Global Health and Molecular Medicine

Introduction

Every year, human life expectancy increases. More sophisticated technology, better nutrition and greater access to care all contribute that people in many regions of the world having a chance of staying healthier longer. This should be great news. But with greater longevity comes a different set of problems. Our bodies now have more years to manifest diseases in new ways. Older people not only need treatment for chronic illnesses and conditions, but also more intensive care every day. Treatment has to be carefully coordinated and financed. While health care in the developing world is still unable to meet basic expectations, the global North is already striving to develop ways to reshape its health care system to deal with demographic changes to come.

As participants at the OCF conference made clear, in developing countries the great killers are still present. People living in economically and politically fragile regions of Africa and Asia are often denied medicine and preventive care. AIDS, infectious diseases and the lack of basic nutrition stalk people young and old. There is often little regulation as to how care is distributed, and the aid that comes is sometimes delivered by international agencies without a clear focus or ability to connect with local populations.

"We have to help politicians on a national and international level to remember that many countries do not have adequate medical services," says Axel Haverich, head of Cardiothoracic, Transplant and Vascular Surgery at Hanover Medical School. "There needs to be more equal access in places like Africa, South America, and China."

On the other hand, for people living in developed countries there are promising cures on the horizon. A stem cell expert says that pioneering therapies may dramatically alter outcomes for some of our most pernicious diseases, like diabetes. Understanding our genetic building blocks better could help turn back our bodies' clocks. Targeted cancer treatments might delay or even defeat the full impact of the disease.

The sessions' scientific advisors and numerous speakers emphasized that to continue making progress at both the macro and molecular level in medicine, people need to talk across specialties and continents. The OCF conference was an opportunity for participants to look past the boundaries of their expertise and day-to-day work: Policy makers talked with doctors on new strategies to care for quickly aging populations. Epidemiologists and development specialists crafted solutions for people who die long before their time because of poverty and preventable disease. Representatives of large health agencies sought the help of grassroots players to better understand the differing needs of populations in different regions.

"Interdisciplinary meetings are difficult to conduct but they are what is needed now," says Karl Rudolph, Director of the Institute of Molecular Medicine at the University of Ulm and, like Haverich, scientific advisor for the sessions on Global Health. "We need to discuss not only basic aspects of science but also look at social impact in different areas of the world." Only through collaborative efforts can medicine make the progress we need to offer people better, sometimes longer and often more comfortable lives.

25,000

people in the European Union die because of a serious resistant bacterial infection each year.

75%

of Africans live in villages or communities with inadequate or no sanitary facilities.

20,000–30,000

genes are in the human genome, coding for up to 500,000 proteins.

3,000,000

people would not die from diarrheal diseases each year if they had access to safe drinking water.

9,000,000

children worldwide under the age of 5 die every year, most from easily preventable causes.

A Graying World

"The average person will be living longer than ever before."

Colin D. Mathers is a senior scientist at the World Health Organization in Geneva. He works in the Evidence and Information for Policy Cluster.

Development in human health is going through parallel transitions. As richer countries begin to worry about diseases of old age, the developing world is pushing past the point where its primary concern is child mortality and communicable disease. Will we ever live in a world where everyone can hope to live to old age? Colin Mathers, a senior scientist for the World Health Organization, shed some light on this question at one of the OCF sessions on Global Health.

According to our best estimates, there's been a dramatic increase in life expectancy in all regions of the world since 1950. In high-income countries, it's gone from a bit over 60 years to around 80 years when you average male and female life expectancies together. In low-income countries, it's much lower – life expectancy has gone from around 40 years in 1950 to close to 60 years today. These statistics can be a bit deceptive, of course: Average life expectancy at birth takes into account the impact of infant-child mortality, early adult mortality and mortality at older ages. That means when a country's average life expectancy is 40, the statistic includes a lot of people who die in their first year of life as well as those who live longer.

I'm not going to dwell on the demographic transition, but rather explore the epidemiological transition from high mortality to low mortality and the associated transition from high fertility rates to low fertility rates. The combination of these two phenomena leads to a dramatic shift in the population age structure. The difference between Yemen, where 44 percent of the population is under 15, and Japan, where only 13 percent are, is very striking in terms of the age distribution of the population.

Over the past few centuries, there have been dramatic declines in both child and adult mortality in developed countries. More people are living to old age. Premature adult mortality and child mortality have both declined dramatically, e.g. in Sweden and other developed countries.

As a result, the population of developed countries has aged dramatically, as in the case of Japan. Currently, around 22 percent of people in high-income countries are aged over 60. By the middle of the century it'll be around 30 percent. The transition will be even more dramatic in developing countries. Today, around 7 or 8 percent of the population of developing countries is over 60. By 2050, it's projected to rise to around 20 percent. That's similar to the developed countries today, but with a steeper curve and more difficult transition as a result.

The developing world is undergoing what scholars in the 1970s first described as an epidemiological transition, or a characteristic evolution of mortality that has been observed in different regions of the world. Initially, populations are at risk of dying from infectious diseases and related diseases like under-nutrition, high levels of maternal mortality and high levels of child mortality due to poor birth conditions. As societies develop, the risk of death from infections and those maternal and child causes diminishes dramatically, and the risk of death from degenerative diseases rises. In part, that's because people are living through the younger ages and so they're getting to older age, where the accumulated damage results in degenerative diseases – in particular, cardiovascular disease, cancer and respiratory disease. The age balance of the population changes as well, as more people make it to old age thanks to a decline in communicable diseases.

"Child mortality is on the decline all over the world, according to the latest analysis of global trends."

