [Potential for primary prevention of Alzheimer’s disease: an analysis of population-based data](#)

- [EPAD](#)

- [FINGER](#)

- [Miia Kivipelto](#)
TIPS FOR A BETTER HEALTHY LIFE EXPECTANCY (HLE)

- Positive Attitude Towards Life
- Social Life Interactions
- Healthy Diet
- Exercise
- Brain Training

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Precision Medicine for treating Alzheimer’s Disease

Professor Harald Hampel
Université Pierre et Marie Curie (France)

Professor Harald Hampel is a neurologist, psychiatrist and neuroscientist and holds the AXA Research Fund and UPMC Chair on Alzheimer’s Disease (AD). He is Scientific Director of the Institute for Memory and Alzheimer’s disease (IM2A) and affiliated to the Brain and Spine Institute (ICM) at Pitié-Salpêtrière University Hospital in Paris. His research involves looking for novel biomarkers to aid successful prediction, detection, diagnosis and treatment of Alzheimer’s in its early, asymptomatic stages, and he says that Precision Medicine is the “golden gate” to effectively and safely treat this, and related neurodegenerative brain diseases.

“Every patient is unique and not everyone benefits from the same treatment for a particular disease in the same way,” he explains. “Some may even suffer more as a result. Precision, or personalized, medicine will replace the traditional and outdated ‘one size fits all’ medical approach to one that will be safe, precise and “molecularly” tailored to each individual. It will focus on an individual’s genetic and biochemical characteristics, as well as environmental and lifestyle factors, rather than simply on late-stage symptoms of the patient.”

*Precision medicine* revolutionizes our way of thinking about disease and will focus on prevention as well as cure. It could particularly benefit neurodegenerative diseases, such as Alzheimer’s, in which the appearance of symptoms (in the so-called prodromal and clinical phases) means that it is already too late to cure the patient since their brain cells are now irreversibly damaged.
Current treatments unsuccessful

Alzheimer’s is a serious worldwide epidemic and an estimated 65 million people could suffer from the disease in 2030, with this figure doubling every 20 years. Healthcare costs to treat Alzheimer’s and related diseases, which already amount to a staggering €600 billion globally, could increase by five times, potentially causing current healthcare systems to go bankrupt. At present, patients with symptoms of the disease, which include memory loss, disorientation and disruptive behavior, are treated at the very late stage with compounds such as donepezil, rivastigmine, galantamine and memantine, but these only moderately reduce symptoms and disease progression. In a word, such treatments simply come too late.

Prof. Hampel says that identifying genetic, biological and neuroimaging indicators of disease can identify at-risk people and help detect diseases in their early, “silent” or “latent” stages, in which there are no outwards symptoms, but where pathological changes are already occurring in the brain. Such stages could begin decades before a person is actually clinically diagnosed with the disease and such an approach has already met with great success in treating other conditions, such as cancer (see box).

Precision medicine tools

*Precision medicine* is now possible thanks to the availability of large-scale biological databases, such as those of the human genome, and a variety of high-throughput techniques to characterize a vast number of disease related biomarkers. Such techniques include genomics, transcriptomics, proteomics/peptidomics and metabolomics/lipidomics.

In the case of Alzheimer’s, scientists believe that it is caused by mis-folding of certain proteins expressed in the brain. These proteins, which are found inside and outside cells, then start to stick together to form clumps of tangles and plaques that partly end up circulating in the bloodstream. These clumps are toxic to nerve cells. Patients progressively lose their neurons and synapses, the biological substrate of cognition and memory, and other pathologies, such as Lewy Body and cerebrovascular diseases, can occur at the same time to complicate matters further.
“The tools we will employ to study AD include neuropsychology, at the stage where the patient begins to develop his or her first symptoms,” explains Prof. Hampel. “Then electroencephalography (EEG), because biochemical changes may induce early changes in neurophysiology. The next is medical imaging: Magnetic Resonance Imaging (MRI) to observe functional and structural alterations in the brain and positron emission tomography (PET) to observe metabolic ones. Finally, biochemical and neurochemical techniques will be used to characterize the composition of cerebrospinal liquid and changes in blood proteins caused by the disease.”

