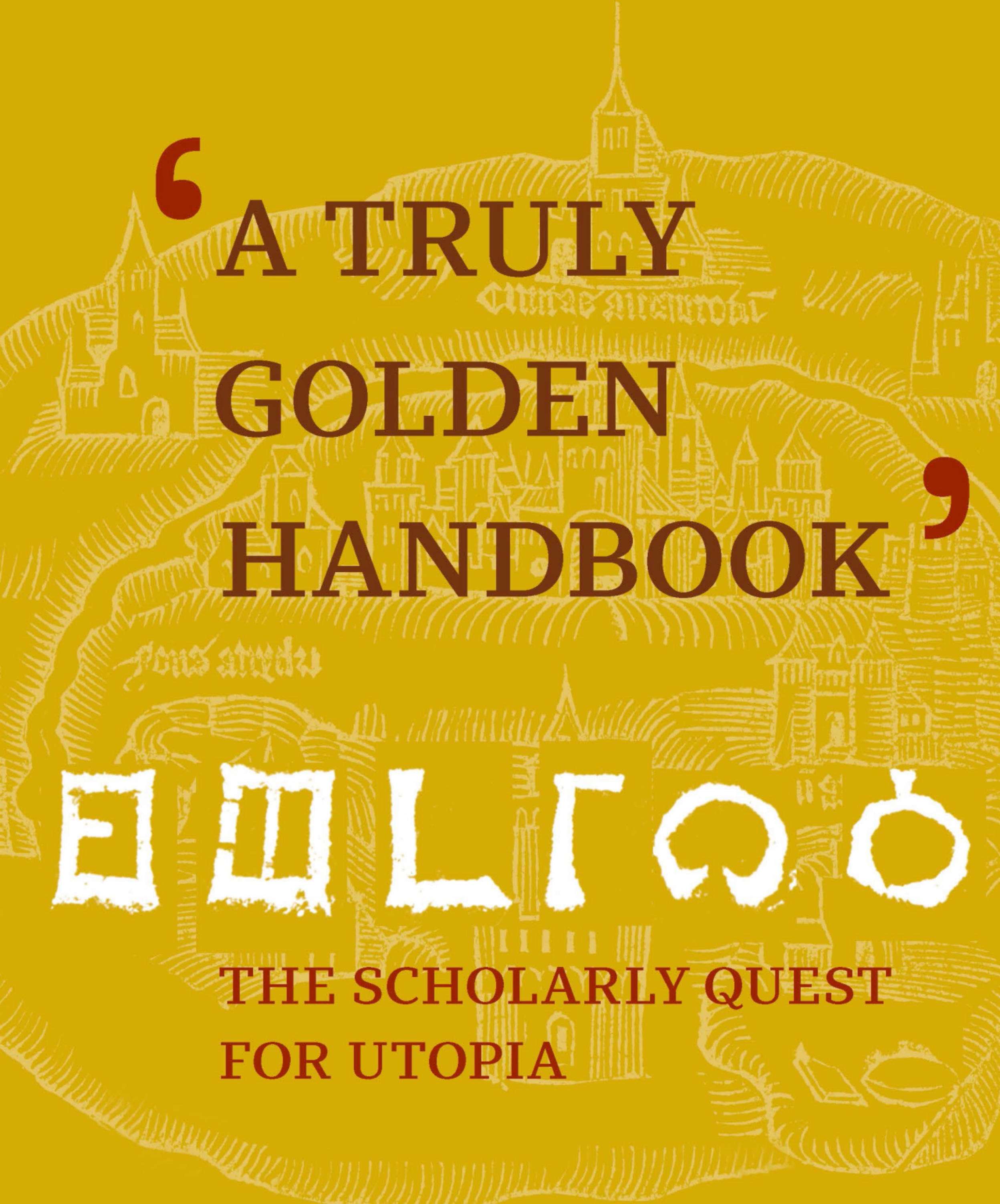

'A TRULY GOLDEN HANDBOOK'

THE SCHOLARLY QUEST FOR UTOPIA

Veerle Achten, Geert Bouckaert
and Erik Schokkaert (eds)

LEUVEN UNIVERSITY PRESS

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Introduction

Veerle Achten, Geert Bouckaert and Erik Schokkaert

What would the ideal society look like? In 1516 the English humanist Thomas More tried his hand at imagining a perfect society on a distant island. His *Utopia* was first published in the Flemish town of Leuven, home of a university that was established almost a century earlier. 500 years later, scholars of this same university revisit More's exercise in an interdisciplinary range of science-based utopias.

More's *Utopia*, a sharp analysis of shifting powers and tensions in society and a description of another (possible?) reality, can only be understood within its historical context. At the beginning of the 16th century the need for a visionary dream of society was clearly felt. At that time intellectuals throughout Europe were analyzing, commenting on, and in some cases actively influencing the changing political, religious, and socio-economic realities. Think of Erasmus' *In Praise of Folly* (1509, written on his friend More's estate in Bucklersbury, London), Machiavelli's *Il Principe* (1513) and Luther's *Ninety-Five Theses on the Power and Efficacy of Indulgences* (1517). Leuven and its university (founded in 1425) were at the center of these debates. Pope Hadrian VI (1522-1523), for instance, was a professor at the university in Leuven, and his friend Erasmus spent many years in Leuven. Erasmus was also instrumental in the Leuven foundation of the Collegium Trilingue (1517) by Hieronymus van Busleyden, friend of More and recipient of one of the fictitious letters opening the *Utopia*. The printer and publisher Dirk Martens, who published More's *Utopia*, was not only the first printer in the Low Countries to print Greek, but a humanist intellectual himself.

But *'A Truly Golden Handbook': The Scholarly Quest for Utopia* is not meant to be only a historical commemoration of the 500th anniversary of the publication of More's *Utopia* in Leuven. On the contrary, we have used the occasion to look into the societal and scientific mirrors of the present and the future. This book is written by (mostly) optimistic academics from various faculties of the university of Leuven who reflect on the future, starting from their own fields of research, and on how future developments in their fields of research may impact our societies. It consists of forty-one chapters by different authors, each describing a different utopia. Some chapters depict visionary dreams for the far future, some envision the likely further developments of cutting-edge technological innovations, some bring the utopia underlying a specific societal development to the fore, and some provide a scholarly reflection on More's *Utopia* and utopian thought. One thing, however, they have in common: all these utopias are written by academics, who have used their scientific background as a springboard.

Today, like in More's time, we still need utopias to push our realities in the direction of imaginable and desirable futures – and to avoid dystopias as imaginable but undesirable ones. It remains essential for our scientists and for our societies to conceive new 'utopias', in both senses. A utopia is '*ou-topos*', a non-existent place. But it is also '*eu-topos*', a good place, a place of happiness. Additionally, this book also contains descriptions of what we could call '*ou-chronos*' and '*eu-chronos*', a non-existent time or a happy time.

Utopias and Realities

Like More's *Utopia*, the utopias in this book have to be read in the light of our own times. Utopias are connected to and embedded in their social realities. Utopias belong to their realities. They evolve with their realities, and realities evolve with their utopias. Realities need utopias, just like utopias need their matching realities. Therefore, different 'types' of utopias will appear in different circumstances. H.G. Wells points to this connection in the ending to his *A Modern Utopia*: "That is my all about Utopia, and about the desire and need for Utopia, and how that planet lies to the planet that bears the daily lives of men."[1]

In the course of the past centuries different types of utopias have been put forward. This book contains examples of all of them – and the tensions between them will be illustrated by the different contributions.

Social and Political Utopias

More's *Utopia* is first and foremost a social and political utopia. According to Micklethwait and Wooldridge,[2] a first revolution, in the 17th century, resulted in kings and queens building centrally administrated states. Cromwell supported Henry VIII in this endeavor, and Thomas More was a witness and an actor in this revolution. This centralized state grew into a Hobbesian Leviathan, which triggered a second revolution, exemplified by the French and the American revolutions, with a focus on meritocracy and accountable administrations, which in their turn in the third revolution evolved into the modern welfare state. This resulted in 'big government', which triggered a fourth revolution, based on ICT and management, which will determine a sustainable state with a future. Each more central. For Elias this helps to re-evaluate the role of imagination in social sciences and opposes the fatalism of pragmatism in research and policies.[8]

But utopian thinking may also be important for natural and biomedical sciences. In many of them the future is seen as open and to be influenced by humanity. Yet, precisely because the future is open, it is crucial to think about the kind of future we want. Scientific research itself is path dependent. Utopias sketch possible futures and invite research that may lead us in the right direction, dystopias act as a warning against possible destructive developments.

Why Utopian Thinking?

Even if for the last 500 years, "utopianism has been one of mankind's principal navigational instruments", the great lesson of the 20th century is that "asking for a blueprint of the ideal society is asking for trouble".[9] When revolutions are driven by utopias, they may result in excesses that conflict with the premises of these utopias. Utopias may be dangerous. Yet they may also be constructive, and perhaps they are even necessary.

Utopias are motivating. Utopias help us to discover possible and desirable futures,[10] dystopias make us aware of possible but undesirable futures. For this reason, utopias are wake-up calls. We need the "courage to be utopian"[11] to motivate us to take action. Utopia is "a uniquely effective form of politics. (…) elements of the utopia are gradually assimilated by the outside world, altering it in subtle but sometimes profound ways (…). Utopias are realized piecemeal, but realized they frequently are."[12] Utopias challenge realities since they allow for a shared analysis, but also for shared imagined ideals, and ultimately they allow for a voluntarist appeal to contribute to change or even revolution. Utopias can be a remedy against fear or even contribute to an agenda of hope for the future.[13]

Utopias confront us with the gaps in our knowledge. They form a 'mental experiment', in which the "imaginary procedure is used to test scientific ideas, not against the real world, but against each other, to reveal the connections between them and to seek out contradictions". Therefore, utopias are "useful as a tool of political thought", since they force us "to look at our unexamined assumptions, to explore those things which otherwise remain undisputed and undiscussed".[14]

Utopias invite a discussion on values, norms and cultures – and on the interactions between values and science. They force us to confront scientific insights with the social consequences they may lead to. In their attempt to sketch a coherent picture of a possible future, they imply a reflection on the place of science in the process of creating that future.

Utopias may contribute to the development of a strategy against fatalism. There is a tendency towards determinism in each scientific endeavor. Yet, a strong belief in determinism makes all action futile. If "guns, germs, and steel" fully determine the fates of human societies,[15] the same societies will always dominate. Utopias force us to consider the limits of determinism. Are there social mechanisms that cannot easily be changed?

Scientific insights are indispensable as well, since they can indicate at which point utopias become dangerous because of unwanted side-effects, or infeasible because they neglect either the imperfect malleability of humanity and society or the ecological and physical constraints that we cannot escape. Utopias put scientific insights into perspective – but we cannot do without scientific insights. When confronted with scientific insights, utopias may be seen to be dangerous, misleading, fascinating, irritating, inspiring, motivating, stimulating – but we cannot do without utopias either.

How to Read This Book

This book uses the occasion of the 500th anniversary of More's *Utopia* to explore different science-based dreams of the ideal society of the future, including perspectives that More could never have imagined. What will our cities look like a 100 years from now? How will stem cell research and 3D printing change the world? Will we be able to cure all diseases? Will fundamental human rights have been secured for all? Will we be traveling to other planets? Will computers take over? Or will humanity find a way to improve the quality of life for everyone and feed a growing world population? From the creation of spare organs, artificial intelligence and the genetic future, to global governance, ecological sustainability and pathways to more equality, this book wants to investigate possible futures in an interdisciplinary overview of forty-one science-based utopias. Together these chapters represent the wide range of expertise available at the KU Leuven. This richness is further enhanced by the diversity in personal and literary styles, which we have chosen to preserve.

We have tried to structure the different utopias into five thematic clusters, spiraling out from the utopian human over the utopian society, city, world and universe, via utopian knowledge, ending with a cluster on utopian reflection as such. Each chapter can be read independently, but whenever the same topic is touched upon from a different perspective in one of the other chapters, cross-references to the chapter in question have been added, as a suggestion for the reader who would like to delve deeper into the topic.

As this book has not been intended as a scientific work, we have tried to keep references to the minimum and limit them to those that could be of interest to the reader who would like to learn more of a specific topic of interest. Unless otherwise indicated, all quotations from the original *Utopia*, including those at the beginning of each cluster, are taken from More, T., *Utopia*, trans. ed. and intr. D. Baker-Smith, London: Penguin, 2012.

Like More's *Utopia*, *'A Truly Golden Handbook': The Scholarly Quest for Utopia* is a book that is clearly connected to its historical context. We are hopeful that this science-based utopian exercise will retain some interest for a reader in the far future who is curious about the utopian reflection at the beginning of the 21st century. For today's reader, we hope that these visionary dreams for society inspire him to start dreaming himself ...

Notes

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13 Thompson, P., and Zizek, S. (eds.), *The Privatization of Hope: Ernst Bloch and the Future of Utopia*, Durham (NC): Duke University Press, 2013; Elias, N., *op. cit.*
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1
The Utopian Human

Will Life Go Live One Day?

Bart De Moor, Mathematical Engineering

During the last century, both physics and biology were characterized by tremendous progress and breakthroughs. In physics, we witnessed the birth of the theories of general relativity, quantum mechanics and the first attempts to design a Grand Unifying Theory, each of them deeply rooted in an almost platonic belief in the consistency of mathematics. A turning point in the phase of intensive scientific search was the invention of the transistor. The exponential proliferation of science, engineering and technology that followed, has been tremendously beneficial for society.

The same sequence of analysis and design will occur in biology. Impressive scientific breakthroughs over more than 50 years have led to a deep understanding of the basic mechanisms of life and its Darwinian evolution. Through mathematics and technology, biology has become an information driven discipline facing a tsunami of data. These provide us with a better understanding of life, health and disease. Based on these insights, we have now started designing life and living organisms. Nevertheless, important issues remain. Among others, we lack a basic understanding of the phenomenon of 'emergence', which is ubiquitous in life and nature and which seems to offer a plausible explanation for consciousness.

In this chapter, I would like to explore three utopian visions. First, I believe that one day, we will truly understand the unreasonable effectiveness of mathematics in physics. Second, one day, we will design and build life from scratch. And third, one day, we will build artificial brains with emerging consciousness.

The Unreasonable Effectiveness of Mathematics

All of science is archeology. Take physics, for instance. The current reality of the universe is the result of 13 billion years of cosmological evolution. It has left many traces: the cosmic background radiation as a leftover of the Big Bang; gravitational waves that squeeze and stretch space-time as they propagate, and which were generated by a collision of two black holes as 'recent' as 1.5 billion years ago. Or take biology. Nature has been executing millions of genetic experiments every single day since millions of years. We call it Darwinian evolution. It has left many traces in the genomes of all living organisms. Today, we are only beginning to understand the basics of life itself. We can now imagine how it originated billions of years ago and how it has evolved ever since. Both in physics and biology, we dig up observations from a remote evolution in the past. The more we unearth, the better we understand.

The fundamental insights from physics in the search for a Theory of Everything appear to form the bedrock of the rest of science, engineering and life itself. And most remarkably, all of this is captured in the language of mathematics with an 'unreasonable' effectiveness.[1]

Mathematics is about geometry and algebra. The classic Greeks were basically geometers, think of Euclides (mid 4th century BC - mid 3rd century BC), Archimedes of Syracuse (ca. 287 BC - ca. 212 BC) or Apollonius of Perga (ca. 262 BC - ca. 190 BC). Centuries later, René Descartes (1596-1650) discovered the notion of coordinates. Geometrical forms could now be 'quantified' and represented by real (and later also complex) numbers. Their spatial properties, like surfaces, volumes and intersections, could be computed numerically. As a result, the classic Euclidean geometry could be extended in many ways, leading to a new mathematical discipline called 'algebraic geometry', considered to be the queen of mathematics. One of these extensions is towards thinking in higher dimensions, leading to 'higher algebra' since the work of 19th-century mathematicians. We can leave behind our intuitive, visual notion of geometry in three dimensions, pictures of which can often be misleading when 'working' in higher dimensions.

Descartes quantified space and time. Then Isaac Newton (1643-1727) entered the stage. It took his genius to introduce the notion of 'dynamics'. He discovered how to mathematically describe 'fluxions', properties that 'flow' as a function of time. We use 'differential equations' ever since: they describe mathematically how the coordinates of an object evolve as a function of time. Using differential equations, Newton formulated three fundamental laws of motion and a law of universal gravitation. Today, it would certainly earn him a Nobel Prize.

Since Newton, we realize that mathematics as a universal language describes nature, while reversely physics brings a lot of mathematics to life. Newton showed us how the very idea of a precise physical law and the mathematics to describe it, are born together. And then came Albert Einstein (1879-1955). For his general theory of relativity he had to fine-tune the language of Riemannian differential geometry to describe new physics. A little later, quantum physics once more impacted many branches of mathematics, from geometry and topology to representation theory and analysis, extending the pattern of beautiful and deep interactions between physics and mathematics.

At around the same time, we started realizing that our geometric intuitive notions of space and time are inadequate. The general theory of relativity taught us that there is a non-Euclidean Riemannian space-time continuum, the one indeed that is stretched by gravity waves. From quantum mechanics we learned that quantities that we intuitively think of as continuous, are actually discrete. Planck showed us that energy comes in discrete packets, called quanta. A quantum, like a photon, can simultaneously be wave and particle. The wave-particle duality was born.

And with the development of string theory,[2] for the sake of mathematical consistency we have to accept that the reality of our universe unfolds in 11 dimensions. String theory forces us to give up the notion of point-like zero-dimensional particles. They are replaced by one-dimensional objects called strings. A string is a mathematical construct. It is 'vibrating energy', and we do not really understand it. Nobody has ever observed a string, and probably we never will. But the mathematics is fine and exciting. It describes how strings propagate through space-time, and how they interact with each other. It describes how from a distance a string looks like an ordinary particle with mass, charge and other properties, determined by the vibrational state of the string. String theory is a theory of quantum gravity, i.e. an attempt to reconcile Einstein's general relativity with quantum mechanics, an attempt to unify the four fundamental forces of nature and all forms of matter and energy into one Grand Unified Theory of Everything.

For sure, there is something unreasonably effective about mathematics. As Edward Witten, one of the founding fathers of string theory, said: "There must be skeptics out there who will tell you that these beautiful equations might have nothing to do with nature. That's possible, but it is uncanny that they are so graceful and that they capture so much of what we already know about physics while shedding so much light on theories that we already have."[3]

Most scientists consider mathematics as a symbolic language in which we can describe reality. We use mathematics to 'explain' and 'understand' observations and to make predictions: why and how is Newton's apple falling to the earth? Obviously, as we increasingly unravel more details of the physical reality, we increasingly need to develop more mathematics. Johannes Kepler (1571-1630) adopted the conic sections of Apollonius to describe the elliptic orbits of the planets. Newton discovered differential equations to describe the proportionality between force and acceleration. Einstein mapped general relativity into the non-Euclidean differential geometry of Bernhard Riemann (1826-1866).

And in string theory, mathematical physicists use Calabi-Yau surfaces – wildly curved complicated surfaces in 11 dimensions, with many 'holes' in them.

The real strength of mathematics lies in its predictive power. Just by logical deduction, we can postulate events that have not been observed yet. The existence of the Higgs boson was postulated long before it was actually experimentally observed in CERN. From the mathematics of the Englert-Brout paper, we knew exactly 'where' to look. We have observed gravitational waves exactly as they were predicted by Einstein's theory of general relativity. His theory hinted at where to find them. We know that in the universe, there must exist unobserved 'dark matter', and quite a bit of it, because without it our mathematical theories cannot explain the increasing accelerations of certain galaxies as they move away from us.

So, mathematics 'explains' reality. But what if it were the other way around? What if physical reality is just a manifestation of a deeper, underlying mathematical 'truth'? Because, actually, what 'is' reality? Why is the speed of light in vacuum exactly 299 792 458 meter per second? Why is the mass of a proton exactly 938.3 mega-electron-volt? Is anti-matter gravitationally attracted or repulsed by matter (actually, we don't know)?

In their deepest dreams, mathematicians and physicists would like to come up with a theory that eliminates the need to experimentally determine the value of the 'universal' physical constants we use (there are about 20 of them). These physical constants, such as the speed of light in vacuum c, the gravitational constant G, Planck's constant h, are believed to be 'fundamental', i.e. universal and constant in space and time. Such a constant-free theory would be based on first principles, in which the value of all these 'experimental' constants derives from pure mathematics, for instance as a discrete eigenvalue of some operator, just like the energy levels of a quantum derive as eigenvalues from Schrödinger's wave equation. This for sure is an almost platonic view of reality and mathematics, cultivated by many, including Penrose and Tegmark.[4] Mathematics is not developed, nor constructed, we do not invent it, but we discover what has always been around as a hidden mathematical truth to be unraveled. Maybe there is an ideal world of perfect forms after all. And maybe all our theories rest on the prior supposition of the existence of an absolute mathematical truth.

And this platonic view on mathematics captures the first of my three utopian dreams: I firmly believe that one day, we will really 'understand', and ruthlessly exploit, the unreasonable effectiveness of mathematics. We will no longer wonder about the seemingly coincidental explanatory power of mathematics, but on the contrary, take its logical consistency for granted, and exploit its predictive power to discover 'new' physical reality. Like the Nobel Prize winning physicist Steven Weinberg once remarked: "Our mistake is not that we take our theories too seriously, but that we do not take them seriously enough". Maybe, after all, reality is just another model ...

Engineering Technology: Design Follows Analysis

In our archeological endeavors to unravel and understand physics, there is another important catalyst besides mathematics, namely technology. Mathematics and technology allow us to understand the origins of space and time. Think of the Big Bang, the cosmological background radiation, black matter and energy, etc.

The word 'technology' derives from the Greek '*techne logos*', loosely translated as the know-how to do something. Technology comprises systems, processes and artefacts that are man-made and realize a specific functionality to achieve certain objectives or implement certain challenges. Without doubt, our modern society has evolved from a biotope into a so-called 'technotope',[5] where the presence and deployment of technology is ubiquitous. Technological systems become more sophisticated, they start interacting socially, they get higher precisions and resolutions, grow smaller and more compact yet stronger, become more robust yet sustainable, and more complex yet increasingly user-friendly. In terms of 'big evolutionary history', one could therefore characterize technology as the trans-biological evolution building on the natural biological evolution. We no longer undergo evolution, we have started to accelerate it. We will shape our evolution.

This acceleration is catalyzed by mathematics and technology. They allow us to design the future and turn it into 'our' future. That's where engineering comes in, the systematic design of objects and systems, to develop new technology that integrates insights from science, craftsmanship, expertise, social experiences and earlier technology. Engineering is not only about hardware (buildings, bridges, cars, airplanes, computers, etc.). Increasingly, it is also about software, optimization methodologies, algorithms, machine learning and artificial intelligence, all of which belong to the domain of mathematical engineering. Engineering technological systems is fundamentally driven by imagination, inspiration, design and creativity. In the technotope, we engineer our own future. We apply the knowledge acquired from the basic sciences and deploy it in the development and enhancement of new technology. The famous physicist Theodore Von Karman once said that "Scientists study the world as it is, engineers create the world that has never been".

Let's look at physics once again. In the second half of the 19th century, James Maxwell (1831-1879) wrote down his four fundamental equations that describe electromagnetic fields, a gigantic achievement from which we have developed all the technology that generates and uses electricity and magnetism, light and

Sanger, Allan Maxam and Walter Gilbert (1977), the Polymerase Chain Reaction (1985), Herman the bull, the first transgenic animal (1991), the appearance of genetically modified tomatoes on the market (1994), the sheep Dolly as the first cloned animal (1997) and in 2001, the unraveling of the full human genome: we have come a long and exciting way. And the road continues.

Step by step we are unraveling the archeology of biology: we are starting to grasp how evolution did its job, how it made us into the complex living beings we are today, how species come and go, how we survive and die. In a famous abiogenesis experiment in 1952, Stanley Miller and Harold Urey demonstrated how putative conditions on the primitive Earth could have favored chemical reactions that synthesized more complex organic compounds from simpler inorganic precursors. Miller showed how amino acids can be formed by continuously firing electrical sparks (simulating the effect of lightning) through a gaseous mixture of water, methane, ammonia and hydrogen. Simply turning on the sparks in that prebiotic experiment yielded several amino acids in every case. These experiments and later more refined ones convincingly show how organic compounds of building blocks of proteins and other macromolecules can be formed from gases with the addition of energy.

Nevertheless, the whole story turns out to be much more complicated than we ever envisaged. Four billion years have created an enormous complexity. Take genes. At the beginning of the 1970s, we thought that every gene specified one protein. The basic idea was a one-to-one mapping between a gene and a protein. The genome was like a linear program, like a tape being read from beginning to end. The genes in the genome were like subroutines in a computer program, a list of parts that together would produce an organism. And the 'junk DNA' in between the coding regions of the genome was thought to contain the deactivated leftovers of millions of years of biological evolution, preserved like a useless archive.

Today, almost 50 years later, we know that the genome is not a linear script, but rather, it is a dynamic, three-dimensional structure, heavily interacting with its environment.[9] Genes are no longer considered to be static unchangeable subroutines. They may be fragmentary and act combinatorially because there is a complete jungle of badly understood regulatory and modulatory elements hidden in the 'junk DNA'. These elements can switch on and off genetic networks like we do on the World Wide Web, where we can connect with or disconnect from any other person in the world. In other words, genes can cooperate in genetic networks, the composition of which can be modulated by the environment in which specific cells are active. Epigenetics is the study of external or environmental factors that turn genes on and off. These alterations may or may not be heritable.