Impacts on Mortality

Child mortality – the risk of dying under the age of five – is on the decline all over the world, according to the latest analysis of global trends in child mortality from UNICEF and the WHO. The trend has varied across all regions, and in fact in terms of percentage decline, the decline is actually lowest for sub-Saharan Africa, with around a 30 percent decline over 20 years. Some regions have had declines of 60 or 70 percent since 1990. In most places, the risk of dying under the age of 5 has been halved since 1990. Still, the United Nation's Millennium Development Goal is to have a 75 percent decrease by 2015, and the world is not going to achieve that, although some countries and regions will.

Maternal mortality is also dropping. Africa, India, and parts of Asia still have dramatically higher maternal mortality rates than the rest of the world. India alone accounts for more than a quarter of the world's maternal mortality deaths, for example. In developed countries, however, maternal mortality is so low that it's essentially nonexistent – take Australia, for example, which has 10 or 15 deaths per year, each of which is obviously very carefully looked at individually.

HIV obviously has had a dramatic impact on global health, and particularly African health and mortality. In parts of Africa, there have been significant reductions of life expectancy due to HIV of 20 years or more. But our best estimates now are that the epidemic, at least in global terms, appears to have peaked and is on the decline. Part of that is associated with antiretroviral therapy, which keeps people alive much longer. Widespread antiretroviral coverage may well be also impacting incidents in that it reduces the viral load and reduces the risk of transmission. So if you have everyone on antiretrovirals, even if they're not practicing safe sex, you will reduce the epidemic.

When it comes to tuberculosis, there have been major efforts to scale up coverage with "directly observed short-course therapy", also known as DOTS. These efforts have had some impact, but have been slower than anticipated, in part because tuberculosis is an opportunistic infection in HIV-positive people.

The high levels of HIV in Africa, therefore, have kept tuberculosis levels relatively high.

So, turning now to look at adult mortality or the causes of death and the levels of mortality risk for adults between 15 and 60, there is a dramatically high death rate in Africa, which is to a large part due to HIV/AIDS and other infectious diseases, not to mention hunger and malnutrition. In Europe, there remain gaps between the lower-middle income countries of Europe, predominantly former Soviet countries, and their richer neighbors. Eastern Europe has the second-highest level of premature adult mortality in the world, largely due to cardiovascular disease and injuries. In Russia, for example, mortality rates due to cardiovascular disease, injuries, and so on remain extremely high. Whether there's a political will to tackle those at a population level in the short term remains to be seen. In South-East Asia, which is dominated by India, there are also reasonably high levels of infectious diseases. But other developing regions have largely passed through the epidemiological transition in terms of the impact of communicable diseases, maternal diseases and other factors. Most importantly, China and India are amongst the countries that will have passed through this epidemiological transition.

"It's reasonable to expect research breakthroughs on things like cancer, Alzheimer's, and regeneration and rejuvenation technology."

China, in fact, already has. Its adult mortality rates are lower than in parts of Eastern Europe, and child mortality also is quite low.

As populations' age and life expectancy increases, we're going to more intensely focus on the fatal and nonfatal diseases of aging. Money will be rolling in for dementia research and for therapies to prevent damage that leads to these diseases.

Narrowing the Gap

Can the mortality gaps between developed and developing countries be substantially narrowed? There are a number of new technologies that may accelerate progress, some of them available primarily to the rich: Nanobots will clean our bloodstream in the near future, and it's reasonable to expect research breakthroughs on things like cancer, Alzheimer's, and regeneration and rejuvenation technology. Such technology will benefit the rich, and will perpetuate the gap between rich and poor in terms of health – although if developing countries can learn from the best of the experience of developed countries, maybe they can catch up.

On the other hand, climate change and environmental degradation may have significant negative impacts. I'm involved with a WHO group trying to model the health impacts of climate change. It's really hard to do. For example, some of the models are fairly simplistic: If temperature rises, then the malaria mosquito will start breeding, for example. Well, maybe. But maybe not. I don't think Switzerland will have a malaria problem, however hot it gets, because the Swiss have lots of money and they'll just kill the mosquitoes. It's really an issue of adaptation and the ability of societies to adapt. And there are harder issues with climate change around the extreme climatic events, which may severely impact parts of Asia and elsewhere in the form of heat waves, diseases tied to floods, and other unpredictable forces.

For the time being, continued global financial instability is thought to be a blip on the horizon, having no long-term impact. Certainly, in the short term, it has had a significant impact on the WHO and other international agencies' abilities to fund some of their primary activities. The global fund for tuberculosis, malaria, and HIV have all had significant shortfalls, partly due to the global financial crisis. That may translate directly into a shortage of bed nets in the next couple of years, which will lead to a resurgence of child deaths in Africa due to malaria.

The projections essentially assume that the risk trajectories in developing countries will be similar to what's been seen in developed countries over the last 50 years. But if the risk trajectories in developing countries end up being worse because they fail to control tobacco, alcohol, blood pressure, and other public health threats, things may well be substantially worse than in high-income countries down the line. Already, the age-specific risks of cardiovascular death are higher in many middle-income countries than in high-income countries, in part because of poorer health systems and uncontrolled primary risk factors.

"As diseases mutate and shift in response to antibiotics ... there's a risk that we'll face new killer diseases."

And there's always the risk of new or resurgent infectious diseases. The devastating toll of HIV over the last three decades is a warning on that front. As diseases mutate and shift in response to antibiotics and other countermeasures, there's a risk that we'll face new killer diseases – drug-resistant tuberculosis, for example – in the future.