Big data and large population samples

The massive amounts of data generated by these technologies will be analyzed with advanced computational tools to produce patient-specific algorithms for early disease prediction and screening in general aging populations, before any irreversible brain damage occurs.

“In Precision Medicine, individuals will be on the table,” says Prof. Hampel, “and become active participants in research and therapeutic trials. They will no longer be just passive subjects.”

To this end, governments around the world are launching Precision Medicine Initiatives, or PMIs. In the US, for example, President Barack Obama and NIH director Francis Collins have announced the PMI Cohort Program, in which an estimated population sample of over 1 million US citizens will take part. “This population will provide biological specimens and behavioral data that will be complied into electronic health records. International collaboration is envisioned, and we intend to be a partner in this endeavor,” he adds.

An important paradigm shift

“We will see a paradigm shift towards earlier Alzheimer’s characterization, definition, prediction, detection and diagnosis to establish successful interventional prevention trials,” he adds. “This change in thinking will encompass both primary prevention (that is, actually preventing any molecular and cellular changes in the brain) and secondary prevention (preventing pathophysiological progression mechanisms and subsequent symptoms).
“Other important international initiatives include the Organization for Economic Cooperation (OECD) Task Force on AD, the EU/US Task force on Clinical Trial Development in AD and The Campaign to Prevent Alzheimer’s diseases by 2020 (PAD2020). The goal is to establish a worldwide database by integrating different cohorts and registries.”

**AD is a multifactorial disease**

“We now know that sporadic late-onset AD is a very complex brain disease,” continues Prof. Hampel. “It is a syndrome rather than a disease, with polygenic origins in which a multitude of risk factors impact diverse interacting molecular mechanisms responsible for progression. “We will mathematically model the biological processes occurring using concepts from systems theory, advanced mathematics and computational neuroscience and this will lead to the discovery and development of novel therapeutics to reverse or halt disease processes. In this context, our strategy will be to discover and investigate a wide array of drug targets.

“It will also be important to characterize and model the complex systems network nature of the brain, which makes the causes of diseases of this most complex organ so different from that in other organs, such as heart or liver. We have only just started to understand how complex the complex network nature of the brain actually is.”

Prof. Hampel’s team is developing technologies to precisely detect neurodegeneration in its earliest stages as well as develop effective interventions to prevent these neurological disorders, comments Zaven Khachaturian, who is President of the Campaign to Prevent Alzheimer’s Disease by 2020 and a Senior Science Advisor to the Alzheimer's Association; Editor-in-Chief of Alzheimer's & Dementia: Journal of the Alzheimer's Association. “Prof. Hampel is physician-scientist, with an international reputation, leading a team of outstanding investigators in the battle against the most ominous global health crisis of this century – dementia.
“All human behaviors are reflections of various aspects of brain function. Some of these ‘brain-behavior’ relationships are relatively linear and well understood (for example, sensory or motor function), while others are more complex, non-linear and not well understood aspects of brain function in neuropsychiatric disorders (for instance, cognition, personality, intelligence, memory and language). The essence of Prof. Hampel’s research program is to work out the biological mechanisms for ‘individual differences’ in people at risk for dementia by teasing-out the complexity of such chronic brain disorders using research approaches based on systems theory and applying analytical tools derived from computational biology. The successes of this team’s endeavors in this arena will no doubt revolutionize the future of neurology and medicine in general.”

The research field of oncology could serve as a model for neuroscience and neurology, but also for psychiatry, which traditionally has been treated as separate discipline. Precision medicine cancer therapies are specifically designed to interrupt oncogenic molecular pathways, which are often driven by mutations, overexpression or translocation of specific genes. Such targeted treatment works best in patients carrying a specific biomarker with their tumor metabolism and cells.