And there are many, many new and exciting technological developments. Take for instance genetic editing. Researchers have long sought better ways to edit the genetic code in cultured cells or laboratory organisms, to silence, activate or change targeted genes, to gain a better understanding of their role. Recently, a new groundbreaking genome editing technology was developed, known as 'clustered regularly interspaced short palindromic repeats' – or CRISPR.[10] The discovery grew out of the surprising observation that bacteria could remember viruses.[11] This mechanism was then adapted by researchers to edit DNA in higher organisms. CRISPR provides a relatively easy and effective technique for modifying a cell's DNA in precise and targeted ways. Some researchers claim it has brought about 'the democratization of gene targetting'.[12]

Many experiments with the CRISPR technology are going on these days, e.g. in some embryos researchers try to unpick the genes that control early development in humans, they disable three to four genes in the first embryonic cells and then observe what happens. Similar work in animals has taught us a lot about how mammals in general develop. One of the objectives is to try to understand why IVF success rates are so low, with only half of the embryos implanted in the womb developing sufficiently, and also to identify mutations that might lead to miscarriages. Other applications are: modifying plants, enhancing pest resistance in wheat, fine-tuning rat models of human disease, reproducing the carcinogenic effects of specific chromosome translocations in mouse lungs, or correcting a mutation in adult mice that in humans causes the disease of hereditary Tyrosinemia, a serious metabolic condition. Clinical researchers are already applying CRISPR to create tissue-based treatments of cancer and other diseases.

CRISPR is but one fine example of many fascinating technological breakthroughs. Because of technology, our basic understanding of biological systems is exploding. Multidisciplinary teams of biologists, medical doctors, statisticians and engineers deliver and digest the tsunami of data. As a result, biology has turned into an information science, in which mathematics becomes an indispensable tool. Just like in physics, there is now a 'mathematization' of biology, with the same unreasonable effectiveness. There is for instance systems biology, in which we try to understand the system theoretic interaction of all the modules in a living organism, intercellular and extracellular, and their interaction with the environment. This description of biological systems as a networked connection of interacting modules on several hierarchical levels is very reminiscent of the modular way in which we describe microelectronics circuits of billions of transistors. Actually, the methodology is identical, but the language and toolbox differ.

And these observations lead to the second utopian dream I would like to launch here: one day we will design life, in forms that do not exist in nature. Inspired by the design of electronic systems, we start thinking about designing and building biological systems, in a brand new discipline that is called 'synthetic biology'.[13] It combines biological research with engineering principles, so as to design and assemble biological systems that process information, manipulate and produce chemicals, fabricate materials and structures, produce energy or food, or maintain and enhance human health. In synthetic biology, genetic code is abstracted into modular chunks, known primarily as 'bio-parts', which allow us to build increasingly complex systems. Putting parts together creates devices such as biological 'clocks', on-off switches, cell-death mechanisms, color-changing mechanisms, etc., with a design methodology based on modular thinking that is identical to designing very large scale integrated circuits (VLSI chips) from scratch.

By combining the profound new insights in biological mechanisms with the principles of engineering complex systems, scientists can now use computers and wet lab environments to design new living organisms – 'new' in the sense that they do not exist in nature. This utopian dream, when fulfilled, would heavily impact our daily life in particular and society in general.[14]

Think of cancer cell detecting bacteria that eliminate themselves after a week if no cancer cell is found. If one is detected, however, the bacteria will destroy it, long before the cancer can be detected by any macroscopic scanner in a hospital environment. Think also of bacteria that turn purple when they detect heavy metals in polluted water.

Of course, before we can start to deploy genetic editing and synthetic biology in real world applications or commercial products, there are many important legal, ethical and democratic concerns and deficits that have to be resolved.[15] CRISPR and related technologies have the potential to revolutionize the treatment of disease, but when abused they are not beneficial to society at all. The CRISPR-Cas9 nucleases are widely used in gene editing and can be readily customized. But they can also induce substantial, genome-wide off-target mutations at sequences that resemble the on-target site. For instance, in the human embryo experiments that have been performed so far, CRISPR also cut many non-targeted genes. If one copy of a disease gene is repaired, sometimes a healthy copy is mutated as well by CRISPR. If editing is attempted in an early stage of a human embryo, sometimes CRISPR only reaches some cells and not all of the targeted ones, resulting in a mosaic embryo with some mutant tissues. Another sensitive question is whether genome editing techniques could be used for non-medical enhancement. Governments, regulators and other stakeholders are largely unaware of the breathtaking pace of genome-editing research.[16] Should the global scientific community not refrain from using any genome-editing tools to modify human embryos for clinical applications until we have sorted out all the medical and ethical ramifications?

Emergence

In all the aforementioned scientific endeavors, the aim is to get down to the basic 'atomic' levels. We start top-down, and dig our way down to lower hierarchical levels to understand how physics and biology really work. We deconstruct reality to find its basic building blocks and laws. Often this is to be interpreted literally. Think of the Large Hadron Collider at CERN, where all the elementary particles of the standard model, including the Higgs boson, are 'created' through collisions at velocities close to the speed of light. Think of full human genome sequencing, in which we reconstruct the precise sequence of 3 billion nucleotides that are linearly arranged in every double helix of every cell in our body. Here mathematics and technology help us in going from the macroscopic to the microscopic level.

Yet, the reverse is much more difficult, if not (still) impossible. How can we explain, let alone predict, the properties and behavior of a system from the properties of its individual constituents and their interaction? How to predict the characteristics of a material (e.g. a plastic) from its individual atoms and molecules? How to understand the turbulent flow of water around the rocks in a river from our knowledge of the chemical structure of water molecules and their interaction? How to understand the functioning of a human liver from the properties of its cells? How do large numbers of cells organize in processes such as tissue growth, wound healing or the spread of tumors? What is life? How can the present conditions here on Earth even exist in an otherwise cold universe? How to understand consciousness from our knowledge of neural networks? What is free will?

The fact that often the whole has macroscopic properties that are not effectively 'computable' from the knowledge of the properties of its constituents and their basic interaction laws is called 'emergence'. Emergence is a phenomenon whereby larger entities, patterns, regularities, properties, behaviors and characteristics arise through interactions among smaller or simpler entities that themselves do not exhibit such properties.

Most physical variables that we can measure are emergent. The temperature of a body or a gas is an emergent characteristic: it is basically a measure of the average kinetic energy of constituting atoms or molecules. Forces like gravitation are emergent, the emergence in this case being explained by the Englert-Brout-Higgs theory. And even the basic notions of space and time may be emergent from a different, more fundamental picture. Indeed, there is a fundamental problem with time. In physics, at an elementary particle level, almost all of the basic equations are time-symmetric: whether time ticks forward or backward does not make any difference. Yet, at the macroscopic level, we age, we build up memories and we forget, all of which are irreversible processes. There is an obvious arrow of time here. We know and experience causality in our physical reality, in which cause and effect are not interchangeable. According to the Russian-born Belgian physical chemist and 1977 Nobel Prize winner Ilya Prigogine, the arrow of time is dictated by the dissipation of energy, and is quantified by the thermodynamic notion of entropy. Entropy is a fundamental measure of the messiness, the lack of order in a physical system. As entropy grows, time ticks forward. Where entropy is involved, there is no time-reversibility. But currently we do not really understand how time-irreversibility in real life processes emerges from the lower, smaller scale layers where interactions are time-reversible.

Not only basic physical variables are emergent. Most of the laws of physics that we use every day, and that describe relations between physical variables, are emergent laws. Think of Ohm's law of electricity (the proportionality of voltage over and current through a resistor, involving billions of charged electrons and atoms of the conductor 'resisting' the flow of electrons). Think of Newton's law of the proportionality of force and acceleration. These are all physical laws that emerge from deeper, more fundamental physical laws.

Actually, emergences occur at all possible levels of reality, in physics as well as in biology, whenever one jumps from one level of description to the level immediately higher. In physics, already in 1928 the physicist Werner Heisenberg, of quantum mechanics fame, came up with a model in which he imagined every atom to be a freely rotating bar magnet and then found that large scale magnetism emerges from interactions between these atomic magnets causing the majority of them to align. Emergence in the realm of physics is called 'active matter'.[17] It is increasingly being made in the laboratory. Synthetic components on a micrometer scale that consist of light-sensitive plastic 'swimmers' form structures when a lamp is turned on.

Researchers hope that more mathematical insight in 'active matter' will coincide with more insight in the way biological systems really work. Because in biology emergence is ubiquitous. On a macroscopic scale, think of social insects, e.g. ant colonies.[18] They work without a central control, yet collectively, they achieve specific goals. Termites for instance build impressive 'cathedrals', in such a clever way that even heating and ventilation is taken care of. Yet, we assume that an individual termite has no comprehension of what they are doing collectively. Understanding how ant colonies work, might help us to understand

Prigogine's framework could perhaps be used to explain why in our earthly biotope, due to the gigantic flow of energy from the sun, nature could develop life as we experience it, surrounded by a cold and hostile galactic cosmos.

And what about our own (self)consciousness as an emergent behavior?[19] Does it emerge as the collective behavior of billions of neurons that interact? Do we lose it as soon as our brains no longer dissipate energy, or a certain critical density of interactions is locally destroyed? We don't know. In his book *Shadows of the Mind*,[20] Penrose speculates that Gödel's Incompleteness Theorem implies that conscious awareness cannot be simulated. Yet, billions of years of evolution have shown us that building an intelligent brain from scratch is possible, since every day about 350 000 babies are born worldwide, who later develop into intelligent beings. Maybe our brain uses algorithms and methods of reasoning that do not comply with the formal axiomatic systems in which Gödel thought. There seem to be several levels at work, in which "the unconscious system pieces together fragments of our perceptions, anticipating patterns and filling gaps when necessary, to devise a single meaningful interpretation. It tells a story. The conscious system experiences that story but can also reflect on it and question it."[21]

Will we one day build living organisms that reproduce and procreate? Will we one day build true artificial intelligence that can convincingly withstand the Turing test?[22] Will we one day build artificial brains in which self-consciousness emerges? There is the 1931 quote of Max Plank: "I regard consciousness as fundamental. I regard matter as derivative from consciousness. We cannot get behind consciousness. Everything that we talk about, everything that we regard as existing, postulates consciousness."

Therefore, the third utopian dream I would like to put forward here is my deep belief that one day, we will indeed build a conscious 'non-human' brain from scratch; that, in order to do that, we will understand in one way or another the phenomenon of emergence, and that we will have learned how to design it. This capacity to build artificial brains that will reason and interact emotionally and empathically, will be deeply rooted in an understanding of fundamental physics and biology, based on and inspired by sophisticated mathematics.

Physics, biology and emergent consciousness: they are deeply rooted in mathematics. Maybe, one day, in Utopia, we will bring them all together in a thorough understanding of our world.

Notes

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7 See also Philip Dutré, 'Thinking and Conscious Machines?', in this book (p. 454).
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10 Doudna, J.A., and Charpentier, E., 'The new frontier of genome engineering with CRISPR-Cas9', *Science* 346, 1258096, 2014; Travis, J., 'Making the cut. CRISPR genome-editing technology shows its power', *Science* 350:6267, 1456-1457, 2016; See also Koen Devriendt & Hilde Van Esch, 'Healthy Genes for Everyone', in this book (p. 93).
11 Looking for that mechanism, researchers found remnants of genes from past infections, sandwiched between odd, repeated bacterial DNA sequences – the 'clustered regularly interspaced short palindromic repeats'. The viral scraps serve as an infection memory bank: from them, bacteria create guide-RNAs that can seek out the DNA of returning viruses to chop up the viral genes with a nuclease, a genetic scissor.
12 In essence, the method consists of a DNA-cutting enzyme called a nuclease (usually Cas9) and a piece of 'guide-RNA' that homes in on a DNA sequence, enabling researchers to create precisely targeted mutations, corrections to mutations or other alterations. Along with two other earlier genome editors, zinc finger nucleases and TALENS (Transcription Activator-Like Effector Nucleases), CRISPR is transforming basic biology in a spectacular way. In a variation, by making 'dead versions' of Cas9, scientists have eliminated CRISPR's DNA cutting ability but preserved its talent for finding sequences. In this way CRISPR can be turned into a versatile, precise genetic delivery vehicle. For instance, one can 'ship' various regulatory factors, hence enabling them to turn on or off any gene, or adjust its level of activity. In this way, CRISPR is turned into a control device (in control theory this is called an 'actuator').
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14 For a glimpse of the near future, and the thousands of synthetic biology applications in health, energy, environment, etc., that await us, have a look at the website of the international Genetically Engineered Machine competition (iGEM), organized by MIT. Every year selected student teams convene in a large scientific 'jamboree', to present their synthetic biology designs. The iGEM *Registry of Standard Biological Parts* is a growing collection of genetic parts that can be mixed and matched to build synthetic biology devices and systems, and is in open access mode available to academic labs.
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Preventive Maintenance for a Future without Disease

Rudy Lauwereins, Medical Electronics

Imagine your car breaking down on the freeway and having to be towed to a garage. When the emergency repairs are finished, the mechanic tells you that you can now take the car with you, and if you remember to add a bit of oil here and there every so often, and don't push it too hard, you should be able to continue like this for a few more years. And should you ever be in need of a spare part: fortunately there are always traffic accidents that generate parts that can be reused.

Would you be satisfied with this approach? This is actually how health care functions today. When you break down, you are collected by an ambulance and taken to the hospital for emergency repairs. Upon dismissal, you are told to rub a bit of something here and there every so often, not to push yourself too hard, and you should be able to continue like this for a few more years. And if you should need a new part: fortunately there are accidents that generate parts that can be reused and implanted. They never quite fit and your body doesn't really like them, but if you take it quietly, you should be fine.

What we lack, is real preventive health care. Additionally, at the moment diagnostics are slow and very expensive. We have no spare parts, at least not of our own 'make', and very often health care is reduced to treating symptoms instead of actual reparation. This is not to blame physicians. The main reason is of course technical: a human being is so much more complex than a car. Even worse, the manufacturer has omitted to add the construction and repair manuals. But could we envision a different world for the future, one in which preventive maintenance can lead to a world without disease?

For this dream, perhaps we could let the recent developments in car production and maintenance inspire us and look at the options that electronics offer. I can think of four ways in which medical electronics could contribute to a world without disease, four concrete visions that make up the overall utopian dream. My first dream is that preventive monitoring would lead to a world in which we no longer have to make an appointment to visit our family doctor once symptoms occur, but in which our family doctor contacts us when it is time for a check-up or when we need a bit of maintenance, long before these symptoms appear. My second dream is that we can eventually eliminate cancer through the early detection of tumor cells, long before they reach a critical level and start causing symptoms. The third utopia is the possibility of constructing real spare parts from one's own stem cells. This may still be in the far future, but there are already some ways in which electronics can combine with stem cells in a personalized way to contribute to a world in which diseases can more easily be cured. Finally, my fourth dream is a world without neurological problems, once we are able to interact electronically with the electrochemical signals in our brain.

Preventing Disease through Monitoring

Let's look again at our car. How can we know, preventively, that anything is amiss? Modern cars are full of hundreds of sensors constantly checking every aspect of the car's functioning. As soon as something is not quite working as it should, a message is generated that advises the owner to visit the garage for maintenance. Could we do something similar, monitoring through sensors, in medicine? We could for instance build a 'health patch' full of electronics that measure many kinds of parameters simultaneously. Such a patch could take an electrocardiogram, measure movement using an accelerometer, measure stress levels via bio-impedance (measuring the amount of sweat on the hands with an extremely low strength electrical current), and even take chemical tests, e.g. the analysis of sweat. Today chemical analyses are still being developed, but in 2050 they would be widely available. The battery could be integrated into the patch, allowing it to function independently for at least a week. It could include algorithms (self-contained step-by-step sets of operations to be performed) that could predict for instance epileptic seizures, cardiac arrhythmia, etc.

This health patch could be extremely small in size. There are already several very small measuring devices available or in the final stages of development. For instance, in the near future the band of a wristwatch will be able to take your electrocardiogram, to optically measure your blood pressure (eliminating the need for invasive tests or pumping), to measure the oxygen saturation in your blood, your movement, temperature and a whole range of other parameters. Even sooner a 10 gram tiny patch will be available to be stuck to the chest with tape that is so flexible that it can accommodate your every movement so you don't notice it is there. It will again measure cardiogram, respiration, etc. Research is increasingly evolving in the direction of devices that are flexible, stretchable, very thin and, most importantly, very cheap. Items like these will eventually be available for the price of several euros instead of hundreds of euros.

Figure 1 Flexible patch for electrocardiogram, taped to the chest

What kind of measurements could be made available on such a patch? There are currently several kinds of physical measurements possible. For instance in stress analysis: a patient's stress levels can be measured by means of a band around his chest and a wrist device. Together they measure four parameters: the heart rate, the frequency and depth of respiration, skin temperature and electrical conduction on the skin (impedance) – which indicates the amount of sweat present. All four are controlled by the autonomous nervous system and therefore cannot be consciously influenced. These four parameters are then combined to calculate the stress level by means of an algorithm. The resulting level is shown in a graph. When during a stress test the patient is watching a film, for instance, the stress level will suddenly increase at the moment of suspense and drop again in less than a second as soon as the suspenseful situation has been resolved. The stress level thus fluctuates over fractions of seconds, which is instantly reflected in the moving graph. Compare this to the current standard stress test that involves using a cotton swab to take a saliva sample that is then analyzed in a lab for the stress hormone cortisol. This obviously takes a lot longer, far too long in fact to measure the many fluctuations that occur in the course of seconds.

So far for the physical measurements. An electrocardiogram, for instance, is just an electric measurement and quite simple from an electronic point of view. Chemical measurements are still more challenging, although we can expect to see these available too before long. In fact, within the next ten years

image
not
available

course be a range of different cells: several types of white blood cells, red blood cells, platelets, and possibly other cells such as circulating tumor cells. Each cell in turn is illuminated by a simple light from a LED-laser. The light interacts with the cell features, which results in holograms that are recorded by the image sensor. This technique does not require a lens, which makes it compatible with standard electronics production processes. The holograms will then be reconstructed into 3D-images – this is where the calculations come in – which can be used to distinguish between different types of cells based on their size and nuclear morphology. When the cells arrive at micro heaters further down the channel, this information will be used to sort them in different groups. These micro heaters generate small and short-lived steam bubbles that push single cells to a particular outlet. The technique is similar to that used in bubble jet printers, where ink drops are pushed through specific holes when a fluid in a chamber next to them is heated and then expands. At the very small scale used here, this heating and cooling again can happen in fractions of microseconds. This way the white blood cells can be pushed into a different outlet than for instance the tumor cells. The sorted cells can then be further analyzed.

Figure 3 An image of each individual cell is made in the cell-sorter

The type of microfluidic chip that forms the channel to guide and select the cells has already been developed, as has the chip that allows taking a 3D-picture of every individual cell using a hologram. The current challenge is distinguishing between benign cells and cancer cells using classification algorithms. Cancer cells are typically hard to distinguish because they are in fact mutated versions of regular body cells. Once this challenge has been overcome, we should be a step closer to the early detection of cancer. In fact, as soon as we are able to isolate tumor cells, this will open further options. We could for instance analyze their DNA to better understand what type of cells they are, which will give us more information on the type of chemotherapy that will probably be the most effective. For the far future, we can even imagine a larger and faster cell-sorter that could analyze all of a patient's blood cells, during a kind of 'cleaning' session, and simultaneously eliminate all the cancer cells.

Growing Spare Organs

And once we're playing with cells, we can even start looking at the possibility of constructing spare parts – my third dream. Recently, functioning lungs have been created from the stem cells of a rat – albeit only functioning for 6 hours so far. First all the cells and blood vessels are stripped away from an existing lung, leaving behind a scaffold of connective tissues, to which the missing cells are re-grown using stem cells. Lungs are notoriously bad at regenerating or repairing themselves, while a traditional lung transplant is expensive, the demand for donor lungs far exceeds their supply, and less than 20% of the patients survive for longer than 10 years with the new lungs. The aim of current research in this field is to ultimately be able to provide patients with a transplanted lung made of their own stem cells that are grown onto a donated scaffold. Since 2006 pluripotent stem cells (still having the potential to propagate indefinitely and develop into any type of specific body cell) no longer need to be multiplied from embryonic cells but can also be converted from adult body cells, by means of the introduction of four specific genes. The resulting cells are called 'induced pluripotent stem cells'.[4] This technique makes it possible to use a specific patient's own cells to create their individual pluripotent stem cell line. Because the differentiated cells will still contain the patient's own DNA, they can be used to generate transplants without the risk of immune rejection.

Where does electronics figure in this story? There are two ways in which it can contribute. The production of that many stem cells in their pure form obviously requires an efficient production system. Building an organ takes many billions of stem cells, while the commonly used static tissue culture vessels can only generate a low number of cells. To provide enough cells for clinical applications, bioreactors are needed: large tanks in which the chemical reactions that create stem cells out of mature body cells take place. These reactions also need to be very precise, with as little variability as possible, to produce such very small items at very high quality. Quite a challenge, but fortunately the know-how of such complex production processes is already available in the electronics industry, where billions of components even smaller than cells are integrated on every single chip with high yield and quality. This know-how could therefore be used to support stem cell production processes and upscale them to industrial quality and production speed. Secondly, electronics can also contribute through specific applications. Because the techniques to convert adult cells into stem cells do not always work for all the cells present in the bioreactor, it is important to check the cells after the process and eliminate the ones that have not reacted. A system that analyses the stem cells, cell by cell, and sorts them according to quality, similarly to the sorting of circulating cancer cells, would then be very useful.

We haven't quite reached the stage yet where we can reliably grow stem cells into organs ready for implantation, but an interesting side track is using stem cells to build 2D organs on a chip. It is for instance possible to grow cardiac tissue on a chip embedded in a petri dish that contracts like a regular heart, starting from a central point and then spreading out. You can actually see the heartbeats on the chip. The fact that there is only one layer of cells also means that each cell is visible. This type of 2D organ is therefore very useful for toxicity testing. The development of a new drug typically costs years of research and millions of euros. Before official approval, the drug is tested on tissue in petri dishes, on animals, and finally on human volunteers. But animals are not necessarily good analogues for humans because of fundamental differences in biology. It may happen that side effects, leading to the retraction of the medication, are only discovered in the final stage of testing on human volunteers, or worse: after the drug has been approved for widespread use. Incorporating organs-on-a-chip, grown from human stem cells, into drug testing could therefore save millions of euros and years of time on drug development. For instance, having 2D organs grown from the stem cells of thousands of different individuals available in a lab structure would make testing much more efficient,

Figure 4 Cardiac cells of a 2D heart on a chip since many different substances could be tested in parallel and for a significant section of the population. Working with 2D organs would also allow researchers to carry out experiments that are too risky for human volunteers.

Further, these 2D organs could make an important contribution to personalized medicine. The 2D heart, for instance, could specifically be used to test for cardiac toxicity. There is a particular heart drug that is used in the treatment of hypertension and cardiac arrhythmia, but that turns out to be toxic for a very small number of people. For the general population the said medicine is beneficial, but for this specific group of patients it lengthens the period of relaxation of the heart muscle, with the result that the new pulse arrives before the heart has relaxed from the previous one, causing fibrillation and ultimately a heart attack. It is hard to predict who will react in this way. Instead of having to ban this medicine altogether, with the loss of its benefits for the main group of heart patients, the problem would also be solved if we could, for specific patients who may be at risk, grow a 2D heart from stem cells and test their personal reaction to the medication before prescribing it. For this toxicity testing a system would be built around such a heart on a chip, with all the microfluidics to supply nutrients and remove waste. When adding medication and following the heartbeat of such a 2D heart for a long time, we could actually measure the same side effects as those that appear in a human heart. Such 2D hearts therefore allow a much earlier detection of problems with new medication.

Electronics in Our Brain

How can electronics help us to reach a future without neurological problems? For instance in the case of Parkinson disease, one of the possible treatments of the symptoms is deep brain stimulation, which involves the implantation of wires with four electrodes (electrical conductors across which a voltage can be applied) deep in the brain, giving electrical pulses every so often. For a reason we don't quite understand yet, this helps to repress the symptoms of Parkinson disease. It is rather like giving some of the neurons a shake every so often. The result could actually be that someone who was no longer able to even eat or drink without help, can now function fairly normally, and even work in the garden again. The drawback, however, is that the person in question experiences changes in personality. The side effects to this treatment are quite substantial because of the current size of these electrodes: they are a millimeter in size, while a cubic millimeter in the brain correlates to 50 000 neurons. This means that a much too large region of the brain is stimulated: not only the area that causes the symptoms of Parkinson disease, but also the area around it, leading to side effects. However, since electronics engineers specialize in making things smaller, improvement is only a matter of time. Currently it is possible to place 456 electrodes on a wire of a centimeter, including an amplifier for each electrode to improve the quality of the signal, and including processing electronics. And as you know, once we're working with silicon, Moore's law (the observation that the number of transistors in a dense integrated circuit doubles approximately every two years) applies, allowing a doubling of capacity every two years. This means that we'll soon have a device with thousands of electrodes per centimeter, which will make deep brain stimulation so much more effective – and safe.

Figure 5 The current size of a neuroprobe

In search of a world without neurological problems, what we first of all need, is more research into the fundamental way the brain functions, so that we can learn to interact electronically with the electrochemical signals in our brain. To measure brain activity, optical and chemical measuring are now being added to electric measuring. A typical experiment involves rats that have a chip with electrodes implanted in their brain and that then have to follow a route through a maze. While the rat explores the maze and memorizes its route, we measure what goes on in its brain. The way in which a rat (or a human being) knows where it is in space, can be coded by the 'firing' of specific neurons in the brain. Neurons are electrically excitable cells in the brain and nervous system that process and transmit information by electrochemical signaling. The electrochemical pulses they use to communicate with each other are what we refer to with 'firing'. So at certain points in the rat's route, specific neurons fire. This also works the other way round: when we know which neurons are firing, we are able to deduce where exactly the rat is. Following the rat through its maze, however, we may suddenly see something surprising: halfway through stability assessment. As a result, Mrs. Jones is advised to sign up for a local Tai Chi class, which helps the elderly regain stability. Her grandchildren think that this is very amusing, and call her 'Kung-Fu Granny'.