It is almost certain that the developing world will largely pass through the epidemiological transition and also contend with aging populations in which chronic conditions dominate. This should not be seen as a bad thing, since the average person will be living longer and most likely with lower mortality risks than ever before. But such optimistic trends may be offset to unknown degrees by climate change, population and resource pressures, and the potential emergence of new diseases.

This is a condensed version of a speech given at the OCF conference's session on Global Health and Molecular Medicine. More material can be found at www.ourcommonfuture.de/mathers

Fighting the Diseases of the Future

"The revolution in information and communication technology opens up new possibilities."

Rudi Balling is a German geneticist and director of the Luxembourg Centre for Systems Biomedicine.

Infectious disease is one of the greatest threats facing the world in the decades to come: unpredictable, fast-moving, difficult to track, and potentially more deadly than anything we've ever seen before. Rudi Balling, a German geneticist and director of the Luxembourg Centre for Systems Biomedicine, says the solutions to the epidemics of the future are cooperation between scientists and a holistic approach to biology that accounts for the complexities of today's world.

Infectious diseases have had a major influence on the course of history. More than once, the casualties in wars from infectious diseases outnumbered those from man-made weapons. Up to the end of the 19th century, not much could be done. The development of public health hygiene principles, the discovery of penicillin, and the development of vaccines, however, have dramatically changed this. The public health measures were so efficient that in 1967 the Surgeon General of the United States declared the end of the era of infectious diseases.

This was, of course, premature, as we know by now. Today we are not only faced with newly emerging pathogens, i.e. HIV, SARS or avian influenza, but also with pathogens that we thought we had eliminated, such as tuberculosis and malaria. The most serious of all is the increase in antibiotic resistance. Multi-resistant bacteria are now identified in many hospitals and even in public places outside of hospitals. Our antibiotics have started to fail and for many of the viruses, i.e. HIV or hepatitis C virus (HCV), we do not have any vaccine or efficient antiviral.

The consequences are very severe. Over the last 30 years, more than 25 million people have died from AIDS. Respiratory diseases and diarrheal infections have killed more than 5 million people, most of them children, according to the WHO's senior scientist Colin Mathers. The SARS epidemic, which spread within a few weeks and caused the shutdown of entire cities, such as Toronto, has demonstrated the vulnerability of our society in times of high mobility. Today Boston, tomorrow Hong Kong or New Delhi, and back to Frankfurt, is not an uncommon travel agenda for many people. Viruses often travel along with these passengers. Whereas we enjoy our increased mobility, the global nature of travel and business is one of the major drivers of global infectious disease epidemics and pandemics. Our world is small and for infectious diseases this means that it is easier for them to spread. In addition to increased mobility, climate change has the potential to alter the distribution of infectious diseases on our planet. As a result, malaria may spread into geographic areas where it was far too cold for the parasite to survive.

At the same time that globalization increases the chances of infectious disease transmission, the revolution in information and communication technology opens up new possibilities to fight infectious diseases. Today it is much easier to set up efficient surveillance programs, supporting early countermeasures. We are faced with several main challenges in our attempt to understand, prevent and treat infectious diseases.

Uncertainty

When we try to predict how many cancer, cardiovascular or neurodegenerative disease patients we will see in our hospitals 20 to 30 years from now the demographics of our population does give us a fairly good estimate. Many Western countries still enjoy an increasing life expectancy. This will be followed by an increase in chronic age-related diseases. We already know that in two to three decades the number of Alzheimer's and Parkinson's disease patients will be more than double what it is now. We can also predict that as a result of our changing lifestyle, obesity and diabetes will rise. This is not only a problem for Western countries, but also for many developing countries.

Unfortunately, it is much more difficult, if not impossible, to predict when and which infectious disease epidemic will hit. HIV was first discovered in 1981, but the infection took off rapidly after that. SARS arrived almost overnight, without any warning signal. Scientists had been warning of new influenza viruses for quite some time. Nevertheless, when the swine flu appeared in Mexico and California, the world was not prepared. This unpredictability and the stochastic nature of infectious disease emergence are the largest challenges that we face. This is somewhat comparable to tsunamis or earthquakes. There is an urgent need to come up with "early warning signals" that can better predict when and which pathogens might emerge.

> "Systems biology not only looks at components, but tries to address the characteristics of the entire system."

One of the most promising measures to cope with this uncertainty is the fostering of international relationships between scientists and other professionals. In many cases, when political dialogue has broken down or failed, scientists are still able to maintain constructive relations.

Some of the unpredictability can be reduced through these international personal networks. They can lead to an increase in the quality of infectious disease surveillance, the speed of information flow from one continent to the other or the exchange of key information about the nature of a specific pathogen. Awareness helps to increase preparedness.

Complexity

Almost all diseases are multifactorial and multigenic in nature. It is well-known that individual people can differ dramatically in their susceptibility or resistance to infectious disease. According to British geneticist Adrian Hill, our "genetic background" can have a strong effect on how effectively we are infected, how quickly and efficiently we mount an immune response or whether we become immune after a first infection. There are more than 20,000 genes in our genome, coding for more than 100,000 proteins. The result is a combinatorial explosion when we try to model and simulate the response of infectious diseases to new drugs or vaccines.

Systems Biology

Infectious diseases are the result of extremely complex interactions between two evolving genomes, that of the host and that of the pathogen. These interactions are strongly influenced by environmental factors, such as nutrition or stressful situations. For this reason, knowing the components of a complex system such as an emerging infection is insufficient. The design and development of new vaccines or antivirals require an understanding of the entire system, especially the topology and dynamics of the underlying molecular and cellular networks. It is currently impossible to predict the behavior of a pathogen to evolutionary pressure, such as chemotherapy.