Interview by Bel Dumé

Links
• Prof. Hampel’s AXA-RF page
  • http://dx.doi.org/10.14283/ipad.2016.112
  • http://www.jpreventionalzheimer.com/all-issues.html?article=230
• Moving towards early clinical trials for amyloid-targeted therapy in Alzheimer’s disease Paul S. Aisen, Bruno Vellas & Harald Hampel Nature Reviews Drug Discovery 12, 324
• PMI Cohort Program
• PAD2020
Induced pluripotent stem cells (IPSCs) are emerging as promising tools for modeling and treating human neural diseases.

IPSCs have two main and unique properties: they can self renew indefinitely and they can become any type of cell of an organism - this is why they are called pluripotent. They have properties similar to those of embryonic stem cells (ESCs) but they are produced from adult cells (such as skin cells, for example) rather than from embryos. Indeed, when skin fibroblasts are cultured in a petri dish under the influence of adequate reprogramming factors, they can be reprogrammed into cells that look like ESCs, but which are pluripotent. This seminal discovery by Shinya Yamanaka of Kyoto University was awarded the Nobel Prize in 2012.

“It’s a bit like taking adult cells and making them travel back in time so that they behave like embryonic cells again,” explains Pierre Vanderhaeghen, professor at the Université Libre de Bruxelles in Belgium, AXA Chair in Neurosciences and Longevity. “We can maintain these cells in culture, (suspend them in time if you will) and then allow them to differentiate into other types of cells, such as liver, brain or muscle cells, by placing them in a dish containing specific morphogens (peptides secreted by surrounding cells).”
1st surprise: IPSCs can “automatically” transform into cortical cells

The major challenge here is to make iPSCs become a certain type of cell rather than another by using the right culture conditions, but Vanderhaeghen and colleagues discovered that iPSCs and ESCs can differentiate into cortical cells, without being exposed to any particular type of morphogen (Ref: An intrinsic mechanism of corticogenesis from embryonic stem cells, Nicolas Gaspard et al An intrinsic mechanism of corticogenesis from embryonic stem cells / Ira Espuny-Camacho et al., Pyramidal Neurons Derived from Human Pluripotent Stem Cells Integrate Efficiently into Mouse Brain Circuits In Vivo

“The cerebral cortex is the most complex structure in our brain and the nerve cells (or neurons) that make it up are crucial elements for its function,” explains Vanderhaeghen. “Indeed, loss of cortical neurons can lead to many neurological diseases, including stroke and Alzheimer’s. You would think that making structures as complicated as cortical cells from iPSCs would require very sophisticated cultures, but, to our surprise, we found that doing this was in fact very simple and that the IPSCs can transform into cortical cells through a ‘default’ pathway. This is because they need to receive little or no molecular signals from morphogens - and this is indeed the way that cells in the embryo become neural cells in nature.”
More surprises: forebrain and cortical cells appear and generate neurons of all six layers of the cortex

The neural tissue formed in this way is, in fact, forebrain tissue (rather than mid- or hind-brain) and this is the tissue from which the cortex emerges. But there were more surprises in store for Vanderhaeghen’s team who also observed that the cells in this tissue could then automatically start to divide into neurons that make up all six layers of the cortex.

“We do not yet know how they do this,” says Vanderhaeghen, “but we do know that they do it in a sequential way, and thus in the same way as the process naturally occurs in the developing embryo. It is important to say that although we can generate neurons corresponding to all six cortical layers in a dish, they do not actually form regular layers (as in vivo) but are rather arranged in a disorganized fashion.”