The story above does not sound like a far-fetched science fiction scenario. Unfortunately today, despite all the information that is currently available on osteoporosis (or many other diseases) and its prevention, raising awareness in individual patients remains a challenge. Patients who feel healthy might not be aware of problems until it is too late. The 2016 version of the story of Mrs. Jones might not have such a happy ending. Without the preventive measures such as the yearly scan and movement measurement, the process of osteoporosis will already have set in (as is to be expected for post-menopausal women) long before Mrs. Jones becomes aware of it. Such preventive measures do not (necessarily) involve the taking of medication but can range from the monitoring of movement patterns, over the use of specific footwear to suggestions for life style alterations. As most patients only see a doctor when there is a serious problem, diseases such as osteoporosis can develop undetected for a long time until a point is reached where irreparable damage is sustained. Elderly patients that are hospitalized with a hip or vertebral fracture after a fall have a 30% chance of dying in the following year due to complications that are related to the physically – and mentally – traumatic experience. Clearly, prevention is better than cure, but how can we organize this prevention in a way that is compatible with a sustainable health care system? Some say the answer lies in capitalizing on the recent (and future) developments in biomedical technology, bio-informatics, simulation techniques, as well as wearable mobile devices. The implication of these technologies in medicine is often indicated with the term '*in silico* medicine', with *in silico* meaning 'in the computer' in analogy with other terms frequently used in biomedical sciences: '*in vitro*' (in the laboratory setting outside of the normal context) and '*in vivo*' (in living animals, humans and whole plants). *In silico* medicine is expected to play a key role in transforming medicine from a reactive into a proactive discipline over the next decade – a discipline that is predictive, personalized, preventive and participatory (P4).[2]

Today, this transformation of health through digital medicine draws growing support from popular media and policy reports, as well as medical professionals and public health officials. It also is becoming increasingly popular among individual patients and consumers. Recently, in response to the overwhelmingly positive attention that personalized health care received, critical discussions have begun to emerge in the ethical and social sciences literature. These critical analyses articulate a number of dystopian concerns regarding the social, political and ethical implications of the move towards more personalized digital health care.

This chapter will explore some of the promises (utopian visions) accompanying the advent of *in silico* medicine. It will do so by discussing the concepts underlying *in silico* medicine and the involvement of the social actors. Besides looking at the current technical barriers to realize the potential of *in silico* medicine, it will demonstrate the many ethical, societal and regulatory barriers that come with these personalized health promises. These ethical and societal hurdles are often framed in dystopian terms, as for example expressed in notions of 'Big Society' or surveillance society. After reviewing these ethical and social aspects of *in silico* medicine, we argue that we need to move beyond this utopian versus dystopian framing in order to make *in silico* medicine 'work' in contemporary (European) biosocieties.

'Big Data Is the New Black Gold'

The integration of vast amounts of heterogeneous biological, environmental and lifestyle data lies at the core of the ambitions of personalized health care. Never before have we had access to so much information on patients, obtained from (among others) genotyping studies, biometric analyses and wearable technologies. Generally, this wealth of information is indicated by the term 'big data'. As the definition is rather vague, opinions differ whether big data indicates only a large quantity of similar data on a population level (such as obtained through large-scale population studies) or also a large amount of data of a varied nature (such as typically found in a patient's health record). The latter is sometimes denominated 'complex data' rather than big data.

So let's take a closer look at these various data sources. One obvious source of patient information is the genomics analysis that provides a lot of information on the genomic make-up of the patient. This has received a lot of attention since the completion of the first full human genome sequencing project in 2003 and the more recent achievement of a USD 1000 genome (which means that a full genome sequencing for an individual patient can now be offered for only USD 1000, compared to the nearly USD 3 billion investment that was made for the first human genome sequenced). Popular media often simplify the solution of medical problems to the identification of the defective gene(s). However, the interpretation of this genetic information (the genotype) and its translation into observable health and disease (the phenotype) is not necessarily straightforward.[3] This is due to the large genetic variations that exist at a population level and the many confounding factors that complicate the genotype-phenotype translation. These confounding factors can be lifestyle choices (e.g. smoking) or the presence of comorbidities. Therefore, the genomic information needs to be combined with other sources of phenotypic data collected from patients. Currently, most of this phenotypic information is present in the health records of the patients, but as this data is usually obtained in the context of pathologies, it fails to provide information on the patient in a state of good health (the baseline).

Another source of patient information can to some extend supplement some of the missing baseline data. Currently, all kinds of wearable sensors have been and are being developed.[4] These sensors are able to record a wealth of information on the patient and his environment, not only at specific time points but also in a continuous way. Today, many smart devices can already measure a variety of signals (heart rate, temperature, movement pattern, etc.) and a large range of mobile apps is available that claim to translate these measurements into tangible information on the health and fitness of the owner of the smart device (X minutes of cycling at a heart rate of Y will lead to the burning of Z calories). However, the algorithms that are used for this translation step are typically based on a large set of data collected in the past for other individuals and therefore not necessarily appropriate for any given user of the device.

A third major source of information that is often overlooked in the context of big data, is the information that can be obtained from scientific research into the mechanisms of action of particular biomedical physiological and pathophysiological processes. Centuries of research has generated a vast amount of knowledge that is too often ignored these days. It is buried as it were under the sheer quantity of the data obtained in high-throughput data-driven approaches, which assume that all the relevant information can be extracted from that data alone without the need for the inclusion of prior knowledge. An example of this is Google Flu Trends, the flu predictor launched by Google in 2008. Based on a selection of flu-related search terms entered in Google's search engine, the predictor's estimates were reported to have almost exactly matched the surveillance data over time of the US authority (Centers for Disease Control and Prevention, CDC) that uses more classical scientific approaches, and Google was able to deliver them several days faster than the CDC. However, just one year after its launch, Google Flu Trends failed to predict the outburst of the swine flu. In 2011-2013 the predictor again ran into trouble when it massively overestimated flu prevalence. Due to the well-publicized early burst of flu, the number of google searches on flu-related terms spiked, causing a massive over-estimation of the prevalence as compared to the predictions of the CDC. Google subsequently adapted its predictor in order to incorporate the knowledge and models developed by the CDC, showing an improvement in predictive capacity surpassing either of the two (Google Flu Trends and CDC) alone. In 2014 Google Flu Trends stopped publishing further estimates. This example demonstrates the limitations of the big data-only approach.

The advent of big data has thus been heralded as a disruptive technology generating new insights and solutions for everything, from health care to city planning.[5] In 2011, Neelie Kroes, who was Vice-President of the European Commission at the time and responsible for the Digital Agenda, called big data "the new black gold".[6] She argued that just as oil had once been likened to black gold for its impact on the economy and society, data takes on a similar importance and value in the current digital age. However, oil is not usable in its crude form and requires a vast number of refinement steps, including mixing with additives in order to obtain more useful products ranging from fuels to plastics. In a similar way, big data is not useful unless it is treated by appropriate algorithms and combined with other sources of complementary information, as the above examples demonstrate. Only when treated in such a way can big data result in big knowledge.[7]

In Silico Medicine

Merging information/data from these different sources in order to extract useful information requires yet another piece of technology, namely that of computer modelling and simulation, called '*in silico* research'. *In silico* medicine is the application of *in silico* research to problems in medicine, using computer modelling to assist in the prevention, diagnosis and treatment of diseases. Various scientific communities around the world, such as the Virtual Physiological Human initiative in Europe, focus on the development of the necessary methods and technologies for the adoption of *in silico* medicine in clinical practice. The driving motivation for these scientific communities is the reversal of the traditional reductionist approach prevalent in medicine and biomedical sciences. This reductionist approach has two clear manifestations, the first of which is the careful confinement of medical problems to disciplinary medical specialties (cardiologists focus on the heart, nephrologists on the kidneys).[8] The other manifestation is the focus on the lowest level, the genome, and the wide-spread belief among scientists and physicians that the unraveling of this level will lead to the explanation of all other levels (tissue, organ, organism and population), as discussed in the previous section.

Although conceptually simple, the realization of *in silico* medicine is by no means straightforward. It is a highly interdisciplinary field of research, requiring input and developments from a diverse group of people, including computational engineers, imaging specialists, biomedical scientists and clinicians. Imaging and sensing generate quantitative data in relevant biomedical or clinical situations. Data processing extracts the relevant information from this data that subsequently feeds into the computer models that have been developed to capture the available knowledge. A common language needs to be built to allow all the different sources of information to communicate with each other.[9] To this end, formal languages and ontologies have been proposed.

One of the biggest challenges to date is the production of this mechanistic knowledge, quantitative and defined over space, time and across multiple scales, capable of being predictive with sufficient accuracy. Models built on nothing but this type of mechanistic data are called 'white-box' models. This term has been chosen to contrast with 'black-box' models where there is no information on the processes that generate the output from the input and that are therefore purely based on the data without attempting to find a mechanism. However, white-box models are very rare as there will always be a certain amount of phenomenological information integrated into the model,[10] making 'grey-box' models a much more realistic goal.

At the moment, the concept of one integrated all-encompassing computer model for each patient is a theoretical ambition rather than an actual goal. The most successful examples of *in silico* medicine so far have managed to overcome the reductionism of looking only at the lowest level, but have mainly focused on specific organ systems (the heart, the lungs, the digestive track). However, due to the common language, a (complete or simplified version of) one organ system model can easily be linked to the model of any other organ system when studying diseases affecting multiple organ systems.

Making *In Silico* Medicine Work: Taking into Account Societal Actors

Now that the first clinically validated models are becoming available, the next questions to ask are who will use these models and in what shape or form will they be used best. The answer is that specific interfaces will have to be developed for different categories of end-users: doctors, patients, scientists and industry. However, these different end-users do not simply 'adopt' or 'implement' these new models' technologies, but translate and re-shape them simultaneously. The importance of this phenomenon has been recognized in fields such as science and technology studies (STS) and sociology of innovation.[11] Research in these areas has shown that users – and their internal norms, values, and beliefs – are crucial actors in the technological development process, and not simply passive recipients of end-products. In the case of *in silico* medicine, with different groups of scientists, charged with different tasks and research questions, as well as users such as the industry and patients themselves, databases, data and devices can be seen to be (socially) shaped accordingly. An

Parliament is a strong signal to the other actors involved (regulatory bodies, industry, etc.) to participate in the realization of *in silico* medicine. At the same time, however, potential threats can come from other fields of regulatory policy, as demonstrated by the recent discussions on the data protection regulation.[15] One of the intermediate versions of the document proposed a very strict interpretation of patient consent (which was a direct result of the Prism scandal that erupted during the drafting of this regulation), making it all but impossible to re-use patient data collected in central registries for scientific purposes. After major objections from the scientific community, the strict interpretation was reversed and it is expected that the current compromise version will receive support from the majority of the Parliament. This is a good example to show that the field of *in silico* medicine touches on many other fields and is therefore affected by (policy) decisions in all of these fields.

As far as the regulatory support goes, the Food and Drug Administration (FDA) in the USA has taken a much more proactive approach than its European counterpart. The FDA has approved the use of computational models as valid preclinical evidence, for instance in the case of the dossier of implantable insulin pumps[16] (for which the *in silico* technology was originally developed in Europe). Furthermore, *in silico* modelling is explicitly mentioned as an important tool to tackle many of the FDA's 'priorities for regulatory science for medical products'.[17] The FDA has even gone a step further and has drafted a guideline on the reporting of computational modelling studies in medical device submissions to educate both the industry and its own staff in how to handle this type of information.[18] This example illustrates the important role of regulatory institutions and actors for the implementation of *in silico* medicine.

Brave New *In Silico* World: Some Dystopian Views on Its Ethical and Social Implications

The technologies described above offer many possibilities and should go a long way in realizing the health care of the future that is personalized, predictive, participatory and preventive. These technologies point to a future in which individuals will be actively involved and empowered in the management of their health and will generate data that will benefit clinical decision making and research. Along with these promises (utopias), critics have begun to articulate a number of dystopian views on the broader societal and ethical concerns regarding personalized health care, foregrounding its disciplining and disempowering effects.[19]

First, there are the obvious ethical and legal concerns related to data security and the right to privacy: how will the transfer of information be organized from the patient (e.g. medical images or recordings from portable devices) to the computer facility and on to the doctor's office? Who has access to what data and in which form? Who owns the data that these personal tracking devices generate?[20]

There are, however, many other concerns that are related to how these new technologies are going to affect the doctor-patient relation as we know it today. With the major progress that is being made every day in the field of cognitive machines,[21] we need to ask the question how the results from the *in silico* models will be used. Are these results prescriptive, suggestive or instructive? What does it mean in terms of medical liability when simulation results that correctly predicted pathophysiological events were ignored by the doctor? As for the patient, what will be the psychological effects of constantly being monitored? If the right models can be developed, your family doctor may be given insight into many details of your life that you might not necessarily want to share, such as the occasional hangover (and the preceding consumption of large quantities of alcohol). Furthermore, patients and citizens are expected to take on increasingly active, participatory roles, in both disease management and data collection, and responsibilities are shifting from the collective level onto the shoulders of the individual in many contexts. What are the implications of the redistribution of responsibilities for care among these actors? Moreover, as some critical sociologists argue, these practices of metrication through *in silico* models are seen as another tool in the quest to reduce all phenomena, no matter how complex, to numbers, while simultaneously displacing other forms of meaningful expression and lived experience.[22]

Finally, a growing number of sociological analyses demonstrate that the generation, collection and analysis of digital data is situated in powerful public and private sector institutions, that may use these for aims of government surveillance and profit-making.[23] How will the health insurance industry use this information? An increasing amount of car insurance companies offer (strongly) reduced fees calculated on the data collected by a small device that insurance holders have to install in their car and that provides the insurance company with a variety of risk-related measures (speed, duration, timing, etc.). Many people seem to gladly sacrifice their right to privacy for a reduced insurance fee. Will this also hold for health insurance in the future: reduced fees for those patients who allow the health insurance company to monitor their life (style)? What happens when a patient decides to go offline for a day? Or what will happen in the case of a less than perfect compliance with the prescribed treatment? According to this pessimistic reading, privacy and personal freedom are endangered and, according to some, even at risk of disappearing.

Moving beyond Utopia vs. Dystopia: Realizing *In Silico* Medicine in Societies

This chapter has documented the many promises that accompany the potential of *in silico* medicine. At the same time, these innovations engender rather dystopian views, for instance in ethical and sociological literature discussing the implications of these technologies when diffused in society. Clearly, both utopian and dystopian views of *in silico* medicine serve a purpose. As socio-technical imaginaries they can show us what the future will look like, as a horizon that is (already) 'conceivable', as present in our dreams, fears, and imaginations, that is, as an 'inauthentic future'.[24] In this way, these utopian/dystopian views always entail a notion of controllability of the future. To some extent, there is no place for the unexpected in these visions. Futures are here imagined as already foreseeable and predictable – both in their dream and nightmare/apocalyptic scenarios. However, in this process, both these dreams and their fearful rejections shrink our horizon/future to a rather small and narrow one (that is, to a future that is already – to some extent – foreseeable or made predictable). In this way they may prevent us from living an open-ended future.

The open-ended notion of the future is however the hallmark of science. In close alliance with technology it has put its stamp on innovation-driven societies. This means that science cannot flourish when it is constrained to these utopian and/or dystopian views. It is then already too much framed, too domesticated and made predictable. Science needs the 'cunning' of uncertainty to strive for the new.[25] The uncertain character of science is incompatible with the idea of controllability and its model of the linear implementation of technology implied in utopian and dystopian views. For science to become reality, we have to approach science in society in an experimental way, moving beyond utopian/dystopian thinking.

At the same time, while these utopian/dystopian views on new technologies involve fixed expectations about the future, they also enshrine a technological determinism that puts too much stress on the 'impact' of technology on society. Again, the attractiveness of these relatively simple models concerned with the 'diffusion' or 'implementation' of technology from the place where it is 'produced' to the places where it is 'lacking' lies in the fact that they imply clear causalities and over-promise control. However, as sociologists of science have shown, a lot of effort is required to make these novel technologies actually 'work' in society.[26] Technological objects are thoroughly enmeshed in society, as integral components of the social order. It does not take fictional or futuristic stories to recognize this truth.

In sum, to make the promises of *in silico* medicine come true we need to move beyond these utopian/dystopian claims and look instead at the real-time practices of *in silico* medicine in-the-making. Realizing personalized health care is then about more than simply implementing science and technology in or applying them to society. Questions about how they will be applied in practice need to be addressed. For example, what does 'patient benefit' mean to health care professionals and to patients? How are data and test results communicated and stored across different scientists, medical professionals and patients, moving from *in silico* models to statistical tables and to personal bodies and back again? How can we develop societal institutions that warrant a balance between data-sharing and the right to privacy? These are only some of the myriad of complex factors involved in 'mainstreaming' *in silico* medicine in society that need to be addressed.

One example of such an approach to science-society interaction can currently be found in the EU Horizon 2020 Program, with its notion of Responsible Research and Innovation (RRI).[27] RRI recognizes that 'technological fixes' are not enough and that social, cultural and institutional dimensions are key. This requires the involvement of citizens, users, the public and stakeholders to take societal concerns into account already in the design phase of science and technology. While some have called this a form of 'anticipatory governance', RRI cannot, however, afford to become another 'quick fix' to solve the science-society interface.[28] If we used it as such, we would run the risk of reframing/reducing/taming RRI into just another utopian social planning initiative while placing it again under a logic of controllability and predictability.

To realize the potentials of *in silico* medicine, policymakers and especially scientists and universities have to take the risk of embracing the uncertainty of the science-society mutual constituency. This requires shifting from a logic of control to one of experimentation. We have to experiment with *in silico* medicine in the largest laboratory of the world, that is, society, to inhabit the world with an open-ended future.

Notes

1 Case study developed by Rizzoli, R., Merminod, F., Viceconti, M., and McCloskey, E., in Díaz, V., Viceconti, M., Stroetmann, V., and Kalra, D., *Roadmap for the Digital Patient 2013*, Discipulus FP7/2007-2013/n°288143, www.digital-patient.net

2 Hood, L. and Friend, S., 'Perspectives. Predictive, personalized, preventive, participatory (P4) cancer medicine', *Nature Reviews Clinical Oncology* 8, 184-187, 2011, doi:10.1038/nrclinonc.2010.227.

3 See also Koen Devriendt & Hilde Van Esch, 'Healthy Genes for Everyone', in this book (p. 93).

4 See also Rudy Lauwereins, 'Preventive Maintenance for a Future without Disease', in this book (p. 36).

5 Mayer-Schönberger, V., and Cukier, K., *Big Data*, London: John Murray, 2013.

6 http://europa.eu/rapid/press-release_SPEECH-11-872_en.htm

7 Viceconti, M., Hunter, P., and Hose, R., 'Big data, big knowledge: big data for personalized healthcare', IEEE *Journal of Biomedical and Health Informatics* 19:4, 1209-1215, 2015, doi: 10.1109/JBHI.2015.2406883.

8 See also Jan De Lepeleire, 'Person-Centered Health Care without Fragmentation', in this book (p. 144).

9 Lazebnik, Y., 'Can a Biologist Fix a Radio? or, What I Learned while Studying Apoptosis,' *Cancer Cell* 2, 179-182, 2002.

10 The term 'mechanistic' should in fact be seen as a relative term rather than an absolute one. Researchers focusing on bone fracture healing will use a simple mathematical description of growth factor ligand-receptor binding and will not include a structural analysis of ligand docking based on X-ray crystallography data. The former can be considered as mechanistic, as it describes the mechanism behind the growth factor induced biological processes in fracture healing. However, it obviously lacks the details of the latter description, which is, in its turn, too detailed to be used in the model of bone fracture healing.

11 Oudshoorn, N., and Pinch, T. (eds.), *How Users Matter; The Co-Construction of Users and Technology*, Cambridge (MA): MIT Press, 2003.

12 Nasser, M., Tibi, A., and Savage-Smith, A., 'Ibn Sina's Canon of Medicine: 11th century rules for assessing the effects of drugs', *Journal of the Royal Society of Medicine* 102:2, 78-80, 2009, doi: 10.1258/jrsm.2008.08k040.

13 Viceconti, M., Henney, A., and Morley-Fletcher, E., '*In silico* Clinical Trials: How Computer Simulation will Transform the Biomedical Industry', Research and Technological Development Roadmap, Avicenna Consortium, Brussels January 2016, doi: 10.13140/RG.2.1.2756.6164.

14 https://ec.europa.eu/digital-agenda/en/news/ehealth-action-plan-2012-2020-innovative-healthcare-21st-century; www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+REPORT+A7-2013-0443+0+DOC+XML+V0//EN

15 Casali, P.G., on behalf of the European Society for Medical Oncology (ESMO) Switzerland, 'Risks of the new EU Data protection regulation: an ESMO position paper endorsed by the European oncology community and the Virtual Physiological Human Institute', *Annals of Oncology* 25, 1458-1461, 2014, doi:10.1093/annonc/mdu218.

16 Kovatchev, B.P., Breton, M., Man, C.D., and Cobelli, C., '*In silico* preclinical trials: a proof of concept in closed-loop control of type 1 diabetes', *Journal of Diabetes Science and Technology* 3:1, 44-55, 2009.

17 *Advancing Regulatory Science at FDA: A Strategic Plan*, US Department Of Health And Human Services, US Food And Drug Administration, 2011.

18 www.fda.gov/RegulatoryInformation/Guidances/ucm371016.htm#o13

19 Sharon, T., 'Self-Tracking for Health and the Quantified Self: Re-Articulating Autonomy, Solidarity, and Authenticity in an Age of Personalized Healthcare', *Philosophy & Technology*, 2016, doi: 10.1007/s13347-016-0215-5; in his novel *The Circle*, Dave Eggers provides a quasi-documentary account of what might happen (or already be happening) in the digital world of continuing self-monitoring, voluntary participation in constant surveillance and the forgoing of any right to privacy.

20 Morozov, E., *To Save Everything Click Here*, London: Allen Lane, 2013.

21 See also Yves Moreau, 'The Geek Reformation', and Philip Dutré, 'Thinking and Conscious Machines?', in this book (pp. 464 and 454).

22 van Dijk, J., 'Datafication, dataism and dataveillance: Big Data between scientific paradigm and ideology', *Surveillance & Society* 12:2, 197-208, 2014.

23 Boyd, D., and Crawford, K., 'Critical questions for Big Data: Provocations for a cultural, technological, and scholarly phenomenon', *Information, Communication & Society* 15:5, 662-679, 2012.

24 Nowotny, H., and Mendelsohn, E., *Nineteen eighty-four: science between utopia and dystopia*, Boston: D. Reidel Publishing, 1984.

25 Nowotny, H., *The cunning of uncertainty*, Cambridge: Polity Press, 2016.

26 Engel, N., Van Hoyweghen, I., and Krumeich, A. (eds.), *Making Global Health Care Innovation Work. Standardization and Localization*, New York: Palgrave, 2014.

rather limited. In contrast, contemporary neuroscientists have sophisticated equipment at their disposal to study human brain anatomy and physiology in tremendous detail, and rely on evolutionary homologies[4] between laboratory animals as distinct from humans as fruit flies and roundworms to study the cellular and molecular basis of neural functions.

In the present chapter, I shall elaborate on the utopian concept of the replaceable brain. I start out by illustrating the tremendous complexity and uniqueness of the human brain, and explain that this anatomical structure is not merely astronomically complex, but also the result of an individual developmental process that continues throughout our lives. The idiosyncratic complexity of our brain ultimately determines who we are, and changes to its structure or function will obviously affect our individual identity. During this excursion, one cannot but marvel at the astonishing achievements of 21st-century brain science.[5] Repairing relatively straightforward, focal lesions or reconnecting disconnected parts of our nervous system might not be utopian at all, and in fact, the modern science of neuroprosthetics and brain-computer interfaces would have us predict that repairing damaged nervous systems, or even expanding the abilities of healthy brains, might very well become possible in the not so distant future.[6] However, restoring a brain ravaged by dementia to its original, individual complexity, replacing damaged brains partially or completely, or ultimately, reviving a deceased brain, remain utopian ideas in their truest sense.

The Plastic Brain

The famous experiments of Russian physiologist and Nobel laureate Ivan P. Pavlov (1849-1936) described how a dog can learn to salivate in response to a stimulus that has nothing to do whatsoever with food or eating (such as the ringing of a bell, for example). For a bell to elicit salivation in a dog,[7] which is rather an odd thing to occur when one thinks of it, a learning experience is required during which such a stimulus repeatedly precedes the presentation of food. Even invertebrates change their behavior as a result of experience and are able to learn the association between different environmental stimuli, or between a behavior and its outcome. Snails and slugs contract when they are touched, but learn to ignore these touches after a while, when they turn out to be harmless. Researchers including Nobel laureate Eric Kandel, who studied such desensitization phenomena in the large sea slug *Aplysia,* have shown that they are ultimately based on changes in the ability of sensory cells (that respond to touch) to evoke responses in motor cells (that help the slug contract). As it turned out, processes of neuroplasticity, which underlie such changes in the ability of neuronal cells to excite one another, also form the basis of learning and memory in humans and other mammals. Pavlov definitely lacked the neurophysiological knowledge to explain these phenomena, which neuroscientists presently ascribe to processes of neuroplasticity that either strengthen existing contacts (synapses), or generate synapses between nerve cells (neurons), which did not exist prior to the learning experience. Moreover, it is now known that all learning and memory abilities depend on such processes of neuroplasticity, which appear to occur in many, if not all, synapses throughout our brains and those of other animals. Learning to ride a bicycle as well as memorizing the shortest path to your friend's house, or remembering the name of her mother for that matter, all ultimately depend on brain plasticity. In fact, our brains are continuously altered by experience and remain plastic throughout our lives. This enables even octogenarians to learn to speak a foreign language, although they might never become as fluent as native speakers who learned the language in early childhood.