As a result of the Human Genome Project and the technological advances in DNA sequencing, transcriptome, proteome and metabolome analysis, we have made great progress in identifying most of the components in the human body and importantly of the pathogens that infect us. However, we are far away from understanding the mechanisms of infectious disease pathogenesis. Without this understanding we cannot expect to be able to design efficient drugs that not only kill or slow down the pathogen, but that also avoid the development of antibiotic resistance.

Biomedical research during the last 50 years has succeed by focusing on increas-

ingly smaller parts of the systems and by an attempt to reduce complexity by an analytical approach. We now realize that this approach is limited if we want to understand and predict the behavior of entire multiscale emerging systems, such as those that we find in living organisms. Complex systems such as infectious diseases often show a highly nonlinear behavior. It is for this reason that we now see a strong interest in systems biology.

Systems biology not only looks at components, but tries to address the characteristics of the entire system. Systems approaches have been very successful in engineering, social sciences, and many other disciplines. This approach is now also moving into the life sciences, mainly because of the revolution in genomics. A key factor was the development of technology to sequence DNA. Within a decade, the cost of sequencing an entire human genome has come down from tens of millions of dollars into the range of a few thousand dollars. This trend will continue and has also moved into the high-throughput generation of RNA expression data. Single molecule sequencing and mass spectrometer-based proteomics and metabolomics will further accelerate the transformations in biology and biomedicine.

University of Washington researcher Jay Shendure and his Stanford University colleague Hanlee Ji have argued that it will not be long before genomic sequencing will become a commodity and, as a result, constitute an integral part of biomedical research, medical routine diagnostics and therapeutics. These developments will have a great potential to improve our understanding of the mechanisms of infectious diseases. This will guide future vaccine and antiviral drug design and enable the development of effective public health policies and measures. The challenge will be whether and how we are able to transfer these technologies to the developing world. Rapid DNA sequences of pathogens at the "point of care" has tremendous potential, but as described requires a rather high tech environment, which is often not available in less-developed countries.

Interdisciplinarity

High-throughput functional genomics and genetics need to be combined with information technology, mathematics, computational biology and engineering approaches. It is a combination of experimental and theoretical approaches that will be necessary to describe, analyze, and predict the behavior of complex biological systems. Most biologists do not have adequate training in mathematics, statistics, or physics, all of which are required for successful modeling and simulation of infectious diseases. It will be necessary to change the curriculum of the next generation of students. Biological systems and human diseases can only be understood using a highly interdisciplinary approach. This will not be restricted to the classical natural sciences such as biology, chemistry, or physics, but also needs to encompass an understanding of our climate and the changes we observe using the social sciences, psychology and economy.

Top-Notch Infrastructure

Research in the life sciences has undergone another change within the last decade. Collaboration and resource sharing have become an important element not only in the design and implementation of the experiments per se, but also in the establishment of large-scale, capital- and human resource-rich infrastructure. Top-notch infrastructure is a key attractor for becoming competitive on an international level and staying that way. As a result of the progress in sequencing the human genome, the analysis of biological systems has largely been driven by efforts to automate and miniaturize individual assays. This has led to "Big Biology"– laboratories which are characterized by major capital investments, i.e. in robotics, automatic imaging capture devices and IT infrastructure. The costs for equipment and human resources to operate and manage high-throughput infrastructure are substantial and the replacement cycles become shorter and shorter. We need to come up with solutions to enable developing countries to participate in the potential and opportunities in the biotechnological and biomedical area.

As a result of the increasing efficiency in genomics, proteomics and metabolomics, we are currently witnessing an explosion in the amount of data derived from biological experiments and clinical research. This requires the development of new bioinformatics tools. The challenge of data-rich biology and medicine is not only in pattern recognition, but becomes increasingly a problem in data security, data handling and data archiving. The increase in the amount of data produced greatly exceeds our storage capacity. Individual institutions are not able to maintain the fast and expensive cycles in equipment and infrastructure necessary for genomic, proteomic or bioinformatics analysis of biological data. For this reason it is necessary to share technology platforms, i.e. in bioinformatics, high-throughput fast sequencing, proteomics or metabolomics, which serve not only a few research centers, but also increasingly a larger number of research institutes, i.e. within a region, a country or even beyond. This demands new modes of international cooperation.

Outlook

Infectious diseases will never be completely eliminated. Fighting them will always be an arms race, driven by evolutionary forces, between the infected host and the infecting pathogen. Uncertainty and complexity are the hallmarks of infectious diseases. Our best counterattack is probably the ability to work across disciplinary boundaries in order to understand in detail the underlying mechanisms. Maybe we will discover and understand general rules of complexity and new ways to dissect complexity. This will not only be relevant for biology and infectious diseases, but will touch upon many other areas.

This is an edited version of a lecture given at the OCF conference's session on Global Health and Molecular Medicine. A full version and bibliography can be found at www.ourcommonfuture.de/balling

African Researchers Join Forces to Solve Continent's Troubles

In Africa, the continent where basic drugs are needed most, home-grown research moves slowly due to a lack of infrastructure, funding and coordination. Cameroonian drug design researcher – Fidele Ntie Kang hopes that a new effort will get more Africans involved in drug development, from sorely needed anti-malarial drugs to therapies for AIDS and other illnesses. Addressing participants at the OCF conference's session on Global Health, Kang explained how joined forces of scientists and other players could help the continent.