Nevertheless, we can now study these cortical cells in real time and look at some aspects of cortex development in the lab, he adds. We can also study cortical cells that have been produced from the skin cells of patients suffering from diseases of a genetic origin, such as microcephaly or from neurodegenerative or psychiatric diseases. “All these diseases are little understood because we sometimes lack the right models to study them, which makes it difficult to find a cure.”
Better understanding how the human cortex evolved and developed

The cortical cells produced could also help researchers better understand how the human cortex evolved and developed and why it is so different from that of primates and other animals. (The cortex is said to be divergent – that is, it changed a lot between species during evolution). For these studies, the researchers transplanted mouse-derived and human-derived induced pluripotent cortical cells in a pup mouse brain. They found that the cells can indeed integrate into the animal’s cortex, in very much the same way as they would naturally.

“When we transplanted human-derived neurons into the mouse brain, however, we found that they also integrated well, but that they developed at a much slower pace. The mouse neurons took around three weeks to develop whereas the human ones took around nine months. This is strikingly similar to the situation we see in nature: human brains, which are said to be neotenic, develop over decades, unlike mice or ape brains that develop quickly and in the baby animal. This result suggests that the rate of development of neurons is intrinsic to each particular species.”

This slow pace of development could explain why we as humans are good learners and continue developing our intelligence throughout childhood and into adulthood. This is not the case for apes, who although certainly outperform human babies when they are born, quickly flail behind since their development stops early on. Vanderhaeghen believes that some diseases like autism might be caused by impairments in this natural “clock”, but cautions that “this remains speculative at this point”.

Human cortical neurons transplanted in a mouse brain
Towards brain repair?

The most recent aspect of the group’s work is concerned with potential brain repair – for instance following a stroke or trauma. Here, the researchers transplanted induced pluripotent cortical cells into an adult mouse brain presenting lesions (damage) in the visual cortex and found that the new cortical cells connect to (some extent) the damaged host brain. (Michelsen KA et al., *Area-Specific Reestablishment of Damaged Circuits in the Adult Cerebral Cortex by Cortical Neurons Derived from Mouse Embryonic Stem Cells*).

![Diagram showing the process of transplanting neurons into a host brain](image-url)
“Promising though this result is, there is a lot of work still to be done before we can say for sure whether the new cortical cells could actually repair the damaged regions,” stresses Vanderhaeghen. “We observe that the new neurons are present and connected, and that some of the host cells even respond to visual stimuli (as the visual cortex does) but, since our cortex has not evolved to integrate new neurons, we do not yet know to what extent the new cells will be able to interact with the old ones. Although there is evidence that this is possible in some species (amphibians and fish, for example), there is yet no evidence for this happening in mammals.

“This work is still at the experimental animal model stage and whether the strategy can indeed work in real clinical settings will require a lot more research,” says Vanderhaeghen.

Nonetheless, the experiments have successfully proved that nerve cells can be engineered under controlled conditions and that these cells can be transplanted into damaged cortical circuits. These breakthroughs could ultimately lead to new therapies for patients that have had an ischemic stroke or who are suffering from age-related brain illnesses.

*Interview by Bel Dumé for Scientific American - May 2016*

*photo rights arranged by @Scientific American*

**Links**

- [An intrinsic mechanism of corticogenesis from embryonic stem cells](#)
- [*Pyramidal Neurons Derived from Human Pluripotent Stem Cells Integrate Efficiently into Mouse Brain Circuits In Vivo*](#)
- [*Area-Specific Reestablishment of Damaged Circuits in the Adult Cerebral Cortex by Cortical Neurons Derived from Mouse Embryonic Stem Cells*](#)
Smart Stent Monitors Arterial Healing

Pr Abdul Barakat
Ecole Polytechnique (France)

Researchers in France are developing a new smart, connected stent containing sensors that can non-invasively monitor how an artery heals after stent implantation. The sensors can analyze whether the stent is becoming covered with too many smooth muscle cells, which can lead to potentially fatal restenosis, or if blood clots are forming on the device, which can lead to a fresh heart attack. The sensors will wirelessly transmit their data to the outside world so that it can be consulted by both patients and their doctors.