Apart from many similarities at molecular, cellular and even brain-system level, the human brain is in many ways quite different from other mammalian brains. The most remarkable anatomical feature of the human central nervous system, which comprises the brain and the spinal cord, is obviously its relatively large forebrain (cerebrum). This large forebrain controls our cognitive abilities, which are much superior to those of even our closest primate relatives, as well as our propensity for conscious thought and awareness. Bente Pakkenberg and her associates at the Copenhagen University Hospital estimated that the human cerebrum's cortex of grey matter contains the cell bodies of an astonishing 20 billion interconnected neurons. Even more numerous than neurons are various glial cells that support neurons both functionally and structurally (e.g., by forming myelin sheaths around the axons). Neurons have a central cell body

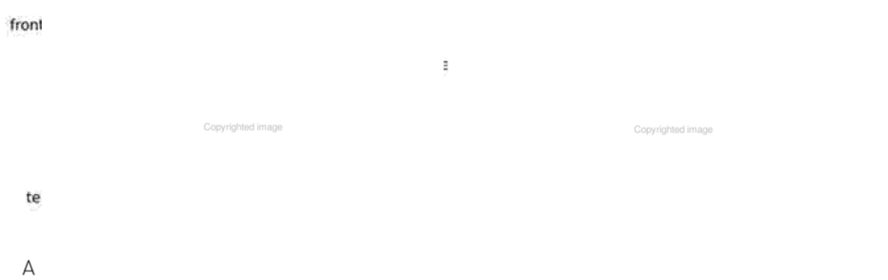

Figure 2 Lateral view of the human brain that depicts the cerebrum with its different lobes and cortical areas, the cerebellum, and medulla oblongata (further connecting to the spinal cord) (A). Schematic depiction of a cortical neuron and glial cells, which include an oligodendrocyte (cell at the bottom of the figure) forming an insulating myelin sheath around the neuron's axon (B).

with a large number of extensions, called 'dendrites' and 'axons' (Figure 2). The neuron's single axon has a sheath of insulating and supportive myelin and usually forms collateral branches that allow the neuron to connect with many other neurons, whereas the dendrites provide ample surface to receive input. Thick, myelin-rich axon bundles form the brain's white matter, and connect different areas of cortex to each other as well as to deep brain nuclei. The largest of these bundles is part of the corpus callosum that connects the two hemispheres of the human brain. The Copenhagen group calculated that the male corpus callosum contains an average of 138 million myelinated fibers.[8]

The frontal lobe, especially its most rostral or prefrontal area, is arguably the most distinctly human part of our cerebrum (Figure 3). For instance, elephants are definitely highly intelligent and brainy animals that display an amazing behavioral repertoire and proverbial memory abilities, but their prefrontal cortex is proportionally much smaller than ours. Even chimpanzees and bonobos, our closest relatives in the animal kingdom, have considerably smaller prefrontal areas than humans. The famous (albeit somewhat controversial[9]) case of the 19th-century American railroad worker Phineas Gage (1823-1860) illustrates the dramatic impact of damage to our prefrontal areas. At age 25, Gage's frontal lobes were damaged by an explosion that pierced a metal rod through his skull. Amazingly, he survived, but according to his treating physician, his mental capacities and personality were drastically altered after the accident. Symptoms of frontal lobe damage such as behavioral disinhibition and loss of decorum, which were specifically mentioned by Gage's physician, also occur in frontotemporal dementia (FTD). A patient with FTD, whom I met many years ago, was rather difficult to

The corticolimbic system

Figure 3 Sagittal view of the human cerebrum with prefrontal areas and their functions, as well as amygdala and hippocampus. These interconnected cerebral regions comprise the corticolimbic system that controls our most human cognitive and emotional functions.

engage and fidgety during clinical interview, continuously looking about himself, examining the underside of my desk. The patient, a kindly man in his late fifties, was quite unaware of his condition, which was understandably very upsetting to his wife, who was especially bothered by his restlessness and uncharacteristic gluttony. More disconcertingly, other FTD patients are often inappropriately imposing, on occasion even outright abusive. On the basis of such cases, prefrontal cortex is now regarded the seat of the central executive control of various emotional, social, attentional and cognitive functions. It has been shown to be crucial for working memory as well, which British psychologist Alan Baddeley defined as a temporary store for newly acquired as well as recalled information that allows the use of this information in reasoning and memory updating.

Uniqueness of the Individual Brain

Each brain develops a unique anatomical architecture and functional organization as a result of idiosyncratic, epigenetic interactions between its genetic blueprint and the environmental input it receives. The human brain contains billions of neurons that each may receive dozens of synaptic contacts from other brain cells. The resulting neuronal network has truly astronomical dimensions. Determined by genetic predisposition as well as environmental molding, it is both an extremely complicated and uniquely individual structure. The most drastic neuroplasticity-related changes definitely occur early in life. Nobel laureates David Hubel and Torsten Wiesel were amongst the first to study the development of the visual cortex experimentally, demonstrating that early environmental input contributes decisively to adult cortical organization and function. During brain maturation, connections between brain cells become stronger and receptive fields more tightly organized. The particular architecture of the visual cortex, partly established prior to any visual input, is fine-tuned by the visual environment of the developing animal.[10]

Hubel and Wiesel noted that there appears to be a critical period in the development of the visual cortex, during which it is most susceptible to the effects of environmental input. Consequently, visual deprivation in the adult does not affect synaptic organization of the visual cortex in the same way as it does in the young. In fact, critical periods and nature-nurture interactions determine the development of many brain systems. Lifelong rehearsal influenced the size of the motor cortex in violin prodigies, whereas adult taxi drivers demonstrated changes in brain areas involved in spatial navigation. Critical periods were indeed described in learning language or playing the violin, but the possibility of neuroplasticity has been asserted much beyond these periods, during our entire lifetimes, in fact. Structural and functional imaging revealed that brain development may actually continue well into the third or fourth decade. Different brain areas, however, develop at different rates. Maturation appears to be particularly slow in human prefrontal cortex, which may explain why it takes children such a long time to become responsible, conscientious adults. Prefrontal neurons grow extensions and connect to one another over the course of many years (Figure 4). Unfolding of all the necessary developmental processes such as dendritic arborization and myelination may, in fact, take more than 20 years, and render the slowly maturing prefrontal areas and their associated functions (e.g., emotional control, personality) particularly susceptible to environmental influences, and extremely vulnerable indeed.

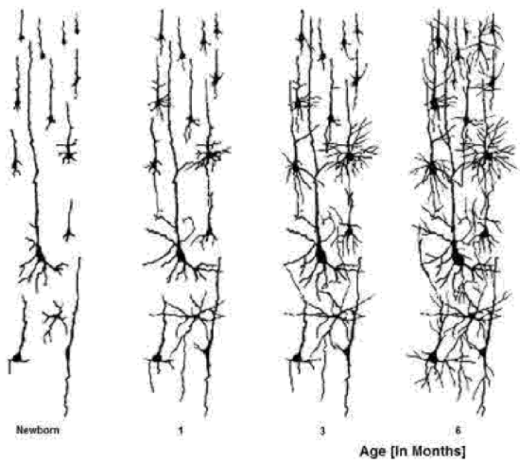

Figure 4 Development of the cerebral cortex during the first two years of life. During this period cortical neurons develop a tremendous amount of extensions that connect these cells to other cells of the cortex and deeper brain structures.

Developmental neuroscientists still have a long way ahead to understand why some people end up with exceptionally brilliant brains, whereas others suffer life-long disability due to defects in neural development. Many aspects of brain development remain quite poorly understood, but recent research uncovered some of its cellular and molecular mechanisms. At the very beginning of life, a symphony of molecular processes helps the layer of cells at the outer surface of the embryo to fold and form a neural tube. Cells in the front or rostral part of this tube divide very fast and increase in number to produce large expanding shapes, which eventually become the different parts of the brain. Huge numbers of dividing undifferentiated cells migrate and reshape the morphology and cellular composition of the developing brain and spinal cord. Initially undifferentiated cells are converted into glial cells and neurons, which start connecting to one another. In the developing brain, connections between neurons quite realistic to predict the development of electronic eyeglasses that deliver images directly to the visual areas of the brain (Figure 6), much in the same way cochlear implants are already helping deaf people bypass their defective middle ears. Cochlear implants include an external microphone, which transfers sound signals to an implanted microelectrode array that stimulates the auditory nerve. The same principle could bypass damaged eyes or optic nerves to send image information directly to the brain. However, the task of building an electronic optic prosthesis seems to be considerably more formidable than producing functional cochlear implants. Ophthalmologists at the University of Erlangen (Germany) counted more than a million nerve fibers in the human optic nerve, which transmits visual signals from the eye to the brain. The effectiveness of an optic prosthesis would depend on its ability to deliver high resolution images to the brain, which would require digital imaging and brain stimulation technology that is definitely not available for the moment. Replacing retina functions with a digital camera would be the first obstacle, since quite some visual processing already occurs in the eye. Next, an optical image transformed into weak electrical signals would have to be wired to many thousands of perfectly positioned brain microstimulators. Miniaturization of the technical equipment is another foreseeable hurdle, whereas managing infections from chronically implanted microarrays could prove quite a challenge as well. Scientists agree it is impossible to predict what people wearing an optic prosthesis would actually see, and whether or not they would be able to create a coherent image from relatively limited electrical input. But utterly utopian the idea definitely is not, and there is realistic hope that optic prostheses might become available in a not so distant future.

Figure 6 Theoretical image of electronic eyeglasses that directly interface their image to the visual areas of the brain

Electronic devices could be used in several other ways to interface between the nervous system and external equipment. An experiment at the University of Pittsburgh has allowed a group of paralyzed patients to control a robotic arm using signals directly derived from an electrode array implanted in their brains. For the time being, this technology allows these patients to convey instructions to a robotic limb that is able to perform a number of computer-controlled operations. This technology undoubtedly means a tremendous step forward for patients who have limited capacity to use keyboards or remote controls, but it is still a long way from prosthetic limbs that are fully working as moving and feeling real limbs. Coordinated limb movement would require a finely tuned prosthetic to react to tiny instructions from the brain as well as feed impulses back to the central nervous system such as our actual limbs do. Although the technology is not yet available, the development of prosthetic limbs, far superior to those presently available, appears to be more than plausible. Moreover, advanced brain-machine-brain interfaces (BMBIs) might one day be able to transmit neural signals from above the lesion site to parts below the lesion, and vice versa, to restore sensorimotor abilities in patients with spinal cord lesions. The first successful experiments in rats have demonstrated that BMBIs could be used to bridge damaged parts of the brain as well.[16] Despite this optimism, it remains difficult to imagine how we might ever be able to replace the millions of fibers of the corpus callosum that connect the brain hemispheres.

Conversely, technology that allows reciprocal interfacing of neural signals to electronic devices, could also be used to build plug-in devices to enhance, for instance, memory capacities of the human brain. As it seems, keyboard- or voice-controlled devices might eventually become outdated as engineers envision all sorts of electronic devices that directly feed into our brains or other parts of our nervous system. For the time being, we are definitely lacking the microelectronic miniaturization as well as the computing power required, but since both are increasing exponentially over time, this kind of technology might become available sooner than we think.

Utopian Brain Replacement

"Being wrong is a natural gift. You cannot learn it. Some of us have a particular genius in this direction and can be wrong for months at a time."[17]

There have been so many heroic failures in predicting the future, one might as well stop trying. Although they eventually became the most successful rock band of all times, The Beatles were rejected by several record companies that all thought they would not amount to much at all. And Albert Einstein's school teacher is supposed to have said something along the same lines about young

Albert. Odds are very much against anything I am writing here ever turning out to be true. But let me be absolutely clear about one thing: it would be wonderful to be able to repair a damaged brain or replace malfunctioning or lost brain cells. Losing the function of one's brain is definitely amongst the most devastating conditions imaginable. It remains the ultimate hope of many basic and clinical neuroscientists to use the fruits of their research to restore the ability to walk in people with spinal cord lesions, or cure a patient with advanced Alzheimer's or Parkinson's disease. The strongest hopes in this respect are obviously maintained by patients themselves and their caregivers. Some of these hopes are certainly justified and realistic, given the present state of neuroscience, and its accelerating pace of progression. However, it should be kept in mind that restoring gait by bypassing a spinal cord lesion is a much more manageable task than restoring lost functions in a brain ravaged by a degenerative disease. At the most extreme end of the spectrum are cases such as that of Kim Suozzi, recently reported in American newspapers, who sadly died from cancer aged 23, but chose to have her brain frozen for future restoration. In fact, cryonics companies are keeping dozens of frozen brains from people who hoped science may one day be able to revive their mind.

Apart from neuroelectronics, neuroscientists think there might be another way to reconnect or repair damaged parts of the central nervous system, and restore their functionality. We have explained how our embryonic nervous system starts from a set of undifferentiated stem cells to produce the various neuronal and glial cell assemblies that eventually mature into a fully grown nervous system. Scientists have found new ways to produce pluripotent stem cells[18]

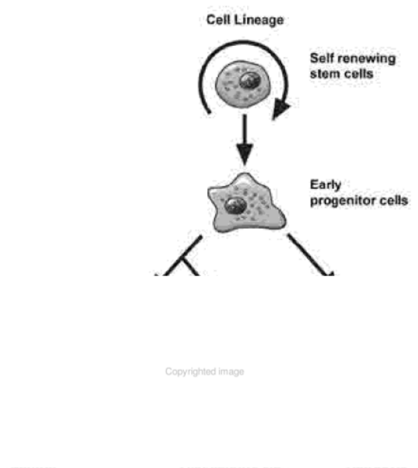

Figure 7 Stem cells can be prompted to become either neurons or glial cells

(Figure 7) that could be injected into the brain or other parts of the central nervous system to replace lost neurons or glial cells, and eventually restore connections or damaged brain areas. The first experiments have shown that injection of altered neural stem cells might help to repair the neurochemical defects and restore motor functions in monkeys with neurotoxic brain damage. Patients suffering from Parkinson's disease may certainly hope stem cell research might one day alleviate their devastating condition by replacing degenerated brainstem cells. Also, stem cell technology could help reconnect a severed spinal cord in paralyzed patients or disconnected brain regions in stroke patients.

It should be noted, however, that these latter treatment possibilities refer to conditions of localized brain damage or neural disconnection. The situation is, unfortunately, quite different in, for example, patients with advanced Alzheimer's or other neurodegenerative diseases, who have lost a large portion of their brain. In fact, our brain loses neurons all the time, and even without pathological aging, brains of healthy seventy- or eighty-year-olds will inevitably show considerable atrophy. People with neurodegenerative disease will eventually lose a lot, if not all of their brain functions, but even early in the course of their disease, they might suffer marked personality changes. Tragically, we could say that the brain of such patients has partly died already. The damage resulting from aging or neurodegeneration occurs diffusely all over the brain, and even if we would know exactly where to place them at microscopic detail, the mere task of replacing all these millions of lost neurons and glial cells would be quite formidable indeed. Restoring the identity (memories, personality) of people who have lost a large part of a brain that has been molded by a lifetime of experience and environmental input, might actually be impossible altogether. Leading neuroscientists such as Colin Blakemore have argued that it even appears to be impossible to be ever able to stop brain aging, or death for that matter. Conversely, even if science would be able to prolong the human lifespan considerably or indefinitely, an infinitely growing number of senescent individuals might bring intellectual and cultural innovation as well as biological evolution to a standstill, and would be utterly unsustainable. However strong the hopes might have been in people who had their brains frozen, it will be impossible to revive a brain that has been profoundly damaged by the breakdown that occurs during the dying process. Apart from all that, one could seriously doubt the quality of a regained life without loved ones or peers around.[19] Of course, the hope of bringing people back from the dead is as old as humanity, but the more we learn about the physical and chemical processes of life, the more it becomes clear that such a revival would be a biological impossibility. By and large, replacing (or reviving) brains appears to be quite utopian … so far.

Notes

1 It took Michelangelo 4 years to complete his famous ceiling fresco at the Sistine Chapel. In his page-turning account *Michelangelo and the Pope's Ceiling* (London: Penguin Books, 2003), Canadian art historian Ross King explains the creative process that ultimately resulted in this inspiring work of art as well as Michelangelo's astonishing ability to learn from his mistakes, and progressively improve his artistic skills during the painting of the fresco.

2 Referring to the plane that divides our body in symmetrical left and right halves. A sagittal section that separates left and right hemispheres provides a medial view of the human brain.

3 Also see Paluzzi, A., Belli, A., Bain, P., and Viva, L., 'Brain 'imaging' in the renaissance', *Journal of the Royal Society of Medicine* 100: 540-543, 2007.

4 'Homology' refers to anatomical, developmental or physiological similarity based on common evolutionary ancestry. Notably, many of the microscopic and submicroscopic processes that control interaction and communication between the cells of the much simpler nervous systems of invertebrates such as gastropods and insects, also occur in humans, because we share a common biological origin with these organisms.

5 Several textbooks provide good overviews of 21st-century neuroscience, including Kandel and associates' highly influential *Principles of neural science*, New York: McGraw Hill, 2013. Behavioral neuroscience is nicely introduced in Neil Carlson's *Physiology of behavior*, Boston: Allyn & Bacon, 2010.

6 See also Rudy Lauwereins, 'Preventive Maintenance for a Future without Disease', in this book (p. 36).

7 It should be noted that Pavlov himself apparently never actually used a bell to condition his dogs.

8 I cite these numbers to illustrate what a formidable task it would be to reconnect disconnected cerebral hemispheres.

9 The behavioral change that was documented by Gage's physician might not have been as permanent as often imagined and there is evidence that Gage might have regained some of his functions awhile after his accident.

10 A classic experiment by Oxford neuroscientist Colin Blakemore demonstrated how early experience influences cortical development, see Blakemore, C., and Cooper, G.F, 'Development of the Brain depends on the Visual Environment', *Nature* 228: 477-478, 1970. Blakemore raised kittens in the dark, exposing them occasionally to a visual environment only consisting of vertical or horizontal bars. After a while, he observed that these animals exclusively reacted to stimuli with the same orientation as the bars to which they had been exposed, and their visual cortex mainly contained neurons that responded to the exposed orientation.

11 A classic rat experiment showed how cortical grafts from visual areas, transplanted to the neonatal somatosensory cortex, develop anatomically and functionally distinct barrel fields. So-called barrel fields normally occur in somatosensory cortex and receive sensory input from whiskers on the snout of the animals. The experiment demonstrated how sensory input induces the development of barrel field in cortical grafts from other parts of the brain as well, once more illustrating the profound influence of environmental input on brain development. See Schlaggar, B.L., and O'Leary, D.D.M., 'Potential of visual cortex to develop arrays of functional units unique to somatosensory cortex', *Science* 252, 1556-1560, 1991.

12 Peeters, W., van den Brande, R., Polinder, S., Brazinova, A., Steyerberg, E.W., Lingsma, H.F., and Maas, A.I.R., 'Epidemiology of traumatic brain injury in Europe', *Acta Neurochirurgica*, 2015, online.

13 German neuropathologist Alois Alzheimer (1864-1915) first described this now infamous, degenerative brain disease that is characterized by brain deposition of amyloid peptide plaques and intracellular formation of neurofibrillary tangles.

14 Spreng, R.N., and Turner, G.R., 'Structural Covariance of the Default Network in Healthy and Pathological Aging', *Journal of Neuroscience* 33, 15226-15234, 2013.

15 Gazzaniga, M.S., *Human. The science behind what makes your brain unique*, New York: HarperCollins, 2008.

The Genetic Future

As for medical matters, a companion of mine called Tricius Apinatus had brought with him certain brief works by Hippocrates and the Microtechne *of Galen, all of which they valued highly. While it's true that there is scarcely a country in the world less in need of medicine, in spite of that nowhere is it held in greater honour, since they regard medical science as one of the most noble and useful parts of philosophy. (89-90)*

Blood and Stem Cell Utopia: The Search for the Holy Grail

Marc Boogaerts, Hematology

Blood is much more than the red fluid that transports oxygen. Blood is one of the most powerful and ubiquitous of human symbols. It is the unique subject of numerous mythologies and has, over the ages, been sanctified as 'home for the soul' or the 'elixir of life'. It has been hailed as the eternal spring of youth and health in many rituals, in healing ceremonies, in religious transcendence and in early medicine.

The advent of blood stem cell science and regenerative medicine has created a new curiosity for blood as a source of prolonged (eternal?) life or at least of improved quality of life, for as long as possible. The tension between those who believe in the magical and spiritual power of blood and those who see it as something purely rational and scientific, will likely be revived. The quest for the Holy Grail continues. Will true regenerative medicine become reality or will it remain a utopian dream of eternal youth?[1]

Blood, the Source and Soul of Life

The association between life, death and blood was already apparent for the early humans who, in prehistoric caves like the one in Niaux (France), depicted spilt blood as the cause of death in animals they chased. Ancient civilizations venerated blood and used it in different rituals to please their deities. Bleeding wounds were associated with the emergence of spirits. Early Greek mythology used blood abundantly to 'explain' combat between rival deities, to generate offspring of demons or heroes, or to justify eternal torment or sexual lust.

In pharaonic times early medicine blossomed and blood was used as a remedy for many skin or neurological diseases. A whole armamentarium for bloodletting is depicted in hieroglyphic bas-reliefs on temple walls in Memphis. Pharaohs suffering from what we now think was leprosy, have been depicted as bathing in blood from young healthy boys (preferably Jewish) to regain strength and be cured. In the ten plagues that the God of the Jews inflicted on the Egyptians (to convince pharaohs to let the Jewish people go to the promised land), blood plays a crucial role. In the first plague, the Nile would turn as red as blood and would lose all its feeding power for people and animals (we now know that this was due to the increased growth of red coloring algae). In the last plague, all firstborn males would be killed, except those from houses where blood was applied to the door lintels, so that the avenging angel would pass the doors of the pious. Blood was used to demonstrate the superiority of one god (Jehovah) over the other (the pharaoh).

At the same time blood also became subject to a more 'scientific' approach to medicine. According to Hippocrates (around 400 BC) blood belonged to the four crucial *humores* besides phlegm, yellow and black bile. Illness resulted from a disequilibrium between *humores*, and often bloodletting was considered curative for the restoration of a healthy balance between yellow bile (choleric), black bile (melancholic), phlegm (phlegmatic) and blood (sanguinic types). Galenus (born 129 AD) became his most famous follower and was at the center of medicinal and healing practices for many centuries, right up to the 16th century. He elaborated a complex theory on circulation and blood production (in the liver), mostly by dissecting animals. The latter would partly explain his mistakes, as demonstrated by Vesalius, who preferred to dissect human corpses. Galenus also propagated the drinking of blood as a source of energy and as a potential curative for rabies and epilepsy. Consequently, Roman patricians hastened towards dying, bleeding gladiators in order to drink their blood, and so gain courage and energy from the 'fleeing source of life'.

Masai warriors today still drink the – milk doused – blood of their cattle to gain strength and courage (besides the necessary proteins). If they kill a lion and drink its blood, they become all but invincible. Human sacrifice probably stems from the survival instinct of early man, i.e. in the presence of hungry predator animals it might be wise to sacrifice one member of the group (the weakest or the youngest) to assure the survival of the whole group. The practice of human blood-spilling to obtain a better or safer life was thus not uncommon in ancient civilizations; yet Abraham was forbidden to spill the blood of his son by his God and used ram's blood instead. This tradition of sacrificing (animal) life and blood still persists in many religions, in realistic (Muslim) or transcendent (Catholic) forms. Gradually, blood was considered more sacred, and religious rules on its use (e.g. kosher or halal) became abundant and survive to this day.

The Mayan culture, which arose around 500 BC – about the same time the Parthenon was built in Athens – valued blood highly in all its rituals and used it to mark the notable turning points of an individual's life. In limestone relief carvings, the king and queen are depicted as spilling their blood for the benefit of all, e.g. the queen pulling a rope with large thorns through her tongue and the king being bled from his penis. (Any reference to modern piercing practices is probably coincidental.) While sadomasochism dates back to the earliest times, blood rituals contributed in those ancient civilizations to harmony and a better life, at least for the happy few.

Later, the Aztec culture would push the veneration of blood to a higher level, where blood became the favorite food for their deities and had to be spilled to assure the next day's sunrise. Consequently, many of their enemies suffered cruel fates on their altars where beating hearts were torn from bodies, blood flowed down the steep steps of their pyramids and worshippers sipped the blood and cannibalized the remains. If not enough enemies were found, sacrifices of their own people (also children) were not uncommon. For most rulers of that time (and later) blood sacrifice gradually came to be used more as a sophisticated form of terror to maintain power, to justify decisions, or else to eliminate competitors.

Religion has used blood in many ways, not only in the Catholic tradition of drinking the 'transubstantiated' blood of Christ during the Eucharist, but also as a means of doing penitence through hair shirt or cilice wearing, self-inflicted bloodletting or flagellation. Behind the closed doors of many cloisters blood had to flow in order that an individual may ascend closer to God. Bloody stigmata – mimicking the wounds of Christ – were self-inflicted and venerated. Even today carriers of stigmata are worshipped by some of the faithful (e.g. father Pio).

Mesopotamian worshippers of Baal used to spill their own blood by scarification (cutting themselves to leave scars) or flagellation (of their prisoners) in a way that was meant to please their deity. The practice also survives in modern times and rituals. Blood is used both as a punishment and as a route to salvation. The blood of Jesus had to be spilled to wash away the sins of his fellow human beings. Likewise, the blood of the martyrs was not spilled in vain, but led to a stronger church and helped reinforce faith within non-believers.

Not surprisingly the 'real' blood of Christ became the ultimate relic to bring back from the crusades. The search for the Holy Grail – the cup in which Jesus' blood was collected, supposedly by Joseph of Arimathea – became the ultimate medieval symbol, being later transcended to the womb of Mary or a Merovingian crown. Blood relics carried considerable power, some of them sometimes changed from a solid to a liquid, thereby invariably foretelling a war, a natural disaster or a plague. To possess an important relic conveyed immediate power. Many fakes were reproduced and it took considerable time before the industry of relic-making was brought to a halt. Very recently, the blood of San Gennaro gentle, meek and docile calf for a patient suffering from psychotic spells, during which he used to beat his wife and run naked through the streets of Paris. Twice, Jean Baptiste succeeded in giving a considerable amount of calf's blood and the patient seemed to be doing better (we now surmise that he probably went into shock after the transfusion and therefore was extremely calm). However, he relapsed and beat up his wife, upon which the latter demanded a third transfusion, which Denis refused. In the meantime, the patient worsened and died, whereupon the grieving widow took Jean Baptiste to court. Luckily he was not condemned, since some judges were convinced the widow had helped nature along with some arsenic. Nevertheless, transfusion was from then on considered much too dangerous a practice by both church and parliament and was forbidden for the next 150 years. James Blundell, a British gynecologist frustrated by the loss of many lives during childbirth due to postpartum hemorrhage, decided in 1818 to break the deadlock and to initiate human-to-human transfusions in his (dying) patients. As donors he used their husbands or his assistants, which of course led to a number of disasters due to incompatibility, but the proof of principle was nevertheless made.