Fidele Ntie Kang, born in 1976, is a researcher in drug design and development at the University of Douala in Cameroon with a special interest in promoting trans-African cooperation.

In 2003, Fidele Ntie Kang watched his 31-year-old sister die of tuberculosis in a Cameroonian hospital.

The experience was transformative. Now a drug design researcher at the University of Doula in Cameroon, Kang's work to develop treatments for common maladies that still kill countless Africans each year is motivated by the memory of his sister.

The numbers are stark: Although Africa has 11 percent of the world's population, it is beset with more than 25 percent of the world's disease burden. It accounts for 60 percent of the world's AIDS cases. Malaria, a disease virtually unknown in the global North, is endemic in 42 of the continent's 46 countries and kills a million Africans each year. The tuberculosis that killed Ntie Kang's sister claims the lives of half a million more. The results put some of the region's countries at the extreme end of the world's demographic tables: A girl born in Lesotho can expect to live 42 years less than her counterpart in Japan.

The health situation in Africa causes untold human suffering, as well as a negative impact of tens of billions of dollars to African gross domestic product. Yet Africans play a negligible role in developing drugs for scourges such as HIV/AIDS, malaria and tuberculosis. And because there's little money involved in treating the world's poorest people, the diseases are low on the priority list for major drug companies.

Kang is one of a growing number of researchers trying to fight that trend. He's working with colleagues to create new drugs and acting as a sort of unofficial spokesman for the African Network for Drugs and Diagnostics Innovation (ANDI), a newly formed group sponsored by the World Health Organization, that aims to increase collaboration between African scientists. "We have to take care of our own," he says. "We have to figure a way to make things better here."

The Cameroonian knows the challenges faced by African drug researchers first-hand, because he lives with them every day. At the University of Douala, there are regular power outages and the computers Kang uses are often not powerful enough to do the analyses he needs.

A lack of lab infrastructure means key drug compounds must often be sent overseas for testing, leading to weeks-long delays. An unreliable phone network can make communication between colleagues difficult, let alone contact with researchers abroad.

The toughest problem for African drug researchers, Kang says, is a lack of funding not only for research, but also for basic scholarship. Because the University of Doula suffers from perpetual funding crises, the faculty is short-staffed and there are often more students than professors can handle. Many students also struggle to pay university fees – Kang himself had to work for a few years after high school in order to be able to afford his education.

Nonetheless, Kang says he and his colleagues are making incremental progress. He's especially interested in finding new ways to battle tuberculosis and is conducting computer-assisted research on new tuberculosis drugs. And he hopes ANDI and programs like it will help foster collaborative research in African universities.

Project leaders hope to have ANDI firmly established by the end of 2011. They are working to create a governance structure, recruit staff and plan an innovation fund to spur African drug development. Once in place, the fund could receive money from governments, the private sector or non-governmental organizations. "A few years ago, we didn't have any direction," Kang says. "Now we have a plan to move forward and change things."

Elizabeth Blackburn is a professor of biology and physiology in the Department of Biochemistry and Biophysics at the University of California, San Francisco. In 2009, Blackburn won a Nobel Prize for her work on telomeres, together with her colleagues Carol Greider and Jack Szostak.

Body Clock: Telomeres, the Indicators of Aging

Telomeres are to chromosomes what aglets are to shoelaces: They are like little end-caps that keep the string of DNA from unraveling. Telomere discoverer and Nobel Prize winner Elizabeth Blackburn talked to participants in the OCF session on Global Health about how telomeres have emerged as a good indicator of cellular aging – and have been connected to chronic diseases of aging like cardiovascular disease, diabetes, and cancer. Recent studies show that stress can interfere with telomere maintenance, while meditation may boost these chromosome caps. In an interview, she also pointed to the responsibility scientists have to society at large and the policy implications of her research.

Are telomeres a natural mortality device?

Blackburn: We don't know if that's what they evolved for. But in humans, who live far longer than what we were necessarily selected for evolutionarily, one sees clear relationships between diseases of aging, risks of aging and shortness of telomeres. So they are an indicator of diseases of aging. They're not necessarily an indicator of longevity, but they have emerged in elderly cohorts as a measure of how many years of healthy life a person has, which is really quite interesting. Years of healthy life is the number of years one has before succumbing to one or another of the things that happen in old age – be it disease or frailty or lack of functionality in one way or another.

So are shorter telomeres indicators of aging, or causes?

Blackburn: Well, they're certainly indicators. I think the science challenge is to try to sort out what is causal and what isn't. There are very good reasons to think there's causality, as shown by the somewhat more extreme cases of rare genetic mutations that prevent telomeres from regenerating. There are many people on the planet who have telomerase gene mutation defects, which very clearly cause extreme forms of diseases that mirror a lot of the things that do happen in the more general population as they age. So that kind of causality is clearly genetic.

Are there examples of the reverse situation, where people have unusually resilient telomeres?

Blackburn: People have looked into the situation for centenarians, and there have been surveys of the genetic variants that you find in centenarians. A few things have shown up, and they include telomere maintenance genes – but they include other things as well. How they all play together is unclear, but there's a definite smoking gun there. In terms of wider implications, I'm still very cautious, because centenarians are a pretty rare group. Their numbers are going up, but they're still a minority.

In the gray middle zone, the vast majority of humanity – we have to be cautious about overinterpreting from the extremes about how much is causal, and how much is interacting with other pathways. But if you draw a line between the extremes, it's an extremely reasonable one.

Are there factors besides genetics that come into play when it comes to telomeres?