New connected devices could help doctors prescribe anti-coagulant medication for just the right amount of time

The two leading cardiovascular killers today are coronary heart disease and stroke. Both occur when endothelial cells, which line the artery wall, start to chronically dysfunction. The arterial wall thickens (known as artherosclerosis) and the artery itself may eventually become blocked entirely.

Coronary stents are the main way of treating this problem. These mesh-like scaffolds, usually made of metal, are threaded into blocked arteries and the structures are then expanded, generally by inflating a balloon inside the stent, to hold the vessel open.
Anti-coagulants, yes, but for how long?

The problem is that when a stent is placed in an artery, it damages the arterial wall (and in particular, completely obliterates the endothelial layer). One of the consequences is that blood coagulates on the surface of the stent. Clots formed during this process can lead to the opposite of what is intended – that is, a new heart attack or stroke.

To overcome this problem, patients are given anti-coagulants but it is difficult to know how long to prescribe this medication. Some patients heal within a matter of weeks, while others (especially very old patients) can take years to do so. And worryingly, during treatment, the patient cannot undergo any other surgical or dental procedure.

Enter connected stents

“The connected stents could come into their own here,” explains Abdul Barakat, professor at the Ecole Polytechnique in Palaiseau near Paris and holder of the AXA Chair for Cardiovascular Engineering, who is helping to develop the devices in collaboration with Instent, a start-up created in 2014 with his former PhD student Franz Bozsak. “The stents contain electronic sensors that can send information as to how quickly the artery is healing, so a doctor can stop the anti-coagulants at the right time.”

The sensors, which can be made from metals or other materials, are powered by induction (think of your bus or train pass, which works by swiping it across a magnetic support) and are placed on the different struts on the stent, which are roughly 80 μm thick. They measure around 50 μm x 50 μm x 10 μm and are embedded in a biocompatible 10 μm-thick film.
Sending the appropriate signal

When covered with arterial tissue, the sensors can distinguish between three different possible scenarios and send the appropriate signal. The first, as mentioned above, is thrombosis, or blood clotting. The second is normal arterial wall healing, which is characterized by the stent being covered with new endothelial cells. The third is restenosis, or the uncontrolled proliferation of smooth muscle cells on the stent that can re-block the artery.

“The key thing for us is to be able to establish whether the sensors are covered with endothelial cells, smooth muscle cells, a blood clot or nothing,” says Barakat. “In vitro experiments, and preliminary in vivo testing in pigs, indeed show that different signals are sent depending on the type of situation present and that the signals are sufficiently different to be distinguished.”

Towards better stent design?

Beyond continuous stent follow-up, the data produced by the sensors will also be important for understanding which stent types and designs work best for particular patients, he adds. “This ‘big data/machine learning’ aspect of our work will help us to move towards a patient-specific approach to stenting – something that is lacking right now. Ultimately, we may even be able to design better stents and move away from designs that cause the most problems.

Instent now has seven employees and its mission is to get these smart connected devices to the patient, ideally by integrating the biocompatible film that goes on the stent and the associated wireless communication system with existing stents of large manufacturers. We hope to have a fully operational prototype by the end of this year and the first clinical trials in humans could start in 2018. If all goes to plan, patients could see the first connected stents by the end of this decade.”
The approach is so promising that Ulrich Sigwart, one of the first physicians to have implanted stents into patients and who is now honorary professor at the University of Geneva in Switzerland, has decided to invest in the new project himself. "Stents have fundamentally changed the way that patients with coronary heart disease and other arterial diseases can be treated without major surgery,” he says. “Up to now, there was only one way of finding out how the body had accepted the implant, and this was in an invasive way. What is more, the duration of drug treatment to inhibit thrombosis was vaguely defined. I find the concept of monitoring proper endothelialization of stents from the outside most attractive as it allows us to keep an eye on such implants so that we can make clinical decision without bothering the patient."