Transfusion of blood could be a 'gift of life'. It would take almost another hundred years before Landsteiner discovered the blood groups (1901), which made transfusion a lot safer than before. Unfortunately, it would take two world wars to refine the technology (tubing from goose quills to plastic bottles to plastic bags, anticoagulants, etc.) and to make transfusion the ultimate lifesaving medical intervention. The final breakthrough towards the universal application of blood transfusion came from the Spanish Civil War, during which the first blood bank, donor screening and distributing system were installed. The Red Cross would later – both across the USA and Europe – organize many blood transfusion services, which provided the lifesaving power of blood to all who needed it. But mass application also led to problems.

Blood, a Poisonous Gift

From the early days of blood transfusion, it was well known that patients would likely suffer from fever and faintness or shock after the transfusion of (often incompatible) blood. With the discovery of the ABO and Rhesus blood groups and compatibility testing, these reactions all but disappeared, but another longer term side-effect became apparent: post transfusion jaundice. Military doctors during World War II had noted that many of their casualties returned from trauma units with unexplained jaundice, which put them out of action for much longer than expected and sometimes even lead to fatal liver failure. This secondary loss of lives was dangerous for the war effort, so a lot of military resources were put into finding the cause. It would take many more years before the different types A and B of the hepatitis virus could be isolated. Evidently, blood transfusions could transmit (even deadly) diseases and the gift of life suddenly became potentially poisonous. The whole jaundice story would much later be repeated with the advent of the hepatitis C virus, and many patients succumb (up to present days) to this dormant and clandestine enemy within transfused blood.

This had much to do with the industrialization of blood, turning it into a commercial 'product'. During the early 1940s the American researcher Edwin Cohn had succeeded not only in safely and efficiently isolating plasma from the cellular elements in blood, but also in further fractionating the plasma in useful products such as albumin, specific coagulation factors and antibodies. Whereas red blood cells carried some kind of moral and ethical aura, which meant that they could not be sold or traded, no such limitations were imposed upon plasma products (certainly not in the US). Albumin, even freeze-dried, could be used in the resuscitation of trauma or military victims, as a coagulation factor remedy for hemophiliacs or as an antibody to boost the immune system. Investigators felt the 'market' was free and huge profits lay ahead. Utopia became the reality (for a while). The only problem was how to get enough donors. So, donors were lured with dollars: USD 10 for a pint, or 'ooze for booze' as it was euphemistically referred to. To increase fractionation efficiency (and profit), plasmas from many hundreds of donors were pooled. Soon it would become clear that many companies without too many scruples recruited their donors in the 'lower' classes: drug addicts, prostitutes, alcoholics and the homeless; in hindsight perhaps not the most hygienic members of the population. Inevitably, a horrifying price would soon be paid.

In 1981 a new syndrome of increased susceptibility to unusual pulmonary infections and the development of unusual tumors (e.g. Kaposi's sarcoma) was described in the San Francisco gay community. It soon came to be known first as GRID (gay related immunodeficiency), then later – when it was realized that heterosexuals and drug addicts could also be affected – as the AIDS (acquired immunodeficiency) syndrome. The virus, initially isolated in Paris by Luc Montagnier, was later named HIV. Montagnier received the Nobel Prize for his finding, much to the disappointment of Robert Gallo from the US, who wrongfully also claimed to have discovered the same (or a similar) virus. As became the custom in those days, biological samples were exchanged between laboratories and Gallo had allegedly used some of the slides from Montagnier to 'make his groundbreaking discovery'. Soon it became apparent that HIV could also be transmitted by transfusion through the blood of an infected donor. The latter became apparent from a very vulnerable group of patients, namely the hemophiliacs. They rely on regular transfusions of coagulation factors, prepared from donor plasma, to avoid life-threatening bleeding; and among the commercial donors, HIV positivity was frequent.

It is estimated that in the USA between 1980 and 1985 no less than 12 000 transfusion recipients were infected with HIV, of whom at least 50% died. A reliable blood test to screen donors for HIV positivity would not be developed until 1985. The transfusion world panicked, but the commercial pressure was so high that long after alarm bells were sounding, companies still sold their old stock of contaminated products. In many countries, e.g. France and Canada, transfusion specialists were sent to jail for negligence and involuntary manslaughter.

At present, the risk of contracting HIV or hepatitis C from transfusion is estimated to be somewhere in the order of 1 in 3 to 10 million transfusions, but newer threats have emerged, e.g. transmission of the Western Nile virus, Dengue fever, the Chikungunya virus, the Ebola virus and the Zika virus; agents that often take free rides on the Airbuses or Boeings of the tourism industry. Some of the agents, possibly transmitted by transfusion, have a very long incubation time, e.g. the prions ('new' infectious agents, consisting of specially folded small proteins) of a variant of Creutzfeldt-Jakob disease (a dreadful form of dementia also known as mad cow disease), making symptoms become apparent in the recipient after 10 to 12 years. The transfusion dream may have become a nightmare. So much for the 'gift of life' and utopian expectations.

Blood Stem Cells

The second half of the 19th century – the industrial era – marked the final demystification of blood. The work of giants like Robert Koch, Paul Ehrlich, Rudolf Virchow, Louis Pasteur, Emil von Behring, Claude Bernard and many others heralded more scientific analysis, up to molecular levels, of the once mysterious fluid. Their findings would pave the way to the almost untouchable status of science, with its increasing unraveling of physiological and biochemical processes. The dissection of blood and its cells and proteins became part of the pride and elation of the early 20th century. Blood research evolved rapidly. Not only red cells but also platelets and white cells were adequately described and a beginning was made with the elucidation of their function. Bone marrow was now considered to be the origin of all blood cells and the progenitors of mature cells were characterized via meticulous microscopic analysis. The Russian scientist Maximow is credited with coining the term 'blood stem cells' to indicate that all blood cells 'stem' from the same ancestor cell within the bone marrow, which differentiates in a multipotent way, i.e. giving rise at the same time to red cells, different types of white cells and platelets.

The further studies on this blood-forming stem cell would eventually lead to the whole new field of 'stem cell science'. Stem cells are considered to be the essential building blocks of all living organisms. They have the potential not only to continuously renew and regenerate themselves, but also to differentiate in the 220 diverse cell and tissue types of the human body. We now know that stem cells remain present, often in a dormant state, in different organs after finishing their job of making the organ and will only start dividing again in later life under very special conditions. In the bone marrow, intestine and skin they will regularly divide to give rise to daily new mature blood cells, fresh skin and gut cells; in the heart, lungs or liver they will rather serve as a back-up repair system or even as a regenerative system if needed (e.g. the liver).

As such, a definite hierarchy of stem cells has been described. The primary stem cell of human life is the fertilized egg or zygote, it is considered to be totipotent, i.e. it can make all types of cells and tissues. On a slightly lower level of differentiation capacity one finds the pluripotent stem cells or 'embryonic' stem cells, present in the embryo up until the 8-cell blastocyst. Afterwards, stem cells become only multipotent ('adult' stem cells), e.g. they can differentiate in the different stem cells of the endoderm (intestine, pancreas, liver), or ectoderm (skin, neurons) or mesoderm (blood). Precursors committed to the production of only one specific cell type are considered unipotent.

From the earliest days, scientists hardly needed to be convinced of the potential usefulness of stem cells to repair defective or damaged organs or tissues; if only their growth potential could be guided in the right direction (e.g. to make blood, not fibrous tissue) and their differentiation capacity be harnessed (not make tumors). Pioneers like Don Thomas from Seattle soon realized their utopia: from the 1960s onwards, bone marrow (blood-forming) stem cells were used, with some success, to cure leukemia patients (whose bone marrow was destroyed by cancer and its chemotherapy) or victims from early radiation experiments (whose bone marrow was destroyed by radioactive elements). These early hematological endeavors made many other clinicians believe that one day they too would be able to realize their dream of repairing or regenerating damaged organs (heart, liver, kidneys), instead of having to wait for a whole donor organ to transplant. The question remained, however, where they would find the necessary stem cells, what type of stem cells had to be used and how they would infuse them.

The discovery by Thompson in 1998 of a way to derive human embryonic stem cell lines from leftover embryos put the whole field on alert. It now became possible to produce unlimited numbers of embryonic cells, which could be guided into the differentiation of almost all tissues and organs. Yet with this breakthrough came ethical, moral and religious objections to the 'use of human life' for experimentation. In 2001 president Bush blocked all government funding for embryonic stem cell research in the USA. The ban was subsequently lifted under the administration of president Obama.

In 2002 the research group of Catherine Verfaillie – albeit with an opportune finding – showed that in animals and humans (unipotent) human blood-forming stem cells could be reprogrammed to a higher level of potency and become multipotent again, e.g. in culture they could differentiate in brain cells, muscle cells, fat cells, liver cells, etc. They named these cells MAPC, multipotent adult progenitor cells. Needless to say, this finding produced some shockwaves in the stem cell field because it threatened the old dogma that once differentiated there was no way back for a stem cell and it would surely undergo programmed cell death or apoptosis. Unfortunately, the methods used to produce MAPC, although reproducible, proved to be tedious and inconsistent.

In 2006 a Japanese research group lead by Shinya Yamanaka proved that real adult cells (e.g. from a simple skin biopsy) could be reprogrammed or dedifferentiated to cells with embryonic stem-cell like potency by genetic manipulation, i.e. through the introduction of four transcription factor genes. This technique proved to be much more efficient and robust than the MAPC technology and became the gold standard for the efficient and continuous production of large numbers of pluripotent stem cells, obtained without ethical, moral, legal or religious implications. They named their cells 'iPS', induced pluripotent stem, cells. Obviously this opened unknown perspectives towards clinical applications, e.g. liver cells could be grown in the lab from skin cells not only to provide *in vitro* tools ('liver in a dish') to test new drugs and avoid animal and volunteer testing, but also to grow liver tissue in the lab for transplantation, or heart, kidney, pancreatic cells or even brain tissue.[2]

Stem Cell Utopia

The explosion of knowledge about stem cells has re-introduced part of the mystery surrounding blood. If regenerative medicine is to become reality, blood stem cells will become 'the sources and elixir of life' once more. Utopian beliefs mingle with realistic applications, for instance in the following areas.

Parabionts. Since the 1950s investigators have been intrigued by what precise biochemical or physiological factors make one grow old. To find out, the circulation of a young animal was, via the abdominal small blood vessels or capillaries, connected with that of an older animal, thereby creating (sewn together) parabiont animals. This model allowed cells and biochemical factors to of gradually not knowing your relatives nor yourself anymore, research into neurodegenerative diseases is amongst the most funded in the world.

CVA and posttraumatic paraplegia or quadriplegia. While most cerebro-vascular accidents (CVA or strokes) occur because of small blood clots obstructing lipid impregnated blood vessels and most two limb or four limb paralysis is due to accidents (horse, car, motorcycle, etc.), their physiopathological origins are similar, i.e. death of neurons and nerve bundles. Millions of dollars have already been invested in finding a cure for this interruption between brain and body (e.g. American actor Christopher Reeve or Belgian triathlete Marc Herremans), but results have been disappointing. This may have much to do with the stem cell types used, the length of time it takes nerves to grow or the difficulty in making new connections between nerves and brain, but iPS derived cells may offer new hope.

Stem cells against blindness. When talking about a possible cure for blindness, one comes as close to utopia as possible. Yet, early phase 1 and 2 studies in macular degeneration – a slowly evolving eyesight loss in the elderly – seem to indicate that the use of locally injected stem cells is feasible and not more toxic than classic therapies (laser treatment or injecting anti-vessel growth factors in the eye). It is too soon to tell if this revolutionary therapy will have reliable and sustainable effects. Making the blind see again, may one day become a reality.

Create or reattach teeth. The world of dentistry could be revolutionized if, starting from stem cells on a scaffold, new 'personalized' teeth could be made or if tooth repair and reattachment could be facilitated by stem cells.

Breast implants. Initially few companies or researchers showed an interest in growing fat from stem cells. However, breast repair after cancer surgery or breast enlargement for 'aesthetic' reasons could rely on endogenous fat, grown from iPS cells. The filling of wrinkles with stem cells could one day replace monthly Botox injections or so-called 'vampire facials' (the filling of facial skin irregularities through the injection of one's own blood).

Menstrual blood contains committed unidirectional stem cells from the inner lining of the uterus and could be reprogrammed as readily-available iPS cells. Over the ages menstrual blood has already been credited with mystical and energizing power ('it comes from the same spot as new life comes from'), yet stem cell technology may surpass expectations.

Egg cells made from iPS cells could restore ovarian function in young women with fertility problems, just as sperm cells from the same manipulated iPS cells could create life without 'real' male intervention.[3]

Rheumatoid arthritis and systemic diseases. Stem cells isolated from the supporting tissue of bone marrow (mesenchymal cells) were often discarded and neglected as useless. We now know that they possess powerful immunomodulatory and anti-inflammatory properties. As such, they might be used as a tool against auto-immune diseases such as rheumatoid arthritis, lupus, scleroderma and post-transplant organ rejection.

3D Printing. Undoubtedly one of the most exciting perspectives comes from 3D printing with stem cells.[4] Already windpipes are rebuilt or parts of skulls are printed on scaffolds to restore normal anatomy. Joints will very soon follow.

CRISPR-Cas9. This new genetic technology[5] allows efficient and directed genome editing, allowing for the correction of genetic defects, the introduction of desired genetic properties or the deletion of unwanted characteristics. Brave new world or utopia?

Have We Found the Holy Grail?

Blood, as possibly the Holy Grail itself, has always played a central role in human history. It has been the cradle of mythological belief and symbolic power. More recently – because of its easy access, abundant DNA availability and diverse cellular composition – blood has also become the leading principle of the genetic and molecular labyrinths of the 21st century. But scientific progress has never succeeded in eradicating the mysticism surrounding blood. With stem cells this notion has come back in full force, and blood – once again – provides a fertile substrate for utopian ideas. So let us believe in 'forever young', or at least in preserving or repairing a good quality of life beyond average life expectation. For a moment, we will forget the unbearable financial cost and the new threats and challenges to human integrity created by genome editing. Instead, by making the blind see, the crippled walk and the restoring of hearts, livers and brains we will embrace the dream of what is possible today – even if it may prove a confronting reality for later? Utopia revisited.

Notes

1 Suggestions for further reading: Hill, L., *Blood, The Stuff of Life*, Toronto: House of Anansi Press, 2013; Le Fanu, J., *The Rise and Fall of Modern Medicine*, Boston: Little Brown and Company, 1999; Tucker, H., *Blood Work, A Tale of Medicine and Murder*, New York: Norton, 2012; Hollingham, R., *Blood and Guts*, New York: St Martin's Press, 2008; Rosenberg, S., *The Transformed Cell*, New York: Putnam, 1992; Starr, D., *Blood, An Epic History of Medicine and Commerce*, New York: Alfred Knopf, 1998; Bernard, J., *La Légende du Sang*, Paris: Flammarion, 1992; Bessis, M., Binet, J.-L., et Bernard, J. (eds.), *Histoire Illustrée de l'Hématologie*, Paris: Roger Dacosta, 1992; Gordon, R., *The Alarming History of Medicine*, New York: St Martin's Press, 1993; D'Epiro, P., *The Book of Firsts*, New York: Anchor Books, 2010; Matthieu, F., *Biografie van het Bloed*, Leuven: Van Halewyck, 2003; Verfaillie, C., and De Geyter, G. (eds.), *Van Cellen tot Daden*, Tielt: Lannoo, 2006.

2 See Rudy Lauwereins, 'Preventive Maintenance for a Future without Disease', in this book (p. 36).
3 See Thomas D'Hooghe, 'Universal Reproductive Freedom and Health', in this book (p. 106).
4 See Peter Van Puyvelde, '3D Printing: The Making of Utopia', in this book (p. 442).
5 See also Koen Devriendt & Hilde Van Esch, 'Healthy Genes for Everyone', and Bart De Moor, 'Will Life Go Live One Day?', in this book (pp. 93 and 20).

Healthy Genes for Everyone

Koen Devriendt and Hilde Van Esch, Genetics

We dream of a utopian world without the burden of severe untreatable genetic disorders that appear early in life.[1] Such disorders often involve organ dysfunction, resulting in variable problems with vision, hearing, psychomotor development and intelligence, epilepsy, cardiac and renal dysfunction, etc. They often result in early mortality, and for the surviving child, significant morbidity exists. The burden for the child and its family is high. Individually, these conditions are rare, but because of the severe consequences, collectively, they have a major impact on health care and society. A large proportion of these disorders have a single cause, a mutation affecting a single gene or a part of a chromosome. Imagine a world where the impact of these severe monogenic and chromosomal diseases dramatically decreases as a result of novel therapies such as gene and stem cell therapy but equally more traditional pharmaceutical therapies based on a detailed understanding of how the disease progresses. Where therapy lags behind, systematic efficient prenatal or preimplantation genetic diagnosis will offer future parents an almost unlimited reproductive choice to prevent genetic disease in their children.

However, the way to achieve this is long, and depends on major leaps forward in knowledge and technology. In addition, society will have to find a satisfactory answer to the many ethical issues raised during these developments.

The Basics of Genetics and Heredity

Genetic information is physically located in our DNA, a molecule which consists of four different building blocks called 'nucleotides', named A, T, G and C. The genetic information is coded in the sequence of these four different nucleotides. In humans, a total of approximately 3 billion nucleotides are distributed over 23 different chromosomes, namely the autosomes (1 to 22) and the two sex chromosomes X and Y. Each chromosome, which can be compared to a book, contains hundreds to thousands of genes or recipes. Humans have approximately 20 000 genes, and each gene can be considered as a unit that codes for a particular protein with its specific function. Interestingly, the genes themselves make up only a small part of about 2% of our genome. The intergenic DNA, previously called 'junk DNA', is gradually unfolding its diverse functions, such as maintaining the structural integrity of the chromosomes, regulating the function of the genes or the activity of proteins, etc.

Our DNA carries the hereditary information, which is transmitted from generation to generation using the sperm and egg cells as a vehicle. At fertilization, 23 chromosomes from the father and 23 chromosomes from the mother come together and constitute a starting point for a new individual. Thus, each human being carries two copies of each of the 23 different chromosomes, and therefore also of each gene (except for the X and Y chromosomal genes in the male).

The Human Genome Sequence

In 2003, Bill Clinton together with representatives of the international Human Genome Project (HGP) announced the completion of the entire sequence of the human genome. The HGP gave us the ability, for the first time, to read nature's complete genetic blueprint for the building and functioning of a human being. However, this effort took more than 10 years and was very costly (USD 3 billion; USD 1 per nucleotide in our genome), mostly due to the old and expensive technology used. In contrast, today, entirely novel technology, referred to as 'next generation sequencing' (NGS), offers the opportunity to have one's genome sequenced for EUR 1000 or less. Technological advances will ensure that this price will drop even further. Thus, (repeated) genome sequencing will become affordable and will be introduced as a routine and universal test in our health system. In due time, technology will allow us to determine the genome sequence instantaneously from a drop of blood. This will fulfil a first requirement for advanced medicine based on human genomics.

Sequencing the human genome was an important milestone, but the focus has already shifted towards understanding the role of the human genome. The sequence is one step, interpreting the information coded in this sequence is still challenging. An immense interdisciplinary effort is being made to understand how our different genes ensure a normal development from a fertilized egg cell to a full-grown adult and how they maintain a normal functioning of our cells, tissues and organs. In parallel, researchers try to understand how 'defective' genes contribute to the large number of human diseases.

phenotypic data of each of these individuals. To date, phenotypic information is mostly available in the patient's medical files. However, this information is incomplete since it represents only specific time points, a limited number of data and is heavily biased towards abnormal findings. Novel bioinformatics technologies and health devices will ensure continuous monitoring of a rich number of variables which can easily be uploaded in one's personal digital file.[2] The subsequent analysis of genome sequences coupled with the rich phenotypic data present in the electronic databases of millions of individuals, both healthy and with specific diseases, will establish significant associations between phenotypic features and genetic variants.

The severe genetic diseases described in this utopia are those caused by a change in the genome (or mutation) that has a major impact on the gene function, i.e. that dramatically reduces or alters the function of the gene. One can distinguish between chromosomal imbalances, where large parts of a chromosome are altered, and monogenic diseases with changes limited to a single gene. Currently, 7421 monogenic conditions are known and catalogued in the Mendelian Inheritance in Man database. Every week, novel monogenic disorders are being recognized. Several monogenic disorders are found almost exclusively in certain specific isolated populations, e.g. in Finland or among the Amish people. Since most of the world's populations, especially outside Europe, have hardly been investigated, there is still a long way to go in order to finish the book of all monogenic disorders.

For only 3764 of these diseases the causative gene(s) has been identified. Many rare conditions exist that have been described in only one family. Often such families with unique phenotypes have been found to carry mutations in a gene not previously associated with genetic disease. Confirmation of the found association depends on the identification of new patients or families with the same disorder carrying mutations in the same gene. Progressively, the genetic basis of all severe monogenic conditions will be unraveled. As outlined in more detail below, this will give parents and patients different options, ranging from the early initiation of effective treatment to prevention through screening of couples at risk and early (prenatal) diagnosis. The choice of future parents will depend on various factors, including efficiency of treatment, severity of the disease, but also on changing societal and personal beliefs and values.

Treatment of Genetic Disorders

At present, except for a handful of inborn metabolic diseases, there exist no cures for most of the severe monogenic disorders that appear early in life. Even after decades of intensive research on well-known disorders like cystic fibrosis and Fragile X syndrome, the therapeutic options remain disappointing and most treatments are limited to the supportive management of specific physical and mental disabilities. Many pharmaceutical compounds with a positive effect in pre-clinical animal models failed when applied in clinical trials, necessitating other and novel strategies.

As an alternative, human gene therapy is a promising and rapidly evolving field. As mentioned above, severe monogenic disorders arise from mutations in our genes, which in many cases affect the normal function of the genes and their corresponding proteins. One could 'replace' the defective gene by the 'normal' copy to cure the disease. The major challenge, however, is to safely and effectively deliver the 'normal' copy to the affected tissues within the human body. Therefore, most of the successes to date have been generated in treating organs *in vivo* that are easily accessible, such as the eye (Leber congenital amaurosis or early blindness) or the liver (production of blood clotting factor IX). Safety remains an important concern with this approach. The viral vectors used to deliver the normal copy to the affected tissue(s) can trigger an immune response (immunotoxicity), which then eliminates the 'cured' cells and hampers the therapeutic outcome. In addition, some of these viral vectors can insert themselves in our genome and cause mutations themselves (genotoxicity). Therefore, much effort is put into the development of novel vehicles/vectors that are safer in use and that can also be used in more difficult organs such as the brain.

In addition to gene replacement therapy, other gene manipulation strategies are being developed to meet the safety and the efficacy demand. A very promising and new player in gene therapy is the RNA-guided genome editing tool CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats/CRISPR-associated nuclease9). This rather novel tool enables researchers to correct mutations in genes, and hence can be used for correcting monogenic disorders. At present, its efficiency has been proven in adult animals to correct a gene mutation via injection of the specific CRISPR-Cas9 agents into the bloodstream. We believe that this tool holds great potential for future use in humans.[3] In addition, a similar strategy can be applied to manipulate early embryos and even human germline cells in order to prevent severe monogenic diseases from being passed on. A fetus affected with cystic fibrosis will be cured prenatally by injecting the appropriate CRISPR-Cas9 agents into the umbilical cord.

Another emerging field with great translational potential is the use of human stem cells and/or induced pluripotent stem cells (iPSCs).[4] Somatic fully differentiated cells can be reprogrammed into iPSCs and these cells can then be differentiated to any other cell type. Interestingly, patient-derived iPS cells can be genetically modified 'outside the body' using for example CRISPR-Cas9. Next, these patient-derived genetically corrected iPSCs can be differentiated into the desired cells and transplanted back to the patient. This has already been done for some hematological disorders, where it is relatively easy to replace the affected 'organ'. At present, organ-like structures are being developed in the dish, starting from these types of cells, and in the future it will become possible to print a fully developed new organ starting from patients' own stem cells.[5]

Prenuptial Carrier Testing

Some people have a higher risk of a child with a genetic condition, and identification of these persons will offer reproductive choices. Humans have 22 pairs of autosomes, 'normal' chromosomes, of which each individual has two copies, and one pair of sex chromosomes, X and Y, with two X chromosomes found in women, one X and one Y in men. For most genes on one of the 22 autosomes, one single functioning copy on one chromosome is sufficient for a normal function. However, when one inherits two abnormal copies of a certain gene, from both parents, a genetic disease occurs. We all carry an estimated 3 to 4 non-functional genes. This remains hidden, unless one has the bad luck to have a partner who carries the same dysfunctional gene, and both partners transmit this to their child. Carrier testing before starting a family will in the future allow the identification of all couples at high risk for children with such an autosomal recessive condition. Since everyone carries on average 3 to 4 mutations for an autosomal recessive condition, this will only rarely cause high risks for our children. The reason is that these are mostly very rare disorders, and the chance that the partner will also be a carrier is very small, unless he or she is a close relative.

Many of these rare autosomal recessive conditions have a higher incidence in certain regions in the world. Therefore, prenuptial testing often focuses on those conditions that are prevalent in one's ethnic group. For instance, in certain Western countries, couples can opt for cystic fibrosis screening. In Mediterranean countries, programs exist for screening for thalassemia, an inherited disorder of red blood cells. However, due to migration and consequently the rapid mixing of populations from initially separated regions, this approach will lose its usefulness, and be replaced by 'one test fits all'. Clearly, this information will be available in one's personal genetic file, extractable from one's genome sequence. But it will only be relevant when one plans to start a family.

Also, for the same reason, when a couple is blood-related they have a higher chance of carrying the same autosomal recessive conditions. Blood-relationship is therefore associated with a high increase in the incidence of autosomal recessive conditions. For instance, first cousins have a twofold increased risk of having a child with a congenital disorder. In certain regions in the world, consanguineous marriages are the rule rather than the exception, and therefore, in these situations, the benefit of prenuptial carrier testing will be much greater.

Another category of hereditary disorders are inherited in an X-linked way. Females carry 2 X chromosomes, and in most cases, when a woman carries a mutation on one of her X chromosomes, she is still protected by the normal gene on the other X chromosome. However, when this abnormal X chromosome is transmitted to her son(s), they will display the disease (they only have one X chromosome since they inherit their Y chromosome from their father).