Blackburn: A lot of us die of heart disease, of cancer, of diabetes – illnesses where there's not a strong genetic input in the majority of the population. But beyond genetics, that's where things get extremely interesting, because there are further factors that affect heart disease, like chronic stress. You can quantify the effects of chronic stress on telomere maintenance.

How do you eliminate confounding factors that might confuse the picture?

Blackburn: I come from the molecular cellular research world, so I need to collaborate with people who have great expertise in clinical studies. It's important to collaborate with people bringing in really different expertises. I've learned from them that it's important to remember that confounders are not necessarily confounders – they can be interactors, and those can be informative. We're looking very closely at those things as well. We have studies looking at depression, post-traumatic stress, adverse childhood events and telomere maintenance, and there are some very clear links.

Has enough research been done to conclusively say depression and stress have a direct effect on telomere maintenance?

Blackburn: It's just beginning. One has to first of all do the studies and see what shows up, and then push it further and further. But there are clear relationships between chronic stress, extreme forms of clinical depression, and various other syndromes and telomere maintenance. We still need to understand these links.

Are there policy implications to that knowledge?

Blackburn: In the medical and scientific and policy communities, it's often about what we can measure, whereas nursing professionals often say that the gold standard is how the patient feels. Chronic stress, for example, sounds very vague to a lot of people. Yet we have studies of people who are caregivers for people who are chronically ill – mothers of chronically ill children, or caretakers for people with Alzheimer's or dementia, and their telomeres are especially short. These individuals are not the patients, but they are under a lot of stress that goes on for a long time. Their perception of stress is quantitatively related to cardiovascular disease risks, which is a pretty expensive disease when you get it.

Anything you can think of as a policy that gives tools for these caregivers to cope with this stress sounds like a no-brainer, but the health care systems in the United States don't work like that. You can't always take stressful situations out of people's lives, but if they have real disease consequences you can say OK, maybe it's worthwhile putting things in place that treat stress as a serious situation as well.

So the idea is to prove to policy makers that by measuring telomeres you can develop new methods to deal with stress?

Blackburn: You can say someone's just whining, and shouldn't be taken seriously. Some people are born whiners. But if you have quantitative measures of stress, like telomere maintenance, you can give it an objective measure. As we look at health care, there are a lot of situations that may not look that severe individually but add up to quite a large burden. These are worth taking seriously, and we've stumbled into this by having a set of measures.

How deeply should scientists be involved in the larger public debate on these questions?

Blackburn: To me, the primary job of scientists is to do really good science – we must never lose sight of that. But being able to articulate your science is important, and a side effect is you learn to think more clearly. It's a double bonus.

On the other hand, if you're just going out and being articulate all the time, you're not really spending the time to do the science well. Everybody says you should be out communicating all the time, but I think you need to be in the lab, too – and spend time really thinking. That's the hard part, to spend time thinking.

Are today's scientists doing a good enough job, and how could the next generation do better?

Blackburn The difference between my generation and a lot of younger scientists now is that when I was at a comparable stage in my career, we had fewer research technologies to use, so we had to figure out our own ways around the problems. And we generated so much less data that we had to really think about what we had. Now you can do so much in the lab, that stopping and really thinking is really the hard part.

It's a wonderful dilemma that it's now easier to generate data than to force yourself to really grapple with what it means. In the biological sciences, the older generation scientists can encourage people to think about their results.

More can be found at http://biochemistry.ucsf.edu/labs/blackburn/

"Usually demographers underestimate longevity." Natalia Gavrilova

"There's a lot of effort to extend life span." Luis Guachalla

Leonid Gavrilov and Natalia Gavrilova are population biologists who specialize in the mechanisms of mortality, longevity, and aging. Their research has unearthed surprising and intriguing demographic trends. At the OCF conference, they spoke with OCF Fellow Luis Guachalla – a postdoctoral researcher in molecular medicine whose work involves uncovering the biological causes of aging and death – about the links between longer lives and global population growth.

Guachalla: It's not that common for younger researchers to have an opportunity to sit down and interview senior scientists, so I'm really happy to be here. I was interested in your latest paper that showed the consequences of extending life span. There are many fears that extending life span will lead to overpopulation of the world, but your results indicate that may not happen. In fact, your model suggests that in 100 years, there won't be any change in the world's population, partly because people are having fewer children even as they live longer lives. But how would it be in a longer time frame – for example, 200 years, 300 years, 400 years? Would it still be the same trend?

Gavrilov: Well, it depends on the particular model. For example if you consider the situation where you have less than two children per family, the population growth increment keeps decreasing. But in other specifications, there might be different scenarios. The key issue is the number of children per family, on average. Overpopulation depends more on fertility than on mortality. Even in the most radical life span extension scenario, you cannot get big population growth.

Gavrilova: I met the chair of our session, Professor Karl Lenhard Rudolph, director of the Institute of Stem Cell Aging at Ulm University, and I found out that he, for example, is more interested in realistic scenarios of increases in life span up to 100 years than in the very radical forecasts of life span extension. So, I made a prediction program for another scenario, which shows continuation of the current increasing trend in life span expectancy …

Gavrilov: She worked with her computer overnight, and produced completely new data. One of the great benefits of conferences like OCF is not just people coming and presenting their results, but interacting with each other during the conference to produce new results.

Gavrilova: … The consequence will be that the population will still decline, but there will be more very long-lived people and 100 years from now it will not be surprising to find people who live up to 120. But what is interesting is that usually demographers underestimate longevity, and they underestimate the growth of life expectancy. Demographers are usually afraid to assume that people will live past 110, and for this reason they usually underestimate future populations. I made no such assumptions in my predictions. This is simply a continuation of the trend of increasing life expectancy.