A connected future

The new stents follow the trend for connected medical devices in general, and we need to prepare ourselves in the best way possible for this new era, says Barakat. There is huge promise, but we need to be conscientious and responsible. Patient privacy is crucial and the data from these technologies will need to be protected.

Interview by Bel Dumé for Scientific American - May 2016
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Links
• Abdul Barakat:  
• Instent
Selected Bibliography

International reports

- Papers No.3: Dependency, AXA, 2012
International networks

- **BRIDGEHEALTH** - BRidging Information and Data Generation for Evidence-based Health policy and research
  - (see presentations of the meeting entitled 'The EU healthy and active ageing target; aiming for two additional healthy years at birth by 2020. At midpoint, where do we stand?')

- **EHLEIS** – European Health & Life Expectancy Information System

- **IAGG** – International Association of Gerontology and Geriatrics (IAGG) – **GARN** – Global Aging Research Network. **White book on frailty**, Editor-in-Chief Bruno VELLAS,
  - English
  - French
  - Spanish
  - Chinese
  - Japanese

- **INED** – **Groupe De Recherche Longévité et vieillissements**

- **MODEM Project** - Modelling Outcome and Cost Impacts of interventions for Dementia

- **MoPAct** – Mobilizing the potential of active ageing in Europe

- **Reves** – International network on health expectancies– Réseau espérance de vie en bonne santé
  - Interpreting health Expectancies
Research articles

Dementia and cognitive impairments

“A decline in chronic disability prevalence occurred 1982 to 1999 in the U.S. elderly population parallel to declines in severe cognitive impairment. [...] Several possible explanations of such a surprising trend in elderly age dementias are discussed, including (i) increased proportion of better educated people among the oldest old; (ii) recent declines in stroke rates (these may contribute to decreasing risks of post-stroke dementias); (ii) expanding use of neuro-protective medications working prophylactically for selected dementias”

A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II,
“This study provides further evidence that a cohort effect exists in dementia prevalence. Later-born populations have a lower risk of prevalent dementia than those born earlier in the past century.”

A comparison of health expectancies over two decades in England: results of the Cognitive Function and Ageing Study I and II,
“During the past two decades in England, we report an absolute compression (ie, reduction) of cognitive impairment, a relative compression of self-perceived health (ie, proportion of life spent healthy is increasing), and dynamic equilibrium of disability (ie, less severe disability is increasing but more severe disability is not). Reasons for these patterns are unknown but might include increasing obesity during previous decades. Our findings have wide-ranging implications for health services and for extension of working life”
Research articles

Dementia and cognitive impairments

New Insights into the Dementia Epidemic, The new England journal of medicine

Incidence of Dementia over Three Decades in the Framingham Heart Study, The new England journal of medicine
Claudia L. Satizabal, Ph.D., Alexa S. Beiser, Ph.D., Vincent Chouraki, M.D., Ph.D., Geneviève Chêne, M.D., Ph.D., Carole Dufouil, Ph.D., and Sudha Seshadri, M.D. (2016)
“The 5-year age- and sex-adjusted cumulative hazard rates for dementia were 3.6 per 100 persons during the first epoch (late 1970s and early 1980s), 2.8 per 100 persons during the second epoch (late 1980s and early 1990s), 2.2 per 100 persons during the third epoch (late 1990s and early 2000s), and 2.0 per 100 persons during the fourth epoch (late 2000s and early 2010s). Relative to the incidence during the first epoch, the incidence declined by 22%, 38%, and 44% during the second, third, and fourth epochs, respectively. This risk reduction was observed only among persons who had at least a high school diploma [...]. The prevalence of most vascular risk factors (except obesity and diabetes) and the risk of dementia associated with stroke, atrial fibrillation, or heart failure have decreased over time, but none of these trends completely explain the decrease in the incidence of dementia”