In a utopian world, all couples will have the option to undergo extensive carrier testing, which will identify whether their child is at risk for X-linked or autosomal recessive conditions. This will allow them to make appropriate reproductive choices. While this technology will be viewed as an opportunity, it also implies threats such as a changing view on disabilities, free choice and solidarity, concerning disease. This is discussed in more detail at the end of this chapter.

Reducing *De Novo* Mutations in Germ Cells

Parental age is one of the main factors influencing the risk of new or *de novo* mutations. Advanced maternal age is associated with increased chromosomal imbalances (with trisomy 21 or Down syndrome being the most frequent one compatible with survival), whereas advanced paternal age is associated with an increased incidence of single gene mutations. For instance, the average number of mutations carried in an individual sperm cell is 50, and it increases with 2 every year.

Early storage of egg cells or sperm cells will therefore be a valuable alternative in order to reduce the mutational load in offspring. Already at this moment, social 'egg freezing' is offered to women in anticipation of having their children at a more advanced age.[6] This will enhance our freedom to plan a pregnancy at the time it suits us best.

As discussed above, stem cell technology will allow us to create any specialized cell type. The germ cells, i.e. sperm or eggs, are not only specialized cells, but they have the unique feature that they contain only one copy of each chromosome, and not two as all other cell types. This requires a distinct type of cell division called 'meiosis'. Unravelling the secrets of meiosis will permit us to create mature germ cells *in vitro*, starting from stem cells or even somatic cells. It will be only a small additional step to correct mutations with the new techniques, yielding genetically normal germ cells from an affected individual.

Preimplantation Genetic Diagnosis

The expected advances in *in vitro* fertilization technology will offer an additional opportunity to identify severe Mendelian disorders, already in the embryonal stage. At present, preimplantation genetic diagnosis[7] is used for couples who are at high risk of transmitting a severe disease to their future children. However, inherited mutations form not the only risk, since most of the severe disorders are caused by new mutations occurring in the sperm or egg cells. In the future we will go a step further, and not only screen for the familial mutation(s), but look for mutations in the whole genome by sequencing a few individual cells from embryos conceived after *in vitro* fertilization. Only normal embryos will then be transferred back to the uterus of the mother.

One must keep in mind, however, that mutations not only happen during the formation of the sperm or egg cells, but that they can also occur during the first cell divisions, after fertilization, and even later during embryonic life, e.g. after a few cell divisions, resulting in a mosaic pattern of normal and mutated cells. Therefore mosaicism cannot always be detected if one samples only a few cells at a very early stage. Thus, this may be one reason to try and culture embryos sufficiently long to be able to analyze more cells, detect more mutations and correct them.

Prenatal Testing

Inherited monogenic conditions represent only a small proportion of Mendelian disorders. Therefore, prenuptial screening will only have a small effect on the incidence of severe congenital disorders. Most of the severe monogenic disorders occur *de novo*, arising typically in the germ cell of one of the parents. Universal *in vitro* fertilization and embryo screening is unlikely to become mainstream, especially if early, noninvasive prenatal diagnosis will be available. One of the main challenges of prenatal diagnosis is timing. To date, the earliest time during pregnancy when fetal cells can be examined is when the embryo is 9 weeks old. This corresponds to a gestational age of 11 weeks when calculated from the first day of the last menstrual period. An invasive biopsy at 11 weeks of the placenta (called 'chorionic villi') yields sufficient cells and DNA needed for any genetic test. However, implantation and formation of the placenta already occur in a two weeks old embryo. This is accompanied by shedding of embryonic cells and cell free embryonic DNA in the maternal circulation, be it at a very low level. In the future, reliable sequencing of very low amounts of DNA, single cell genomic sequencing and sequencing of cell free DNA recovered from mother's blood will provide us with the genome sequence of the embryo at a very early call for a moratorium in 2015. Thus it is a utopia that radical, non-conservative changes in ethical, legal and societal views and attitudes will speed up the acceptance and introduction of the new technologies. Rather, we will have to accept gradual, stepwise changes.

One of the aspects that need reflection is costs and prioritization or commercialization. At present, the costs for total genome sequencing and analyses are still high, necessitating the prioritization of the patients who benefit the most from this type of information, and who can be reimbursed within the current health system. In a parallel circuit, more and more commercial companies offer genetic testing outside the clinical care context, creating a two-speed (non-supervised) medical care. As prices drop and the interpretation of genomic data becomes feasible, it is the task of (the representatives of) our society, prompted by an increased societal awareness, to create a novel health care framework that combines the best care for the population with respect for each individual.

Another issue is personal freedom and responsibility. Currently, study protocols often suffer from inappropriate informed-consent procedures, to safeguard privacy and individual approval of any use of genomic and phenotypic data. Given the huge advantages of genomic medicine, in our utopia, the idea that one's genome sequence and detailed phenotypic information (both regarding normal features and diseases) need to be shared would be mainstream. Another interpretation of solidarity would be that one cannot benefit from medical advances if one refuses to contribute. In discussions about personal responsibility and health, one's genetic make-up has often been described as unavoidable. For instance, a recent proposal by the Belgian Social Security Institute denies smokers the reimbursement of medication for lung fibrosis. This was countered by the argument that healthy behavior is not merely a free choice, but also depends on genetics and socio-cultural environment. Clearly, in our utopian world, it would be a free choice to accept certain genetic conditions or not, and this undermines the much valued principle of solidarity when disease is concerned. How will society deal with individuals who opt not to take part in the prenuptial/prenatal screening programs that are available? Likely, some couples will continue to accept genetic disorders as part of life, because of cultural or religious beliefs. Will society remain solidary or will these parents be held personally responsible for their 'irresponsible' behavior? And how will children react when they realize that their suffering could have been avoided if only their parents had made another choice? Many more potential legal cases of 'wrongful life' might be the result.

Another challenge is the view on disability and health and the definition of 'normal' versus 'disease' and 'severe' versus 'mild'. The advances in treatment and prevention will challenge how society views handicap, disability or disease. The current focus on acceptance and guidance (making the best of it) for the majority of congenital disorders will have dramatically changed once prevention is widely accessible. However, milder diseases will still occur, and society will still need to protect these disadvantaged persons. On the other hand, these milder diseases will rapidly become the focus of next-generation strategies to cure or eradicate them.

And finally there is the issue of eugenics: prevention or enhancement? The advances in genetic diagnosis, gene therapy and gamete engineering will eventually allow the targeting of other genes that are not necessarily linked to diseases but to other genetically determined features such as physical strength, intelligence, height, etc. In the early 21st century, this is still totally unacceptable (at least in Western societies). But many variants have two faces. They may be involved in genetic disease, but in other circumstances, they may be beneficial. Genetic variation is therefore a safeguard for the human species to ensure survival in a changing environment. Overzealous selection against or correction of certain variants that are now linked to genetic disease may, in the long run and in different circumstances, threaten the survival of the human species. However, this macro view on genetics and health is not a major concern for the growing eugenic movement: 'if we can already change human genes now, we will be even better at it in the future'.

Notes

1 Suggestion for further reading: Borry, P., and Matthijs, G., *The Human Recipe. Understanding Your Genes in Today's Society*, Leuven: Leuven University Press, 2016.
2 See Rudy Lauwereins, 'Preventive Maintenance for a Future without Disease', and Liesbet Geris & Ine Van Hoyweghen, 'Digital Health Care for Real Patients', in this book (pp. 36 and 47).
3 See also Bart De Moor, 'Will Life Go Live One Day?', in this book (p. 20).
4 See Marc Boogaerts, 'Blood and Stem Cell Utopia: The Search for the Holy Grail', in this book (p. 78).
5 See Rudy Lauwereins, 'Preventive Maintenance for a Future without Disease', and Peter Van Puyvelde, '3D Printing: The Making of Utopia', in this book (pp. 36 and *442*)
6 See Thomas D'Hooghe, 'Universal Reproductive Freedom and Health', in this book (p. 106).
7 See also Thomas D'Hooghe, 'Universal Reproductive Freedom and Health', in this book (p. 106).

Universal Reproductive Freedom and Health

Thomas D'Hooghe, Reproductive Medicine and Biology

In this chapter, I will look at a utopian future for humans with fertility problems. There are two dreams for this future. In an ideal world the global burden of fertility, especially in low and middle income countries where it causes a lot of personal suffering, would be lifted. This is a public health issue. The second dream, of unlimited possibility through scientific progress, is especially prevalent in high income countries. Here I will look at the question whether preimplantation genetic diagnosis, social egg freezing and the creation of artificial gametes may represent progress towards a utopian fertility world, or towards a dark 'brave new world'. Should preimplantation genetic diagnosis be used to prevent serious genetic diseases only or also be allowed to create 'designer babies'? Should egg freezing be limited as an option to women with medical problems, or should it also be offered to all ambitious women from the age of 18 onwards? Will the creation of artificial gametes fundamentally change human reproduction and allow each individual to create their own eggs or sperm to reproduce without sex?

The First Dream: Universal Access to Infertility Care

Infertility as a disease affects many people throughout the world, both men and women, and often leads to personal suffering and social stigma. The World Health Organization (WHO) recognizes that sexual and reproductive health and rights are fundamental to individuals, couples and families and to the social and economic development of communities and nations. There are three different definitions for infertility in use. All these definitions refer to a heterosexual couple trying to conceive, but in practice relate to women trying to conceive within the context of a couple (excluding individual women or men with the desire to have a child within a same-sex relationship, or as individual people).

Infertility has been clinically defined by the WHO as a disease marked by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse. This clinical definition is used worldwide in a clinical context (i.e., for research on effective treatment).[1] From an epidemiological point of view (i.e., the study of disease conditions in the population, for public health), infertility is defined as the situation in which a woman of reproductive age, at risk of becoming pregnant, reports unsuccessfully trying for more than 24 months.[2] Demographic infertility can be defined as the absence of a live birth for women who desire a child and who have been in a relationship for at least 5 years without the use of any contraceptives. In the case of a childless woman this is called 'primary infertility', with 'secondary infertility' referring to a similar absence of a live birth for at least 5 years after the birth of the first child.[3] Strictly speaking, if a couple is physically unable to have intercourse, this does not qualify as a form of clinical infertility, but would be labelled as infertile according to the definition of demographic infertility. In clinical practice, such couples are considered to be eligible for infertility treatment, depending on the overall medical, psychological, social and legal context.

The Global Prevalence of Infertility and Its Causes

It has been estimated that clinical infertility affects 10-15% of all couples, but this prevalence is possibly increasing worldwide due to various factors. The female age at the birth of the first child is increasing, so are overweight and obesity, the prevalence of sexually transmitted infections is increasing, there is a possible reduction in sperm quality and an increase in testicular cancer, stress and pressure can affect the important role of coital activity, there is an increase in survival after cancer with often reduced infertility, the higher acceptability of and lower threshold for infertility diagnosis and treatment lead to more visibility, and new medical and scientific developments lead to new treatment options. Globally, 186 million couples suffer from demographic infertility, based on data collected between 1995-2000,[4] with primary infertility present in 2.5% of couples (18 million) and secondary infertility observed in 25% of couples (168 million) of reproductive age. No doubt, this prevalence would be much higher if the clinical definition would be used. A more recent study[5] led to the conclusion that about 48.5 million couples were affected by demographic infertility in 2010. This number would increase 2 to 2.5 fold, to 97-121 million couples, if the time frame were reduced from 5 years (demographic infertility) to 2 years (epidemiological infertility).

Infertility can be caused by factors in the man (at least 1/3), the woman (about 1/3) or a combination of both (1/3). In most cases, infertility is associated with a significantly diminished monthly fecundity rate, and a cause or explanation for the infertility can be found after a complete diagnostic evaluation. Often, a combination of male and female factors can be observed, strongly influenced by female age and duration of infertility. However, in rare cases full sterility, with a complete inability to conceive, is observed. This can for instance be the result of sterilization, blocked tubes, and specific disorders (lack of sperm, ovulatory dysfunction, genetic disorders, etc.) Both male and female fertility are negatively influenced by smoking, overweight or obesity, and environmental exposure to heavy metals, dioxins and other pollutants.

Even though sexually transmitted infections (STIs) play a larger role in infertility in low and middle income countries, they are not the main cause of infertility in these countries, in contrast to what most people think. According to data published 30 years ago,[6] 1/3 of female infertility in Asia and South America was related to ovulatory dysfunction, and 40-50% of male infertility was not related to STIs. New data are not available but I speculate that the proportion of primary infertility would be much higher if STIs were an important cause. Instead, I believe that there is an increasing role of other non-STI related factors causing female infertility, like ovarian ageing due to female age, ovulatory dysfunction, gynecological disorders like fibroids (abnormal but benign growths) and endometriosis that may cause both pelvic pain and infertility, and the impact of smoking and obesity. In this context, it is also important to take into account racial and ethnic disparities in reproductive medicine, infertility and its causes.

Infertility due to unsafe abortion and/or maternal sepsis is reported[7] to affect 32.5 million worldwide, and was ranked as the fifth most prevalent health condition associated with moderate to severe disability among women 0-59 years old from low and middle income countries.

The Psychosocial Impact of Infertility

The impact of infertility is strongly related to the cultural and religious context, involving both psychosocial and economic consequences. Indeed, in many countries a person's social and moral value is linked to reproduction. In high income countries, reproduction is mostly a free and personal choice made by a couple or individual, with social and economic factors stimulating low birth rates. However, in low and middle income countries, having children is a religious, cultural and social obligation, both for women and for men, expected by the family (and family-in-law) and extended community, leading to social pressure and stigmatization.[8] Having children secures one's marriage, confers social status, guarantees rights of property and inheritance, provides assistance with labor, offers social security in old age and provides continuity for the family infertility represents a 'medical and social poverty trap'.[19] Furthermore, in view of the social stigma associated with infertility, men and women use ART services in a secret way, without informing family or the community at large.

The proportion of countries offering ART services is increasing: from 24% (45/191) in 2000 over 31% (59/191) in 2005, to 55% (105/191) in 2010. However, only 31% of the Sub-Sahara African nations had at least one IVF clinic in 2010.[20] Furthermore, access to ART services is problematic in many Central Asian countries and low in some South Asian states like Bangladesh and Pakistan. In this context, the high costs of ART (if available) or total absence of ART clinics are important drivers of cross-border reproductive care.

Although affordable ART initiatives like 'Walking Egg' or the 'Foundation for Low Cost IVF' are emerging, they are still very preliminary at present. Access to infertility care (prevention, diagnosis and therapy) can not only be considered as a human right, but access to this care, including ART services, can also change gender relations in various positive ways, lead to increased public knowledge of both male and female infertility, normalize both male and female infertility problems as medical conditions that can be managed, decrease stigma for infertile men and women, and increase marital commitment among couples seeking ART treatment together, characterized by love, commitment and fortitude in the face of adversity.[21]

However, from a public health point of view, infertility is unfortunately not considered as a core priority by many donor agencies. Indeed, infertility is perceived by some as a way of population control, especially in regions where high rates of fertility co-exist with high rates of infertility, a demographic paradox known as 'barrenness amid plenty'.[22] This position is based on a tacit eugenic view that infertile people in low and middle income countries are unworthy of infertility prevention or treatment. However, the burden of overpopulation should not be carried by the infertile alone, but instead the fertile population could be encouraged to have fewer children.[23] Others just consider infertility as a low priority if public health resources are limited. However, prioritizing public health issues based only on epidemiological indices is problematic and ignores the importance of the psychological, sociocultural and economic impact of infertility at the individual and community level.[24]

Interestingly, due to the importance attached to the social, cultural and religious impact of child bearing, several national governments support infertility care, while still paying attention to family planning. In Iran, Egypt and Turkey, but also in Vietnam, ART services are (partially) reimbursed by insurance (in Algeria and Turkey) or provided by government clinics for free or at a low cost (in Egypt, Iran, Vietnam), supported by high profile medical experts and by active patient support organizations.[25] According to the Centers for Disease

Control (USA), infertility diagnosis and treatment is relevant to public health since infertility is associated with significant health care costs and important economic and racial disparities, and since early diagnosis and treatment of underlying medical conditions (secondary prevention) may restore fertility. Furthermore, infertility (treatment) can be associated with adverse health outcomes for mother and child, requiring epidemiologic surveillance efforts for tertiary prevention.[26]

A Utopian Dream for Global Fertility

In short, a utopian dream for global fertility would consist of maximal prevention of infertility and maximal access to infertility services for those who need them, to end the individual suffering that is caused by infertility worldwide, especially in low and middle income countries.

However, this dream of a world without infertility can only be reached if reproductive rights of women are fully recognized. If those who wish to do so, are allowed to reproduce in their 20s and early 30s, and if society relieves the pressure on young couples forced to combine careers, relationships, the purchase of a house, and having children all at the same time. The importance of having children at the right time should be stressed, from a society perspective. Women wishing to have children at the right time should not be discriminated in terms of career perspectives, but should be able to retain all their prospects for career development after they have had children between their 20s and their 40s.

But suppose that from now on, all women would have most of their children before 30 and make sure to complete their fertility wishes by the age of 35 or so, in order to avoid the consequences of fertility starting to decline slightly after age 32 and strongly after age 35. Suppose as well that we could convince all couples seeking to conceive to stop smoking, preserve a normal body mass index, exercise regularly and drink alcohol with moderation. Even if this were possible, infertility would not be prevented and would continue to exist. Therefore, full access to infertility diagnosis and treatment, as a human right, should be provided by national governments, including reimbursement, to avoid discrimination related to social or financial status. Access to and affordability of infertility care from a patient perspective could be combined with quality of care, by setting limitations on the number of reimbursed cycles, female age, and number of embryos that can be transferred, in order to reduce the incidence of multiple pregnancies and associated costs after ART treatment. Infertility should become a global public health priority, since infertility affects many people throughout the world, often leading to personal suffering and social stigma. Ideally, a hundred years from now, the world would look very different.

The Second Dream: The Technological Revolution and Its Consequences

Preimplanation Genetic Screening

Historically, preimplantation genetic diagnosis (PGD) has been used to prevent the implantation of genetically abnormal embryos.[27] This allows couples at risk of having a baby with a severe genetic disease (X-linked, monogenetic, or linked to abnormal chromosomes) to avoid prenatal diagnosis after implantation, with its difficult decision regarding a potential selective abortion for genetic reasons. Such a diagnosis requires the use of Assisted Reproductive Technology, including the biopsy of one or two cells from an embryo at day 3 or 5 of its development in the laboratory after in vitro fertilization, followed by genetic analysis. Improvements to biopsy and diagnostic protocols have increased the efficiency and accuracy of PGD over the last years. Although governments and professional societies will continue to draw up guidelines for and set boundaries to the reasonable uses of PGD, the demand for the technique is likely to continue to increase as we enter an era of personalized medicine, including genetic risk assessment for ourselves and for our children. With more genetic information to guide reproductive decisions, PGD will become useful for people beyond those who are personally affected, have affected family histories, or have already had affected children, and will possibly include screening for adult-onset disorders, cancer predisposition alleles, etc.[28] In this respect, ART with PGD will become increasingly interesting for all potential future parents, and may completely change the way we look at the prevention of disease in individuals before they are even born. Obviously, this development will result in intense and difficult ethical discussions to avoid totalitarian eugenic policies like those described in *Brave New World*. The use of new technologies allowing the prevention of disease will need to be balanced with the rights of all human beings 'not to know potential genetic risk' and to have access to affordable medical care when they become ill.

Egg Cell Banking for a Lifelong Preservation of Fertility

As mentioned above, the decline of human fertility with female age is related to a reduced genetic quality of the eggs, which starts at age 32, becomes more prominent after age 35, and very outspoken after age 40, with the result that very few women achieve a live birth after age 45 and menopause starts at around age 50. It has been questioned whether women need to accept this biological reality and alternatives like egg cell banking have been promoted. According to some experts, egg cell banking for anticipated gamete exhaustion (AGE) due to advancing female age can be seen as a preventive intervention to keep open reproductive options before it is too late.[29] Similarly, it has been questioned what this new egg cell tissue economy means to the women who use this service. Women use egg freezing to reconcile otherwise incommensurable differences between the time scale of their reproductive biology, the steadily elongating nature of the modern life course and the increasingly iterative structure of portfolio careers and relationship formation. Their sense of urgency arises from the way in which the loss of fertile capacity steadily accelerates, the sense of lost time becoming more and more acute and compelling. In this context, egg freezing could potentially redeem both past and future, by arresting fertile time, creating new timeframes not limited by reproductive age only, extending beyond the logistics of in vitro fertilization into a more general social space where women can decide when to use their eggs depending on their social and relationship status.[30] This would allow women to create a margin for deliberation and relational negotiation, without the ever-accumulating pressure created by dwindling fertility, as a way to ensure family continuity in both the genetic and the social sense.

The Creation of Artificial Sperm and Eggs and the Transformation of Gender Identity

According to a recent review paper[31] representing the state of the art regarding the creation of artificial sperm and eggs from stem cells, artificial eggs from a male animal have been created and fertilized and artificial sperm originating from a female animal has been able to fertilize eggs and result in viable offspring. In humans, artificial sperm has been generated from not only male but also female stem cells,[32] whereas artificial eggs have been developed from both stem cells and somatic cells (i.e., regular body cells). Fertilization of a human artificial egg cell by transplantation of a somatic cell nucleus into a donor egg cell from which the nucleus was removed, was also reported. At present, there is no information yet regarding the normal developmental potential, genetic stability, and health of children after the use of human artificial gametes. It can reasonably be expected that in the near future, it will be technically possible for all human beings to generate their own eggs or sperm, regardless of their gender, without the need to have ovaries or testicles producing these gametes. This will fundamentally change our concepts of gender, reproduction and life, and human identity and dignity, far beyond *Brave New World*. Obviously, the possible applications of this technology are not clear yet, and will require scientific, medical, public, legal and ethical debate, but in principle, this technology will allow reproduction for heterosexual couples without functional gametes, post-menopausal women and homosexual couples, and may obviate the need for donor cells.

Utopia or Brave New World?

In the not too distant future, technological revolutions will allow preimplantation genetic screening for an increasing variety of health risks and the lifelong preservation of fertility will be possible by gamete banking or the generation of artificial gametes. The first and very important concern will be that these technologies are proven to be safe before they are ever applied to humans, which will require more research on animals with reproductive systems similar to humans, for instance nonhuman primates.[33] Also their efficiency will have to be tested in clinical research using the highest ethical and scientific standards. Finally, their application within or outside a medical context will have to be debated from a societal point of view, including scientists, physicians, patients, ethicists, lawyers, politicians and the general public. It is clear that these developments will change the way we look at human identity, dignity, responsibility and solidarity. In fact, they will fundamentally change the way we look at gender, reproduction and sexuality. They may also be perceived as dangerous because they could offer a methodology for eugenic programs. But they could also be used to prevent or reduce the risk of serious diseases later in life and allow genetically homologous reproduction for couples who currently cannot have children, or who have to use sperm, eggs or embryos from donors. At present, it is not clear whether such an evolution represents a utopia, or dystopia, or both. Hopefully, in the end, universal human rights and values focused on human dignity, safety and the future of mankind will prevail.

Notes

1 Zegers-Hochschild, F., Adamson, G.D., de Mouzon, J., Ishihara, O., Mansour, R., Nygren, K., Sullivan, E., and Van der Poel, S., on behalf of The International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO), 'Revised Glossary on ART Terminology', *Human Reproduction* 24, 2683-2687, 2009.

The Health Care of the Future

Priority is given to the sick, who are cared for in public hospitals. There are four of these situated around the periphery of each city, just outside the city walls, and they are built on the scale of a small town. This is so that the sick, however numerous, won't be squeezed into overcrowded wards, and so that those suffering from contagious diseases that might spread from one to the other can be isolated. The hospitals are so well planned and equipped with everything necessary to restore health, the care provided is so gentle and attentive, and the presence of the most skilled medical specialists so constant that while no one is sent there against their will, scarcely a sick person in the entire city would not rather be nursed there than at home. (70)

Eradicating Depression without Losing Humanity

Stephan Claes, Psychiatry

A world without depression by the year 2100, would that be a utopian dream or a nightmare? Isn't being depressed, feeling sad, feeling unhappy a natural part of human existence? Weren't many of the greatest works of art born from a fundamental feeling of unhappiness? If we eradicate depression, will we not also eliminate a fundamental human trait in the process? In short, can we eradicate depression without losing humanity?

"We hold these truths to be self-evident, that all men are created equal, that they are endowed by their Creator with certain unalienable Rights, that among these are Life, Liberty and the pursuit of Happiness." According to the Declaration of Independence of the United States, happiness is a key goal of human existence. However, as the Founding Fathers of the USA cleverly implied in this statement, society cannot create happiness for its citizens, it can only safeguard the possibility to pursue it. In the eyes of Thomas Jefferson and the Founding Fathers, happiness remains a personal matter that cannot be settled by government.

Nevertheless, utopian thinkers often take it one step further, and envisage creating a society that through its organization causes happiness to emerge in the lives of people. This is also the case in Thomas More's *Utopia*. Happiness is a major goal of the Utopian society, and is linked tightly to the experience of pleasure. However, it is not left to the Utopians to decide which pleasures lead to happiness: the Utopian society has clear guidelines on this matter, distinguishing true and false pleasures. The concept of true pleasure is based on Epicurean philosophy: a natural delight in leading a good life, doing the right thing at the right moment, enjoying natural movements of body or mind, focusing on true knowledge, eating and drinking well, but not voraciously. False pleasures however are based on distorted desires. In an undeniable critique of society in Thomas More's time – and in ours – Utopians consider pride in appearance, wealth or honorific titles to be examples of such distorted desires, leading to false pleasures. The Utopians will do everything in their power to eradicate distorted desires and the associated pseudo-pleasures. The Utopian society will tell you what to enjoy and what not.

The creation of happiness by a centralized government is not only a theoretical concept from More's *Utopia*, but is also a key goal of dictatorial regimes in the past and present. Eager to show its capability to produce happiness, North Korea released an international 'global happiness index'. The greatest surprise was that North Korea itself came out only second, with communist China taking the first spot, while, as could be expected, the United States scored a meager 203rd place in the ranking.