Guachalla: In your paper you use the example of Sweden, a very well-developed country. You're already showing a declining population. Can extending longevity maintain the population, or do Swedes need to increase their reproduction rate as well?

Gavrilov: This is very important, because people are very concerned about overpopulation, and often objections to life extension are made on the basis of "there will be too many people in the world." What they do not understand is that in developed countries like Sweden and Germany, the real problem is not overpopulation but on a long time horizon you have a drastic decline in native-born population. You have a demographic catastrophe. Of course you can solve this problem with immigrants, but then you can lose your cultural identity, you can lose your language. Life-extension technology is not a part of the problem, but part of the

Luis Guachalla, born in 1980, works at the Research Center for Molecular Medicine at the Austrian Academy of Sciences.

Population biologist Natalia Gavrilova is a research associate at the Center on Aging, NORC (National Opinion Research Center) at theUniversity of Chicago.

solution. Any intervention that increases healthy human life span would really help in this situation.

Guachalla: One observation to this point – extension of life span is not always associated with improved health quality. If human beings reach 130 years of age, what would be your recommendations on retirement age? There's a hot debate in Europe right now on this topic. The French for example, are complaining that they are not willing to work two, three or five years longer. But if people live to be 130 and keep the current retirement age, it means that they will only spend half their life working.

Gavrilova: The main consequence of longevity is accelerated population aging. Current societies are not ready for this challenge. But I believe that it is not only a challenge, it is an opportunity. Older people have more experience and knowledge, maybe require only short education for new jobs. This is an asset to society. But current regulations do not encourage older people to work, and sometimes there is even forced retirement after a certain age. Governments are doing this in a not very gentle way, just raising the retirement age without giving people a choice. But you could, for example, give people who want to work longer some incentives and let people who are frail or don't want to work that option. Currently, though, Western societies are not ready for the challenges of an aging population.

Guachalla: Ideally, it would be nice to not only live longer but also have a good quality of life. The aim is being 80 or 90 but still being able to do tasks a young person can do. We can live until we're 130 or 140, but we don't want to be trapped in bed connected to oxygen tubes. I think there's a lot of effort to extend life span and also improve quality of life in the elderly.

Gavrilova: The few people who survived to old ages in the past were much healthier at age 80, because otherwise they would have succumbed to disease at an earlier age.

Leonid Gavrilov is a research scientist at the Center on Aging, NORC at the University of Chicago.

Guachalla: I come from a developing country, Bolivia. Would you say the same rules would apply for life span extension in a developing country as in a developed country?

Gavrilov: This is a more political question than scientific. It seems to me there is a lot of low-hanging fruit, so to speak. It is much easier to clean water to avoid cholera epidemics, for example, than apply expensive antiaging treatments. There are so many things that can be done in developing countries to increase healthy lifespan that it would be a waste of resources to push the idea of anti-aging interventions at this point. In many countries with short life span, there are much easier ways to add years of healthy life than high tech antiaging interventions.

Gavrilova: It's interesting, because the trends are diverging in the developing world. Take Malaysia: We found that in Malaysia the life expectancy is close to Western countries. They're really healthy, even though it's a rapidly developing country. On the other hand, Russia, which is considered a highly industrialized country, has a very, very low life expectancy. For men it is 59 years, lower than in China.

Gavrilov: It has to do with heavy, heavy alcoholism. It would be insane to make some antiaging intervention before you eradicate alcoholism from the culture in Russia. They simply refuse to do the easy part.

Guachalla: Talking about external factors, something that has been discussed a lot is climate change. Do you think climate change will have an impact on life expectancy?

Gavrilov: Just recently, there were extreme heat waves near Moscow that hadn't been seen in 100 years. There was a spike in mortality among older people, and there are different estimates but the most conservative estimate is that the death rate increased by a factor of two. Climate, if it becomes a systematic problem, really adds to the pressure on life expectancy.

Educating Peers

Youth Education and the AIDS Crisis

The global fight against AIDS is waged on many levels. International, national and local advocacy organizations all try to educate people about the disease and fight its spread. But for years there has been a major flaw in AIDS advocacy: Organizations rarely engaged young people in the process. Kenyan Constance Walyaro, a member of the Global Youth Coalition on HIV/AIDS, points out that a key to solving the African AIDS crisis is engaging the young in spreading public-health messages. Invited as OCF Fellow to the conference she talked to workshop participants at the session on Global Health.

How do AIDS and HIV specifically impact young people?

Walyaro: Well, in 2003, about half of all new HIV infections in Africa were among people between the ages of 15 and 24 and they were the most vulnerable population. Right now, we have made progress, but young people still remain vulnerable. In terms of infection rates, those numbers have gone down thanks to better information, treatment and care.

What tactics have made an impact when it comes to education and prevention?

Walyaro: One thing that has been working well is the capacity building and technical assistance. We, at the Global Youth Coalition on HIV/AIDS, have been providing a lot of free online courses. We have been providing young people opportunities to attend health conferences, where they get to meet with professionals who have more information about what is happening. We also give them an opportunity to showcase what they are doing. At the same time, we have made it possible for international aid conferences to actually have a section that just focuses on people under 25. This is much more engaging. Before, many youths attended these conferences, but there was no space for them. Right now, people under 25 are driving the process much more.

Kenyan Constance Walyaro, born 1979, is the president of Citron Wood Foundation, a nonprofit devoted to empowering poor communities. She is working towards a PhD in health economics, policy and law.