Cognitive reserve as a predictor of healthy aging
“Many studies point out the existence of individual differences both in the levels of age-related cognitive impairment and in the way this impairment occurs: some people can tolerate brain damage for a longer time without showing external signs of damage. The concept of cognitive reserve emerges as a useful and interesting approach to explain this phenomenon. This paper attempts to describe the state of the question as regards the cognitive reserve. It refers to an active process by which the brain adapts itself to a situation of impairment by using cognitive resources in order to compensate this impairment. It is a concept that cannot be measured directly but through indirect indicators. The most common indicators to measure the cognitive reserve are: level of education, occupation attainment and lifestyle. Many studies suggest that high values in these indicators go together with a high level of cognitive reserve and, therefore, play an important protective function against the development of dementia. We conclude this article with a set of practical recommendations to stimulate the cognitive reserve and age healthy”
Research articles

**Precision medicine**

**PRECISION MEDICINE - The Golden Gate for Detection, Treatment and Prevention of Alzheimer’s Disease**, JPAD
“The precision medicine strategy facilitates a paradigm shift in Neuroscience and AD research and development away from the classical “one-size-fits-all” approach in drug discovery towards biomarker guided “molecularly” tailored therapy for truly effective treatment and prevention options. After the long and winding decade of failed therapy trials progress towards the holistic systems-based strategy of precision medicine may finally turn into the new age of scientific and medical success curbing the global AD epidemic.”

**Longitudinal studies on disability**

**Educational differences in disability-free life expectancy: a comparative study of long-standing activity limitation in eight European countries**, Social Science & Medicine
“In this study, the socioeconomic differences in disability-free life expectancy were compared among eight countries from throughout Europe in the early 2000s. [...] Our results demonstrate that highly educated Europeans can expect to live longer and to spend more years in better health than those with a lower education. The size of the educational difference in disability-free life expectancy varies significantly between countries. The smallest differences appear to be in Southern Europe and the largest in Eastern and Northern Europe. In Italy and Spain, long life expectancy was associated with long disability-free life expectancy, suggesting that long life expectancy can be associated with the postponement of disability.”

**Trajectories of Disability in the Last Year of Life**, The new England journal of medicine
Thomas M. Gill, M.D., Evelyne A. Gahbauer, M.D., M.P.H., Ling Han, M.D., Ph.D., and Heather G. Allore, Ph.D. (2010)
“Our results suggest that the need for services at the end of life to assist with essential activities of daily living is at least as great for older persons dying from organ failure and frailty as for those dying from a more traditional terminal condition such as cancer, and that the need is much greater for older persons dying from advanced dementia. Nonetheless, the absence of a predictable disability trajectory based on the condition leading to death for most decedents poses challenges for the proper allocation of resources to care for older persons at the end of life.”
Informal caregiving

The relationship between informal caregiving and mortality: an analysis using the ONS Longitudinal Study of England and Wales

Susan Ramsay, Emily Grundy, Dermot O’Reilly (2013)

“Many studies of carers’ health outcomes have found evidence to suggest that informal carers are at a higher risk of experiencing poorer health. However, there is little work looking at carers’ mortality risks and the results from existing analyses are inconsistent. This study [...] finds that carers are significantly less vulnerable to mortality than non-carers. These results are in keeping with similar research on Northern Ireland. However, the England and Wales data also afford more uniform conclusions about a carer’s baseline health status. Importantly, these findings contradict the idea that carers are necessarily healthier than non-carers, and in doing so, they suggest that there is a need for more work which focuses specifically on assessing the validity of the selection hypothesis as an explanation of carers’ survivorship advantage. The comparative mortality advantage revealed in this analysis challenges common characterisations of carers’ health and draws attention to important differences in the way carers are defined in existing analyses”

Prevention / Social policies

MAPT Study: A Multidomain Approach for Preventing Alzheimer’s Disease: Design and Baseline Data, JPAD,


“Due to the multifactorial aspects of AD, multidomain interventions appear to be an original and potentially effective way to prevent dementia”
Prevention / Social policies

A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial,
“Findings from this large, long-term, randomised controlled trial suggest that a multidomain intervention could improve or maintain cognitive functioning in at-risk elderly people from the general population”

Health, frailty and disability after ninety: Results of an observational study in France, Gerontology and Geriatrics,
“This study shows the diversity of health states in very old age and points out that one quarter of the people aged 90 and over said frail are likely to take advantage of preventive actions of disability.”