So we should be very suspicious about any political organization claiming to create happiness among its citizens. Nevertheless, a true utopian society cannot avoid the topic. A major burden of our society is depression, which can be described as a prolonged period of unhappiness or sadness. However, depression as a disease entity is much more than prolonged sadness. I will argue that the eradication of depression as a clinical disease entity is a rightful goal of any society, while sadness is a necessary part of being a human being. Further, I will develop a vision of how in the far future this ideal might be accomplished.

Sadness versus Depression

Sadness is a key emotion that is present in every human culture.[1] We react with joy to pleasurable life events, and with sadness when life hits us hard. Undoubtedly, the possibility of experiencing sadness has evolved in humans throughout evolution because it holds a clear evolutionary advantage. Sadness, even in a prolonged form, can be seen as a necessary adaptation to negative, distressing events. When we are confronted with such events, the experience of sadness will help us – force us sometimes – not to proceed as usual, but to reconsider the condition we are in and to take necessary steps to readjust our lives in order to avoid further unpleasantness. For example, if I fail (objectively or subjectively) to live up to my own expectations in my professional life, I might experience sadness, which will help me to reconsider my professional relationships, to adapt my pattern of expectations, or maybe just simply to look for another job. When someone who is dear to me dies, I will experience sadness, often for a considerable period of time. This will help me to reconsider everything that the beloved person has meant to me, and to integrate any 'unfinished business' I had with the deceased. When the mourning period is successful, it will allow me to integrate my significant relationship with the deceased into my future plans, and thereby maximize the value of our bond in my own interest.

Clearly, sadness is not just an internal emotion, but can be readily observed by others. If a friend has grieved you by his behavior, your sadness will show in your facial expression, in the tone of your voice and in your behavior in general. When observing these changes, your friend will be able to adapt his future behavior accordingly, in order to alleviate your sadness, and might avoid similar hurting actions or remarks in the future.

From these examples, it is clear that sadness, even in a prolonged form such as is often the case while mourning, is an important and constructive aspect of human experience. Even if it were possible to eradicate sadness from human experience, this would be more a part of a dystopian system, not of a utopian one. But sadness, which in its prolonged form is often labeled as 'mild depression', should not be confused with 'major depression', the more severe clinical syndrome that is all too frequent in our society.

The syndrome of major depression has been described by psychiatrists in the 'Diagnostic and Statistical Manual of Mental Disorders – 5' (DSM-5). Major depression is defined as a period of at least two weeks, in which the person suffers from a depressed mood most of the day, and/or shows a markedly diminished interest or pleasure in all, or almost all, activities. One of these two symptoms should always be present in order to conclude that someone suffers from a major depressive episode. However, this is not sufficient. DSM-5 also describes a number of other symptoms of depression, such as changes in appetite and weight, sleeping problems, changes in motor behavior, fatigue or loss of energy, feelings of worthlessness or excessive guilt, a diminished ability to think or concentrate, and recurrent thoughts of death and suicide. In total, a person should show at least five of these symptoms in order to get a diagnosis of depression. Summarizing, the conclusion is that depression as a clinical syndrome is far more than an episode of prolonged sadness. It is characterized by a number of dysfunctions, not only affecting the emotional equilibrium, but also the cognitive and bodily functions.

Why Should Depression Be Eradicated?

There are several reasons why any utopian society should aim at eradicating depression. Three important ones are the suffering of patients and their families, the cost for society as a whole, and the suicide risk.

Those who have experienced it, and those who are taking care of depressed patients, can testify how great the suffering is that is caused by the disease. The sadness experienced by these patients is qualitatively different from 'normal sadness', and described as intolerable and without any hope of future improvement. Often, the sadness is accompanied by severe anxiety and tension.

data', containing full genome DNA data and massive amounts of data on life events and personality in millions of people, depressed and non-depressed. We will know precisely which of the approximately 10 million genetic variants (so-called polymorphisms) contribute to the risk of developing a depression. Not only that, we will also be able to compound a risk score based on these individual risk variants. Based on the combination of variants and the compound risk score in the newborn, we will predict which life events and circumstances are dangerous for a given individual. For example, we will be able to analyze the infant DNA, and predict that the person has a 70% risk to develop depression when confronted with traumatic experiences, such as physical or sexual abuse at a young age. We will predict that a particular newborn, when facing long-term stress at age 35, will only have a risk of 1-3% to develop depression, but will be prone to the development of alcohol addiction. We will know that a particular newborn is susceptible to develop a myocardial infarction (a 'heart attack'), and if so, is likely to suffer from a depression subsequently. We will be able to warn the rheumatologist that a specific patient should not be treated with interferon (a specific drug), because of a 95% risk to develop a severe depression following the treatment.

All this information will be centrally stored and available to the individual, to his treating physicians, and to everyone the person wishes to share it with. It will stress the importance of avoiding specific life circumstances that are particularly dangerous for this person. Of course, this will not always be possible, for example in the case of chronic stress. When the interacting life event occurs anyway, doctors and psychologists will use brain imaging and psychophysiology (see below) to monitor the development towards depression, and when signs are alarming start preventive treatment.

Monitoring Development towards Depression Using Brain Imaging in Daily Life

Brain imaging studies in depression have demonstrated an abnormal activation of specific brain regions in depression, such as the ventromedial regions of the frontal cortex, and in subcortical areas such as the anterior cingulate and amygdala, the latter brain region being associated with a heightened sensitivity to stress. Other studies have indicated that the hippocampus, a region crucial to memory formation, the integration of emotions, and in the control of the biological stress system, is hypoactive and reduced in size in depressed patients.[7] These studies show differences in brain activation between groups of depressed patients versus group of healthy (i.e. non-depressed) individuals, but they cannot be applied on an individual basis to predict the development of depression in a given individual.

In the utopian society of 2100, this will be different. Brain imaging will allow us to measure accurately the activation of specific brain circuits both in normal circumstances and in response to stress. These highly sophisticated imaging techniques will not have to be performed in large hospital based infrastructures, but will be possible using microelectrodes that can be attached to the head and worn at home, in the workplace and at the gym. This will allow us to measure how for example the brain danger alert network responds to the traffic jam that the person is caught in while going to work, and how the heightened amygdala activation persists longer than it should, and interferes with the executive functions of the prefrontal cortex. Furthermore, the concomitant sound registration will teach us that the amygdala of the person is very much activated when he interacts with one specific colleague. Finally, we will also learn that the hippocampal function does not seem to return to its basal levels after an hour of TV watching, but that it does react favorably to specific gym exercises. All of this information will be transferred wirelessly to the treating physician, who will be alerted online in real time about depression-like signals in the patients. The individual and his doctor will know precisely which events and actions lead to specific brain circuit changes that are indicative of the possible development toward depression. He or she will learn that specific psychological techniques, for example a kind of mindfulness exercise, are helpful to switch the brain to a non-alarm mode while standing in yet another traffic jam. If necessary, the doctor will preventively prescribe antidepressant drugs.

Prevention Based on Psychophysiology

Depression is a stress-related disorder, and acute stress experiences (such as negative life events) or chronic stress (such as being trapped in a difficult professional or relational situation) very often precede the onset of the disorder. The relationship between the exposure to stress and the onset of depression is very complex, however. First, as explained higher, large interindividual differences exist in stress sensitivity, based on genetic background. Second, the dynamics of the stress response are poorly understood. It is generally assumed that to be healthy, the biological stress system needs to be able to respond quickly to acute events, and that it also needs the capacity to turn itself down again, once the acute stressor is over. Many studies have indicated that the biological stress response systems are dysfunctional in depressed patients.

One part of the stress response is the autonomous nervous system (ANS), a biological system that is activated when people are exposed to events that are threatening or stressful. Activation of the ANS can be assessed through so-called 'psychophysiological measures', such as heart rhythm, breathing rhythm, electrical conduction at the skin, and the skin temperature.

It is safe to assume that the early detection and remediation of a dysfunctional stress response will lead to the possibility to prevent the development of depression. Already today, smartwear (phones, watches, T-shirts) is available that can assess in a more or less reliable way some of these psychophysiological measures.[8] By 2100, such devices will not only allow continuous registration of all psychophysiological parameters, but also relate them to specific contexts, such as time of the day, degree of activity and food intake. These devices will furthermore contain algorithms that calculate the normal level of psychophysiological activation for a given individual at a given time of the day during a specific activity. When during some time the system detects prolonged periods of heightened psychophysiological activation that are not typical for the basal level of this person, warning signs will be sent to the individual and when desirable to the treating physician.[9] When the patient comes to see his physician, the latter will be able to consult online the pattern of psychophysiological activation, indicative of stress levels, over the last weeks, relate these patterns to life events, and judge whether a collapse into depression is nearing, and which preventive measures should be considered.

Prevention of Early Trauma and Its Neurobiological Consequences

Early trauma, a term which encompasses several negative life experiences at a young age, such as physical abuse, sexual abuse, neglect by and early separation from the parents, is a well-known risk factor, not only for depression, but for a number of psychiatric conditions. While early trauma unfortunately has always been and will in all probability remain a part of the human condition, the situation in 2100 will be very different from today, both through the prevention of early trauma and through the adequate treatment of its neurobiological consequences.

First, alertness for the devastating effects of early trauma has already increased rapidly over the last decades, and will in all probability continue to do so. By 2100, society as a whole will have assumed responsibility for the prevention of the maltreatment of children. Not only primary care workers and social workers, but also members of the extended familial and social environment of children will be alert to signals of early trauma. Sociological and psychological studies will indicate the risk factors much more clearly.

Notwithstanding these improvements, early abuse will continue to happen, albeit at lower levels. We know from recent studies that adverse early life events lead to specific changes in the neurobiology of the victims. More specifically, early trauma, both in animal studies and in an increasing number of human research, leads to so-called 'epigenetic changes'. This means that early trauma affects the function of the genetic material. Evidently, trauma does not alter the DNA code of the individual, but it can lead to the addition of specific chemical substances at crucial spots on the DNA. The best-studied process is methylation: the addition of methyl groups on top of the DNA strand. This in turn leads to a heightened or impaired expression of the genes that have been methylated. It is not so difficult to understand why evolution has created such a mechanism. When a child is confronted with something that is perceived as severe danger, the organism reprograms itself epigenetically in order to be on high alert, to be able to react more swiftly to future threats. While these changes are adaptive in an evolutionary context, they are thought to lead to changes in stress response systems that predispose the individuals to depression and other stress-related psychiatric disorders.

In 2100, we will be able to remedy these neurobiological changes induced by trauma. We will measure the epigenetic changes brought about in specific brain regions such as the hippocampus by the traumatic experiences. Subsequently, physicians will administer demethylating agents that will reverse the methylation changes in these brain regions at the exact locations. By doing so, the neurobiological consequences and the associated increase of the risk for depression will be neutralized.

Prevention of Depression by Social Means

In a utopian society, we will not only combat depression by eliminating risk factors, but also by reinforcing protective mechanisms. A very important protective factor against depression is social support. In the general population, both emotional and practical support can reduce the incidence of depression very significantly.[10] Especially – but certainly not only – in the elderly, loneliness is a powerful predictor of depression. In 2100, the attitude towards the elderly will be completely different from today, and today's practices of putting elderly people together in specialized care units away from other age groups will be considered inappropriate and will be abandoned entirely. Elderly people will continue to live in their trusted environments, with nursing care provided at their homes in function of necessity. Further, elderly people will be assigned specific tasks in the community according to their specific capacities, e.g. in child care and in the knowledge transfer to younger people. This will improve the social integration of the elderly, reducing feelings of loneliness and uselessness, and thereby preventing the development of old age depression.

(Preventive) Treatment of Depression

Through the application of all the measures and monitoring systems described above, the prevalence of depression will be greatly reduced. However, not all cases can be prevented. In our utopian society of 2100, the treatment of depression will be much more efficient than today. These effective treatments will be used primarily to prevent the onset of depression when the neurobiological signals are alarming.

Today, the same kind of antidepressant medication is administered to all patients in a 'trial and error' way. Farmacogenetics, i.e. the prediction of the response to and tolerability of a specific drug in a given individual based on the genetic background, is being studied in depression, but the data are too scarce and too inconsistent to allow any reliable application in clinical practice. In 2100, personalized medicine based on genetic data will allow us to predict which patient will respond better to which drug.

Today patients have to wait for weeks to find out whether a specific drug is effective, but in 2100, advanced neuroimaging techniques and psychophysiological assessments will be used to assess quickly whether the drug affects the relevant stress-related brain circuits within a few days after the first administration.

Also psychotherapy will continue to play an important role. The unfortunate competition between psychotherapeutic schools, which was so characteristic of the 20th and the first part of the 21st century, will be completely abandoned by 2100. Effective elements from different schools will be integrated in one therapeutic approach. In this approach, the focus is not on specific technicalities, but on the nonspecific elements that have been shown to be responsible for the largest part of the effectivity of the older therapies, elements such as the therapeutic alliance between patient and therapist, empathy, shared expectations and adaptation to specific cultural elements.[11]

Case Report: Michael

Let us take a look at Michael, who was born on 1 January 2101. The full genome DNA code of Michael was determined when he was still a fetus. The analysis yielded a number of average risk calculations for a number of highly prevalent disorders. Regarding psychiatric disorders however, Michael's genome

Recovery without Cure

Chantal Van Audenhove, Health Care Research

In most European countries, the population pyramid is characterized by a growing number in the older age groups. As regards the number of people over 80 in Belgium, for example, it is expected that this number will have doubled by 2060 (from 5% today to 11% in 2060). This growing number of older people coincides with an increasing number of people with chronic diseases impacting or even hampering their functioning and participation in society.

For many of the diseases in older age groups a real cure, resulting in a perfect health situation, will not be possible anymore. Even if the symptoms can be cured temporarily, in most chronic conditions the vulnerability and the risk of a relapse remain, resulting from oncological, vascular or mental health problems. For this reason the health care of the future will be more focused on the quality of life instead of on a definitive cure.

These demographic evolutions are the context for the rise of new views on health. The traditional WHO definition from 1948, in which health was considered a "state of complete physical, mental and social wellbeing and not only the absence of disease or infirmity", no longer corresponds with the current ideas. Indeed, at that time most of the diseases were infectious diseases that could increasingly be cured because of the scientific evolutions in medical sciences. Today the chronic and non-communicable diseases are more prominent in our populations.

In 2011, Huber and colleagues[1] introduced a new and more finely-tuned concept of health: "Health as the ability to adapt and to self-manage, in the face of social, physical and emotional challenges." In this new concept of health the focus is on the person and not the disease. Even if someone has a disease, there will still remain many aspects of strength or healthy functioning in their lives. And these healthy aspects can still be strengthened by the person himself or by the health professionals. Most persons with a chronic disease will feel better when addressed from the perspective of their strengths instead of their vulnerabilities or weaknesses. This definition of positive health contains six dimensions: bodily functions, mental functions and perception, the spiritual/

existential dimension, quality of life, social and societal participation, and daily functioning, with 32 underlying aspects in total.

Further, in the field of mental health a new view on recovery has been developed by the user movement and has been received with growing enthusiasm. Anthony[2] defined recovery as "a deeply personal, unique process of changing one's attitudes, values, feelings, goals, skills, and/or roles. It is a way of living a satisfying, hopeful, and contributing life even with limitations caused by illness. Recovery involves the development of new meaning and purpose in one's life as one grows beyond the catastrophic effects of mental illness." The recovery concept is currently the basis for a worldwide movement that offers a lot of inspiration for a new and better adapted approach in mental health and mental health care.

In a utopian view the concept of recovery is not limited to mental health care but – in line with the new vision on positive health – it can also lead towards useful and inspiring new practices in the care for the elderly and for persons with disabilities. In this utopian view, I borrow the concept of recovery from the mental illness literature and explain how it can be successfully applied in the broader range of diverse chronic diseases that will increasingly characterize our society in the near future.

Indeed in 2100 the new views on health and health care will have been integrated in the whole care system as well as in society. Recovery and recovery oriented care will be generally accepted as the basic approach to living with a chronic disease that cannot be cured. By that time, the recovery and health paradigms will have replaced the cure paradigm. Despite a chronic illness, people can still regain control over their lives and improve their quality of life. Participation and social inclusion are considered important for the wellbeing of persons with any kind of disability. Focusing on competencies and strengths generally leads to more quality of life than a focus on disability and deficits. However, when cure is possible, it will of course have its place in the care vision. And last but not least, the recovery paradigm offers a strong antidote to burnout and negative emotions of professional and family caregivers. Indeed, it opens the door to optimism, hope and wellbeing without denying the grief and sadness that accompany important losses in life.

In a utopian vision the concepts of recovery and recovery oriented care have important implications for an inclusive society in 2100. This chapter will explore the meaning of recovery and recovery oriented care as a new paradigm that can form a valuable addition to the traditional medical model. I will first define the concepts of recovery and recovery oriented care. Then I will present my vision of how this new paradigm will contribute to a better quality of life and more social inclusion in our society in 2100.

Personal Recovery Is Not the Same as Clinical Recovery

The concept of recovery has different meanings.[3] The concept of 'clinical recovery' has its origin in the professionals' perspectives and focuses on quantifiable positive changes on validated scales. Recovery is thus completed after a restoration of functioning or a decrease of the symptoms. This clinical view of recovery implies that rates of recovery can be distinguished and people can be compared on an underlying scale. In contrast, 'personal recovery' has emerged from the users' perspectives and refers to the process of regaining hope, rebuilding a positive identity and gaining control. This second conceptualization of recovery was brought forward by 'users, ex-users and survivors' of psychiatry in the USA who felt that the 'clinical' recovery missed vital facets of what they felt as important. With the second concept of personal recovery, recovery now also refers to giving a new meaning to life and developing goals even though the illness may continue to involve setbacks or barriers. Consequently, recovery is not the same as being symptom-free, but entails quality of life.[4] Note that recovery not only comprises medical and personal recovery, but also for a large part social (e.g. social network, housing, work, study, and hobbies) recovery.

Overall, there is a shift from the traditional clinical paradigm to personal recovery.[5] As such, personal experiences of (ex-) service users form the basis for studies of how recovery develops. These experiences (i.e. recovery stories) have led to some important insights.[6] A first finding is that recovery does not focus on the causes of the illness or the dysfunctions, symptoms and complaints, but emphasizes resilience and positive aspects of the illness. Second, recovery is possible without professional interventions. Third, it is sometimes more difficult to recover from the consequences of the illness (friends lost, financial problems, stigma, etc.) than from the illness itself. Fourth, during recovery, it is important to be surrounded by people who believe that recovery is possible. Five, recovery is not experienced as a linear process, but has ups and downs. Six, one does not have to be symptom-free before engaging in recovery. Seven, recovery has an effect on the frequency and duration of symptoms. Eight, recovering from an illness does not imply that the person was not ill before.

There is some widespread resistance to the concept of recovery, expressed in many reactions by professionals who may feel threatened by something new.[7] Very often the resistance concerns a lack of understanding of the real concept of personal recovery. But we can see a positive evolution, inspired by psychiatrists who function as new role models.[8] Less easy to overcome is the general fear of clinicians in in-patient services that a recovery orientation will mean closing down their services. Today recovery oriented services already exist and do not need to be closed down. Yet, services using a traditional cure model should be transformed towards recovery oriented practices. This means that in 2100 the focus will be on supporting people with chronic health problems to feel in control of their life, to develop a positive identity and hope. A good quality of life, even with disabilities and vulnerabilities, is different for every person and can therefore not be defined along the same criteria for everyone.

Stages of Recovery in the Field of Mental Health

Different researchers have analyzed the personal recovery experiences of people with a mental illness. Although recovery is unique to each individual, some overall phases can be distinguished. Andresen and colleagues[9] describe five phases: moratorium, awareness, preparation, rebuilding, and growth. In the moratorium phase people often are in a phase of denial, feelings of hopelessness and confusion dominate. People may experience a profound loss of purpose in life and despair, which is very difficult to overcome.[10] Sometimes self-protective withdrawal can be seen. These experiences can be exacerbated by a lack of (adapted) information or support by professionals and significant others. After a phase of denial and confusion about one's identity, people may become aware that recovery is possible. In this awareness phase, hope increases and people start to feel personally responsible for their recovery and purpose in life. Professionals and especially people with lived experience are important coaches and role models. Having become aware that other roles than the one of patient are possible, the person sets new goals and takes stock of resources and important values. The so-called preparation phase provides the foundation on which a meaningful life can be reconstructed. During the rebuilding phase, the rebuilding of a meaningful life and a positive identity take place. The person actively pursues goals and takes back responsibility and control. Setbacks are normal and overcoming them will improve coping skills needed in daily life. The last phase, the growth phase, is a culmination of the steps taken earlier. Although he or she never stops growing, the person holds a positive identity and views the future in a positive way. There is a feeling of self-actualization and hope though setbacks may occur. These setbacks are handled with more efficiency and self-confidence.

These insights shed a new light on what is important for persons with a vulnerability in their mental health, and by extension perhaps also for persons with a chronic disease in general. I will further elaborate these ideas by focusing first on the key elements of the recovery process as experienced by people with a mental health problem themselves.

Key Elements in Recovery from Narratives of Persons with Mental Health Problems

A further general acceptance of the view on recovery as the dominant one will in my utopian vision have been realized in 2100. This will also involve trying to implement the key elements that contribute to the process of recovery in the experience of the persons with a vulnerability. Our recent research project in Belgium shows that five key processes that are identified in research are recognized by persons with mental health problems and may also be helpful for their family caregivers and for persons with chronic diseases.

Studies of patients' narratives show that the five key elements of recovery that are relevant to clinical research and practice are 1) connectedness, 2) hope and optimism about the future, 3) identity, 4) meaning in life and 5) empowerment (acronym CHIME).[11]

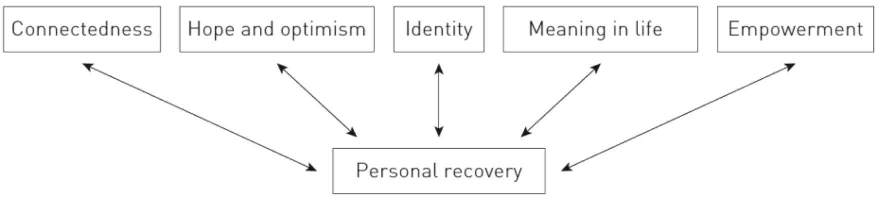

Figure 1 Personal recovery

Concerning the element of connectedness, it is vital that people can count on important others who are understanding, patient and who foster hope in recovery. Recovery is stimulated if people with vulnerabilities can connect with others outside the part of life that is strongly associated with the illness. This is possible by utilizing accommodations offered by the municipality (e.g. sport clubs), informal support and natural social networks. For many, education and employment are useful pathways to become part of the community. As important as connectedness is trying to dissociate oneself from the limited expectations that others hold. It is important not to give up hope and to remain optimistic and confident that many things are still possible. Furthermore, it is important that people redefine or rebuild a positive sense of identity in which the illness is given its proper place. Moreover, it is important to cope with (self-) stigma. The elements of empowerment and self-management refer to the feeling of being in control, of personal responsibility and a focus on strengths. Finally, the recovery process is partly a spiritual journey in which a meaning in life can be rediscovered. Moreover, spirituality is increasingly identified as an important way to increase connectedness and hope.[12]

and task in society, it structures the time and offers learning possibilities and contact opportunities, a sense of belonging. And of course, last but not least, it leads to an income. For people with disabilities, in our utopian world, a job coach or case manager will search and find jobs that match their interests and possibilities. He will build a relationship with employers and believe in the possibilities of the person with the chronic disease (also in difficult circumstances). He is convinced that everyone who wants to work can work if a proper work environment can be found and if the person is supported and coached in the right way.

4. Professionals will have new competences. Recovery oriented care is focused on full citizenship. Recovery happens at home, not in the office of the therapist or in the hospital. This means that professionals will support social inclusion and connectedness. Future professionals will behave like coaches rather than advisors. They will learn from their own experience how to support persons with a vulnerability or a chronic disease in finding a good environment to live in. They will be creative, optimistic and trust in their own insight. And they will persevere in their search for solutions even if the results are sometimes disappointing. They will remain hopeful and keep their enthusiasm, hope and trust. This does not mean that they will try to cure the person. They will accept the inevitability of chronic diseases and deterioration, but they will try to keep hope, trust, and connectedness alive, so that even in the worst scenario the person obtains an optimal quality of life. This means that the focus is on the process, not on the outcome.

   In my utopian vision, professionals will not give uninvited advice. Instead they will help the person with a disability to clarify his own preferences and to make choices to reach his own goals in his own environment, to obtain a good quality of life for as long as possible.

5. Experts by experience and users will be involved in care organizations, in education and research. Evidence-based knowledge will not be the only source of wisdom in 2100. In a utopian world the professionals are not the only ones who have knowledge and expertise. Different types of knowledge have their place in the care for persons with chronic diseases and disabilities. Indeed: the persons themselves have a lot of knowledge that is not available to the professionals. To implement recovery oriented care, organizations have made the service user perspective the dominant model in the organization. They look at the problems and options through the eyes of the patients and focus on normalization and inclusion. This means that together they look at options that can help the person to find better employment or education, adapted to their strengths and vulnerabilities. The self-management of each

person is stimulated so that the impact of chronic illness on the quality of life is reduced as much as possible.

Many professionals are also experts by experience, which is a valuable characteristic. However, in 2100 peer support will also be considered as a very important ingredient of good teamwork. Peers understand better than some professionals what is going on in the experience of the person with a chronic disease or vulnerability. At the same time, their help is highly valued by many patients, just because of the simple fact of being a peer. And in 2100 peers will generally be involved as paid staff in care just because of their expertise as a chronic patient or a person with a vulnerability. In addition, they have a very complementary input in education programs and in research. In the qualification of education and research programs the involvement of the target groups of patients or referents from the target group will therefore be an important evaluation criterion, like today we already know the importance of valorization in research evaluation.

6. The services will be transformed. To stimulate recovery, most health care organizations will have transformed in 2100. First of all the vision and mission statements of the health care organizations will all have the recovery orientation as their leading principles. The focus on the strengths of each individual person, even in situations in which cure is not realistic. This has strong implications in the organizations.