How has involving youth in the process changed AIDS/HIV advocacy?

Walyaro: We found in the past that governments, donors, and big organizations realized that young people were vulnerable to HIV, but that segment of the population was only brought in during the implementation stage of projects. So we did a lot of advocacy work and insisted that under-25s be involved not just at implementation stages but at the decision-making, planning, monitoring and evaluation stages. It turns out they had a lot to contribute to the processes.

What was the first thing that the young people changed about the process? What had adults overlooked?

Walyaro: One of the simplest things that came from it was that young people like to hear from other young people. They'd rather hear about HIV/AIDS and sexual reproductive rights from their fellow peers as opposed to having people who represent their parents telling them to use condoms, practice safe sex and get tested. So having peers talk to each other about HIV prevention and advocacy has really helped and pushed the agenda forward.

Do you find that commitment is flagging?

Walyaro: Absolutely. In the beginning, everyone was talking about HIV and AIDS. That was a major focus. There was so much support. But right now, it is just like any other disease. So it has lost a lot of the clout that it used to have. It is a bit worrying, because if the general trend continues and people begin to forget where we've come from with regard to HIV and AIDS, we could see ourselves regressing and losing some of the gains we've actually made.

How has your youth impacted your work? Do you think you bring a fresh outlook to these issues?

Walyaro: I think a lot of us young people – like the OCF fellows – bring a different perspective because there definitely is a generational gap. It is very refreshing to find young people who are interested in development issues. Because I think sometimes the older generation has this picture of young people that they are rowdy – that they really have no concern for the future and for the world. But there are many people who are doing something positive and contributing to the future of the world.

That sounds like a tenet of your youth-to-youth education: Policy makers should have more trust in young people. Young people have the capability to make impact and be the leaders of tomorrow.

Walyaro: Yes – and not tomorrow. We are actually leading right now.

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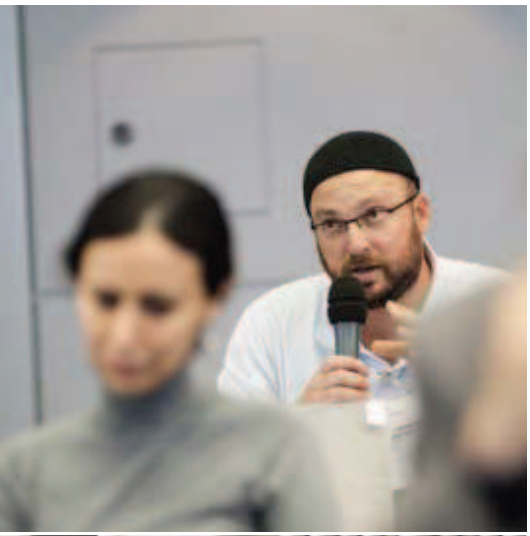




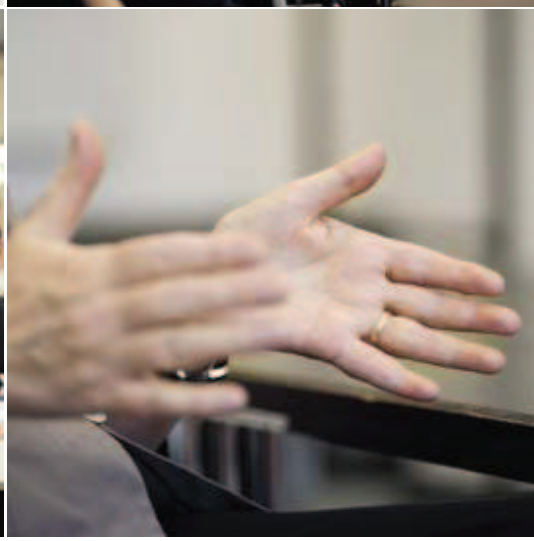

Impressions from the conference.

4 Questions, 8 Answers

"What fact makes you the most optimistic about our common future?"

Haverich: Younger scientists are more willing to look beyond the boundaries of their own research and collaborate with experts in other specialties and regions.

Rudolph: Medical care has improved dramatically over the last 100 years. I think, in principle, we can handle new challenges. Human intelligence will find solutions to the most pressing issues.

"What is the greatest challenge facing us in the next 25 years?"

Haverich: We have to remind politicians to strengthen aid to countries that don't have adequate medical and social support. There needs to be more even distribution and access to medical treatment.

Rudolph: In the medical sector, the biggest challenges are aging and cancer. I also think we need to make sure that industries take better care of the environment. Wasting the planet's resources will ultimately affect health.

"What piece of advice would you give young researchers in your field today?"

Haverich: I would advise young researchers to develop a broader understanding of concepts outside of their fields. Personally, I get most of my ideas when I go to meetings of other specialties.

Rudolph: We need more physician scientists. In order to have further increases in health span, we need physicians who understand the molecular causes of disease.

"What was the most surprising insight you had at this conference?"

Haverich: Elizabeth Blackburn's discussion about biochemical changes in cells and aging was fascinating. She gave some very good examples of how physical exercise can help us live longer and reverse the aging process.

Rudolph: I was really excited to see how stem cell research is translating into medical applications, for example, in the treatment of cancer.

Axel Haverich and Karl Lenhard Rudolph served as scientific advisors for the OCF sessions on Global Health. Haverich is head of the Department of Cardiothoracic, Transplant and Vascular Surgery at Hanover Medical School (MHH). Karl Lenhard Rudolph is director of the Institute of Molecular Medicine and head of the Max Planck Research Group for Stem Cell Aging at the University of Ulm.