Peter Alders, Hannie C. Comijs, Dorly J. H. Deeg (2016)
“Our results show that the decline in institutional care in the Netherlands in the period 1996–2009 is not the result of changes in need for care [...]. Our analysis indicates that there is a substantial time effect, suggesting that with the same level of disabilities and chronic diseases and the same support system, the rate of admission to an institution would be 32–40 % lower in 2006–2009 than in 1996–1999 [...] This time effect might consist of the combined effect of changes in policy (such as more home care or supply factors), technological advances in housing, use of personal alarms and changes in social norms.[...] changes in LTC use are not due to shifts in the disability distribution but can almost entirely be traced back to changes in the way the health care system treats disability. Older adults with mild disability are more likely to be treated at home than before, whereas severely disabled individuals continue to receive institutional LTC. [...] This paper shows the difficulty to make any predictions from new policy actions and how these may impact on the admission rates at large. Further research is necessary to disentangle the developments at the macro-level. To be able to make predictions about future need for care, we need to know whether and to what extent the effect of policy, social values and technology play a role and how they reinforce each other. Ideally, future research takes into account changes in these factors over a longer period of time.”
Prevention / Social policies

Frailty: An Emerging Research and Clinical Paradigm—Issues and Controversies,
Howard Bergman, Luigi Ferrucci, Jack Guralnik, David B. Hogan, Silvia Hummel, Sathya Karunanithan, and Christina Wolfson, 2007
“The work done to date on frailty has opened exciting new horizons. It has the potential of furthering our understanding of the aging process and offers the hope that we can identify vulnerable older adults with the goal to prevent or delay adverse consequences. More work is necessary to advance our understanding of the difference between frailty and aging, its relationship to chronic disease, its determinants and pathophysiology, and the identification of its core components. At this time, it is too early to “close the discussion” on the issue of whether frailty is a medical syndrome with its own pathophysiology. Despite the debate on the exact nature of frailty, there is no disagreement on its catastrophic impact on older individuals, their families (particularly those involved in providing support to the older individual), and on society as a whole. Ultimately, work on frailty will only be relevant if effective health promotion, prevention, treatment, rehabilitation, and care interventions can be identified.”

Iatrogenic disability

Preventable Iatrogenic Disability in Elderly Patients During Hospitalization, Sandrine Sourdet MDa, Christine Lafont MDa, Yves Rolland MD, PhD, Fati Nourhashemi MD, PhD, Sandrine Andrieu MD, PhD, Bruno Vellas MD, PhD
“This study shows that the incidence of iatrogenic disability is high in elderly hospitalized patients and that in most cases, it could be prevented. We need to adapt our hospital care system to an aging society. Because of the fact that each year an increasing number of adults over 75 years of age are hospitalized, if we are able to prevent iatrogenic dependency by 30% to 50%, we can postpone dependency for millions of older adults worldwide.”

Assistive technology

The everyday use of assistive technology by people with dementia and their family carers: a qualitative study, BMC Geriatrics,
Gibson et al (2015)
“This paper reports on a qualitative study exploring the everyday use of AT by people with dementia and their families.”
Actuarial associations

**Long-Term Care – A Review of Global Funding Models**, Institute and Faculty of Actuaries, 2014

**Long-Term Care News**, Society of Actuaries, Long term care Insurance section, August 2016
  - [https://www soa org/Library/Newsletters/Long-Term-Care/2016/august/ltc-2016-iss-42.pdf](https://www.soa.org/Library/Newsletters/Long-Term-Care/2016/august/ltc-2016-iss-42.pdf)
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Facts and Figures*

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