   The human resources management will focus on the selection of staff that not only endorses these basic principles, but recovery will be their own basic vision on life. The five determining principles will have a significant meaning in their own personal lives. Giving care in a way that supports positive health in all its interpretations is their life goal, for which they always go the extra mile. Diplomas are only one aspect in defining the competences of staff. Expertise with processes of recovery in their own life are as important, as well as interpersonal sensitivity and empathy.

7. Caring will be approached as a team sport. By sharing ideas and concerns, inspiration for solutions, but also grief and disappointment, the teams become strong partners for their target groups. A strong team evaluates itself through a regular mapping of its implementation of recovery oriented care. In 2100 a monitoring system for each team will be present to evaluate the degree to which its interventions remain focused on the personal recovery of the persons it is working with. Today the Recovery Oriented Practices Index (ROPI) is a valuable instrument that offers an overall view of the functioning of a service with respect to the attitudes and practices that support recovery. Through an extensive audit it offers insight in for example the degree of fulfilment of basic care needs or of the participation of patients in the

development of the treatment plan. In the current Belgian mental health reform movement, the ROPI has been used as an indicator for recovery oriented practice. It revealed that there is still a lot of room for improvement in long-stay wards as well as in the mobile teams for patients with chronic mental illness. In a utopian system this kind of monitoring will be daily practice. Like the activity trackers that today are becoming popular and helping people to move and sleep in a healthy way, in the future such interventions in work environments will also become well-established.

8. Corporate governance and political leadership will support the new developments. To guarantee a good recovery oriented practice, suitable corporate governance will be necessary. This governance will differ from the type we know today in the fact that no board can exist without the strong participation of the users or referents of users. And with strong participation we also mean full involvement and a strong voice in the decision making. Particularly the surveillance of the realization of the mission in the daily practice and the selection of staff will be important issues to guarantee good results.

   But corporate governance alone will not suffice to succeed in the realization of this dream. A complete change in our policy system will be necessary. First of all the big gap between the biomedical care and social welfare will have disappeared in 2100. Care will then finally be defined as bio-psycho-social care. And the definition of positive health will be prevalent in policy: all sectors will therefore be focused on obtaining that goal for all citizens. This will mean a paradigm shift from deficits towards strengths. And the determinants of these processes of strength and recovery will be the main focus of our education system. Nobody will 'fail' at school. Everybody will discover his competencies, values and strengths and will be appreciated for them. What we cannot realize as an individual, we will realize as a team. Team spirit will be a major learning aim from the early years on. And so we will have entered a new society in which everybody can participate, enjoy life and be valued.

To Conclude

A paradigm shift will be realized in our society. Since we all grow older and are now living longer than before, living with a disability or a disease is not a sign of weakness, but a strength. It is a sign of the prosperity of our society and our era. When everybody shares this vision, good examples like Marc Herremans[17] will be remembered as pioneers of what will have become self-evident in 2100.

Marc (°1973) grew up loving sports, especially boxing, joined the Para Commando elite forces of the Belgian military at 18 and became a volunteer firefighter. Then he discovered triathlon, and trained to become Belgian champion and compete internationally at top level. At 27 he reached the 6th place in the Hawaiian Ironman championship. The following year, 2002, was going to be his year to become world champion. But when training on Lanzarote he fell during a descent, resulting in paralysis from the chest down – he would be in a wheelchair for the rest of his life. Life seemed to have lost its purpose. Then his nephew visited him in hospital and told him how glad he was that his uncle was back. This made Marc realize how lucky he was to be alive, that he had been given a second chance. He then looked at the bucket list that he had drawn up before his accident – winning the Ironman, riding the Crocodile Trophy, and becoming a father – and decided to fulfil it anyway, with the help of his friends and family. Marc started training harder than ever before. He founded the 'To Walk Again Foundation' charity and received a knighthood and prizes for his dedication. Despite his paralysis he became the 2006 world champion Ironman. A year later he was the first wheelchair athlete ever to start the Crocodile Trophy, a 870 mile long mountain-bike competition in the outback of Australia, which he finished. Since 2008 Marc has been coaching athletes. In 2013 his daughter was born. Marc is now in great demand internationally as a motivational speaker, he is the team-leader of a professional cyclo-cross racing team, and CEO of a coaching center. With the help and support of friends and family he made the impossible possible. Marc saw every setback as an opportunity to find new ways to achieve his goals. He is convinced that life itself is the most precious gift, and that we should never give up on our dreams and goals.

Notes

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12 Young, D., art. cit.
13 Huber, M., et. al., art. cit.
14 Kitwood, T., *Dementia reconsidered: the person comes first*, Buckingham: Open University Press, 1997.
15 See also Jan De Lepeleire, 'Person-Centered Health Care without Fragmentation', in this book (p. 144).
16 See also Ann Heylighen, 'Building upon Disability Experience', in this book (p. 237).
17 http://marcherremans.com/about-marc-herremans/biography/

defined as the compartmentation in different parts of a process, in this case the health care process. There are several distinct types of fragmentation at macro-, meso-, micro- and nano-levels. I will discuss seven elements, without attempting to be comprehensive.

First, in many countries with a developed health care system, there is a dichotomy between the medical and welfare sector. Although they are similarly concerned with the care of citizens, there is often a wide gap between these two sectors at the workplace. Often there is a different culture, a different vocabulary and word use, a different approach, and different economic frameworks, e.g. regarding organization, reward systems and financial mechanisms. The amount of government involvement and the organizational models are often very different. In a way this is strange, for presumably during a person's life there is a very strong influence of social, psychological and existential elements and issues on (patho)physiological processes in the body and on the emergence, cure and care of diseases and illnesses.

A second type of fragmentation is the one between primary and secondary care. Primary care is "the provision of universally accessible, person-centered, comprehensive health and community services provided by a team of professionals accountable for addressing a large majority of personal health needs. These services are delivered in a sustained partnership with patients and informal caregivers, in the context of family and community, and play a central role in the overall coordination and continuity of people's care."[8] Secondary care, regardless of how it is organized, we broadly understand as being the hospital sector and the services closely related therein. Many daily problems are solved in primary care. A European study of referral patterns showed that only 10% of patients in general practice were referred to secondary, more specialized treatment. This figure is independent of the medical problem concerned and the way health care is organized. Nevertheless, hospitalocentrism, the tendency to think of medical care as provided almost uniquely through hospitals, remains the main framework of thinking in many Western European countries. But the hospital itself and patient transfer from primary care to the hospital can both be important factors contributing to fragmentation.

An important trend is fragmentation based on pathology, also called 'vertical care programming'. Obviously a focus on the disease to be treated and its cause keeps the treatment more manageable. Evidently, we can offer highly advanced and specialized care, and by using robust outcome measures, we can create good monitoring and evaluation processes. This is at odds, however, with the horizontal approach that starts from the integrated needs of citizens, patients and populations. It has been shown that this vertical approach is very expensive, does not achieve the desired results, and excludes large groups of citizens from adequate care. Let us for example consider mental health care. This field is characterized by an evolution towards hospital wards that specialize in a particular pathology, such as psychosis, depression or addiction. But obviously some people have a combination of several problems, which leads to the creation of new wards for 'double diagnosis' and to patients being refused since they do not meet the criteria for admission. As another example, in Africa vertical organizations are being developed, for example for AIDS assistance, leading to individuals with AIDS receiving high-performance care that is unfortunately unavailable to family members or neighbors without AIDS.

Fragmentation also occurs within a particular organization. It is convincingly documented that even in hospitals with strong management, multiple subsettings with their own dynamics and culture exist.[9] In hospitals, the time is long past when, by day or by night, nuns were available. They are now replaced by paid professionals who want to combine work with their private life. In primary care, even within well-organized group practices, the risk of fragmentation through the profiling of new expertise and care professions increases. This fragmentation is caused by social trends and developments. While many more part-time jobs have been created, the result has led to increased fragmentation.

Additionally, fragmentation also occurs within a single discipline. Take for example a family doctor treating a 55-year-old lady who was hit by a car and cared for in a university hospital. The GP received three different reports: one from the orthopedic surgeon specialized in shoulder injuries, one from the orthopedic surgeon specialized in hip injuries, and one from the orthopedic surgeon specialized in knee injuries. Highly skilled doctors, each specialized in one part of the human body: one joint. In terms of excellence, this lady's care was peerless. But one doesn't need to be an expert to understand that this approach to care entails huge risks. As part of her ongoing treatment the lady received three different anti-inflammatory drugs, independently prescribed, the combination of which drastically increased the risk of her developing side effects such as gastro-intestinal bleeding.

Mental health issues are ever-present within the general population, creating a high 'burden of disease' that is costly and causes significant negative effects to the overall functioning of affected persons. Yet, in many countries, mental health is organized as a separate cluster. For this reason, the World Health Organization has made this problem a top priority and in various documents, projects and policies has attempted to find solutions for this kind of fragmentation.[10]

It is not yet clear what the impact of technological developments will be, but some elements can already be distinguished. Increasingly miniaturized microtechnologies, apps and digital devices are readily accessible to the layman.[11]

New forms of (self)monitoring and surveillance, and new sources of big data are developing. Using powerful software, giant computers and sophisticated data analysis, new capabilities for risk analysis have been created, but not without extensive economic, philosophical and ethical consequences. Insurance companies, for example, see an opportunity to use data for in-depth risk analysis from monitors that we voluntarily wear during exercise, sports and leisure activities. Thus medical decision-making is gradually being supplanted by artificial intelligence.[12]

What Are the Consequences?

The first concrete result of fragmentation is the increasing need for more communication channels to ensure that every person has the information needed to perform a task properly. Stille and colleagues[13] developed a formula, $(n^2-n)/2$, where n is the number of providers involved, in order to determine the number of communication channels depending on the number of people and professionals involved. If five team members are involved, ten different channels of communication are needed, on the basis that everyone needs to know everything, creating of course a high risk of error.

At each transition, handover or transfer, human errors can occur. A 'transfer' (i.e., a handover of the patient) is defined as the transfer of professional responsibility and accountability for some or all aspects of care for a patient, or groups of patients, to another person or professional group on a temporary or permanent basis aiming at informational, relational and management continuity in patient care.[14] This element receives little attention in management and research. It was calculated that on average in a teaching hospital 1.6 million transfers are taking place per year. A very large proportion of hospital admissions for the elderly are related to medication errors regarding the transition between home and hospital or vice versa.

As a third consequence, the cost to the organization is dramatically high, without a corresponding increase in the efficiency and quality of health care. A very important side effect of this fragmentation at different levels is that citizens seeking support for their health and social needs, lose their way in the jungle of care. Fragmentation leads to the loss of the accessibility and personal contact that provided trust (confidence) and safety. The Western European citizen has already lost a lot of frames, concepts and footholds in a secularized world. Now he is required to find his own way in the world of health care and make his own choices autonomously, with all the risks involved, at potentially difficult and pivotal moments in his life.

It is clear that this evolution is caused by a lot of concomitant and mutually reinforcing phenomena and trends. The development of science, knowledge and technology, with more and more opportunities, are obvious elements in this process. Societal factors also play a role. The way people think of and deal with their health, and their expectations of the government both in terms of organization and financing of care (the challenge of revolutionizing health care reform under President Obama is an obvious example) are other elements. People's expectations concerning an ideal health status is partly shaped and framed by scientists and experts and promoted by the press and social media. This creates a world in which state-of-the-art health care should be readily available for everyone.

An element that should not be underestimated is the increase in specialization. Increasingly, newly gained knowledge can only be understood by super-specialized professionals. But fragmentation can lead to almost absurd situations, as with the example of the lady described earlier in this chapter. Combined with the risks caused by successive 'handovers', we create a paradox that, due to the increased potential of expertise and technology designed to create a higher level of health care, the very real risks to the citizens are that performance and quality falls.

What Are the Possible Solutions?

There are many strategies aimed at tackling the problems of fragmentation. Without being exhaustive, I will discuss a number of them to clarify the essential elements.

When many different care providers are involved in looking after the same person, this creates the need for coordination and consultation. In Belgium, a lot of opportunities exist for consultation among care providers, increasingly backed up by financial and organizational incentives. However, there is a lack of good research that underpins the added value of such consultations. In the case of multidisciplinary oncological consultation, research has explored some of the main problems, such as the combination of technical approaches, mainly for structural-organizational reasons, with very limited input from the family doctor.[15] The conclusion was that now that the foundations of this practice of consultation among care providers have been laid, the time has come to focus on the 'quality' aspect of it, and to shift the paradigm from a very technical disease-centered approach to one that is more patient-centered. Research on complex home care situations has also revealed that for consultation as it has been organized so far, the added value could not be substantiated.

In 1967, with the stated aim of improving person-centered care, The American Academy of Pediatrics (AAP) introduced the 'medical home' concept, with operational characteristics including: accessible, continuous, comprehensive, family-centered, coordinated, compassionate, and culturally effective care. The Patient Centered Medical Home (PCMH) is an approach to providing comprehensive primary care. There has been much research on this concept, with positive results as well as critical voices. Research in five European countries has showed that – irrespective of how the doctor's payment or flat-rate reimbursement is organized – the organization of general practices, especially group practices, closely mirrors the Medical Home concept. According to these findings, Flanders is particularly strong in the area of the personal relationship with the patient, leading to feelings of trust and security, but less so in the area of structural organization.

The European Pathway Association, a movement that wants to stimulate the development of clinical pathways, started in Flanders and the Netherlands. It defines a care pathway as a complex intervention for the mutual decision making and organization of care processes for a well-defined group of patients during a well-defined period. Defining characteristics of care pathways include: an explicit statement of the goals and key elements of care based on evidence, best practice, and patients' expectations and their characteristics; the facilitation of the communication among team members and with patients and families; the coordination of the care process by coordinating the roles and sequencing the activities of the multidisciplinary care team, patients and their relatives; the documentation, monitoring, and evaluation of variances and outcomes; and the identification of the appropriate resources. "The aim of a care pathway is to enhance the quality of care across the continuum by improving risk-adjusted patient outcomes, promoting patient safety, increasing patient satisfaction, and optimizing the use of resources."[16] These clinical pathways were initially developed for well-defined problems within the hospital, but gradually they have led to the development of integrated interdisciplinary care pathways, including actors from primary care, especially for prevalent oncological problems. The first experiences and research of pathways for prostate and breast cancer and rheumatoid arthritis show that there is still a long way to go. Developing pathways for team members who have never jointly been present around the bedside of the patient can be very complex. Moreover, developing such pathways requires many agreements on substantive as well as logistical and organizational elements. Pathways also assume cooperation and coordination will exist at all levels.

The coordination of care is "the deliberate organization of patient care activities between two or more participants (including the patient) involved in cancer patients, antibiotic therapy, rehabilitation, dialysis, etc.). Also crucial is the coordination of the software and other information technology that is being used. Discussions in preparation for a new Health Conference in 2017 indicate that this suggestion currently still remains very utopian.

- The integration of health care and social welfare.

Once this has been achieved, in a utopian world, we can start dreaming of professional, person-centered care, fostered and stimulated by its functioning in an integrated way with other professionals, whether medical, paramedical or social.

To achieve this utopia, many conditions need to be met. In the future, the majority of people worldwide will be living in cities. How these cities are managed, how participation is organized and how the limited space is allocated, have substantial consequences for qualitative health care.[20] Obviously the importance of developments in genetics,[21] artificial intelligence[22] and human enhancement should not be underestimated either.

Epilogue

What I have not done in this contribution is to analyze the situation as it currently stands in Belgium. One could write and reflect in great detail about this, but the (political) complexity is such that the core of the discourse would be lost. What I have advocated is, in my opinion, applicable to many Western European countries and societies. Using these mechanisms in the interactions between organizations and within one's own organization, will further strengthen relational coordination, leading to better quality and greater efficiency of care.

Notes

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3 *Ibid.*, p. 70.

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2 Utopian Society

The Governance of the Future

Elsewhere people are always talking about the commonwealth, but they are really concerned about their private interests; here, where nothing is private, public issues are taken seriously. (118)

I could remember that we called it, back in 2016, the 'Internet of Things' or 'IoT' or even the 'Internet of Everything'. Even our clothing industry started to produce so-called wearable devices with smart clothing and body sensors. While in 2013 we had only 140K units of them, the estimation was that there would be about 10.2 million of these units of smart clothing by 2020.[3] Professor Leete said: "Now sensors are just part of our bodies and our clothing, I would feel very odd and disconnected without them." I replied: "I remember when only minor criminals were obliged to wear an ankle monitor, allowing them to stay out of prison during their punishment." Professor Leete smiled: "Well, as you see, we all wear them now, even those who are not punished. We have no prisons anymore, since we combine what you used to call restorative justice with monitoring systems. This is all governed by our Justice Cloud."

Cloudy, Cloudier, Cloudiest

Clouds started to become very powerful back in 2016. I remember that in 2013, 7% of all data was estimated to be stored in clouds. This number went up to 36% in 2016, with data being divided among three major storage providers. That made us very vulnerable. Someone called it 'Government by Google'. We were wrestling with clouds and their governance. We were wrestling with labels too: 'big', 'open', and even 'revolutionary' data. Microsoft was very proactive: 90% of its R&D budget went to the improvement of cloud technology and security issues. But government, especially the US Government, was very proactive too. It pushed for further cloud development and also its control. The US Federal Government estimated that it could yearly save USD 5.5 billion by shifting to cloud services.

Initially, clouds made it possible to analyze large quantities of data to produce specific insights and intelligence. But this shifted radically into autonomous, adaptive and complex systems with their own governance, with special actors and communities.

Suddenly, I noticed small things flying all around me, which looked like large insects, but that was not what they were. I asked Professor Leete. He said: "Oh, these are our personal sensors, they are interfaces between people and clouds." "Oh yes," I said, "I remember back in 2016, Paulo Lozano[4] and his team were experimenting with something like this at MIT's Space Propulsion Laboratory, where they came up with an ion Electrospray Propulsion System (iEPS), which had a charged metal grid on the thrust side of the unit, powered by a battery. But these look much more advanced and much smaller, almost invisible." "Indeed," Professor Leete said, "they are driven by solar as well as wind energy, and they solve so many problems, like avoiding famines by detecting shortages and guiding people to food or water reserves, and improving health in the fragile parts of our world by directing people to safe areas and isolating epidemic areas; these nanosatellites were in fact made so that we could realize all your Sustainable Development Goals, you remember, which you agreed upon more than one hundred years ago in September 2015 at your ECOSOC Council of the UN."

"So, you are governed, or from now on I should say we are governed, by clouds that serve the internet of things?" I could remember that in 2015 we had an estimated 4.9 billion connected things and it was predicted that we would exceed 50 billion interconnected things by 2020. We also thought that about a quarter of a billion vehicles would be connected through the internet, which would give us completely new possibilities for services and driving conditions. In 2015 Google had even self-driven cars that made about 10 000 miles per week.

We had a TEDx conference in Brussels in March 2016,[5] in which some of our frontline experiments were presented. It included smart cities based on such networks. In Porto, Portugal, a Smart City infrastructure was designed by the vehicular network, called CityNet. It not only provided internet access to bus passengers from September 2014 on, but it included a sensing infrastructure, called UrbanSense, which provided low-cost and large range communication support all over the city. One of the key figures was Susana Sargento[6] from the University of Aveiro and the Institute of Telecommunications. In March 2012, she co-founded a vehicular networking company, Veniam, as a spin-off of the Universities of Aveiro and Porto, and the Instituto de Telecomunicações. They started building a seamless low-cost vehicle-based internet infrastructure. At that time, there were about 600 cars in Porto that were connected in the cloud, using a network of wi-fi hotspots where people could log on to the network with their mobile phones. As a result, the cloud was full of valuable collected information on traffic and car movements.

Professor Leete replied: "That was indeed very experimental. As you see, in our cities we now have no traffic lights, nor road signs, nor speed cameras anymore, since all vehicles know when another vehicle is approaching and their speed is regulated accordingly. We have no accidents caused by human (mis)behavior anymore. This has had a significant impact on the public sector since we no longer need traffic police."

"What about garbage collection, another typical job for cities and their governments?" I asked. "Garbage collection in the past, as I remember from history, meant that trucks drove at specific days along well-defined trajectories. Now we have sensor driven garbage cans and containers that signal when they are full. Then an electric vehicle automatically comes and picks up the garbage."

It was clear that all of this had had an immense impact on the organization of the public sector, the private and the not-for-profit sector. I remember that a large company called CISCO had estimated in 2016 that the internet of things impacted the US public sector by reducing crime by 7% through smart lighting, that there would be a 30% reduction in waste collection costs through the usage of sensors, and that there would be a USD 950 saving per court appearance due to the use of video technology.

Professor Leete: "It is interesting that you compare everything in terms of money. For us, the key criterion is quality of life for everybody, it is about having efficient and effective services delivered to everybody. You could not solve the so-called Baumol disease, i.e. the impossibility of the public sector to increase the efficiency of its services. I know from my colleagues in social sciences that you have studied these issues. I once heard a lecture on this at our history department. Around 2010 KU Leuven Professor Christopher Pollitt studied the importance of place and time for the proper functioning of the public sector. Key questions at that time were about how 'place' determined the functioning of the public sector in its provision of services. Technology enhanced mobile government and the scales of delivery, and even resulted in country's capitals moving out of big cities.[7] Professor Christopher Hood from Oxford studied the failure of the UK government to work better and cost less in his famous evaluation of three decades of reform in the UK around 2000. But we solved the Baumol disease."

Professor Leete invited me to join the opening procession of professors to the university's 700th anniversary celebration ceremony. As I was still too weak to walk, a body device had already sent a request to the Transportation Cloud to provide me with a suitable vehicle. This vehicle has no driving facilities. It is fully equipped to automatically move tangible goods (including people) from A to B, based on numerous sensors connected with the Transportation Cloud. These vehicles are also based on the old concept of the Internet of Things/Everything. One pays per trajectory to the institution that manages that Transportation Cloud. Obviously shared transportation is cheaper. People as well as cargo can use this system. The linked transportation apps are very well developed and can directly address almost all needs.

In order to prepare myself for the subject matter of the 700th anniversary ceremony, I asked: "What about education? How does the Education Cloud function?" Professor Leete: "First of all, we have solved the issue of language. The Education Cloud is connected to the Babel Cloud, which translates all languages into all other languages. You speak your own language and you instantly hear the translated version. This facilitates communication across the world, including teaching, which is now not only reserved to the younger population. We all receive frequent updates to make sure we stay in tune with the system, depending on the clouds we are connected to. I am aware that since Da Vinci there was a divergence in the mechanisms to produce knowledge, that art and science were split apart, and that within science there was a move to specialization. Now, we have kept some specialization, but we have benefited from a strong convergence of art and science since technology became a shared opportunity. This was crucial for us to stimulate innovation and creativity to solve our complex, even wicked, problems. We still very actively use the KU Leuven LUCA School of A.R.T.S.S., which still stands for Arts, Research, Technology, Science and Society. To create this School of A.R.T.S.S. was a smart move, back in 2016."

Governing the Clouds

"But how do you govern all this? How democratic is it? And what about the role of the public sector? Or government?" I remembered that the systems were about to shift dramatically, back in 2016. The big data sets were connected and connecting to provide information and services to citizens, to business, to the public sector.

In 2016, Satya Nadella,[8] the Chief Executive of Microsoft and co-chair of the World Economic Forum in Davos, recognized that clouds need to be governed, because we cannot afford another digital divide. He clearly stated that governments, businesses and NGOs must ensure that the benefits of the cloud are shared as widely as possible. In that context he referred to the 17 Sustainable Development Goals of the UN, and was convinced that data and cloud computing will play a central role in realizing these goals. He proposed four elements of a policy framework with cloud computing at its center: first, infrastructure that provides low-cost broadband, offering rural areas access to the cloud; second, build the next generation of skills to ensure data does not just sit in the cloud; third, governments need to lead by example since they are the holders of public data and the biggest consumers of IT services and since government agencies should make data accessible to the public and encourage people to use the cloud by doing so themselves; fourth, we need a balanced regulatory environment that protects both security and privacy while enabling data to flow freely across borders to encourage widespread use of the public cloud for the public good.

It was clear that in 2016 public services (including clouds) were services offered to the general public and/or in the public interest, with the main purpose of developing public value. Public value is the total societal value that cannot be monopolized by individuals, but is shared by all actors in society and is the outcome of all resource allocation decisions. As public services needed to become more efficient and effective, governments had to consider innovative new ways of developing and organizing the public sector for the creation of public value. Thus, transformation was needed to address the way public value was created.

It was also clear that the future of government was less and less in the hands of governments alone. Technology had empowered ordinary citizens by offering them a way to make their voices heard and had challenged government leaders regarding their ability and willingness to address public concerns and requests. It was no longer governments alone (the visible hand) or the market alone (the invisible hand) that responded to these challenges, since also all kinds of partnerships and groups (many hands) were needed. The increased connectivity of citizens and businesses, the possibility for people to work together, perform tasks and distribute workload regardless of distance and boundaries, as well as the availability of previously shielded information and data, meant that government tasks could also be performed – completely or in part – by citizens, companies and others.

Within the European Commission, the Directorate General for Communications Networks, Content and Technology developed 'A vision for public services'.[9] A possible approach to pursue was therefore triggered by the advent of social media, ubiquitous mobile connectivity and web 2.0 activities, which allowed for not just mass dissemination but also mass production and collaboration. The term 'co-production' was not new, but what was new was the ability of this form of citizen and user engagement to function as a source of innovation, leading to the implementation of new or significantly improved ways of providing public goods and services.

Finally, engaging with the wider public was considered to be able to help meet the challenge of rising expectations. It would make the services more user-friendly and effective, improve the quality of decision-making, promote greater trust in public institutions and thus enhance public value. This approach, driven by the opening up and sharing of assets – making data, services and decisions open to all – enabled collaboration and increased bottom-up, participative forms of service design, production and delivery. The kind of public sector organization that was at the heart of this transformation was open government, based on the principles of collaboration, transparency and participation and functioning within an open governance framework.

In 2016, an open governance framework also required more focus on interoperability (with perfect interfaces both at the organizational and the technological level), open standards and cloud computing. In terms of web evolution, this was mainly a web 3.0 development, related to the machine integration of data, knowledge and applications to make the web a more meaningful and collaborative platform. In relation to front-office applications, social media and