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The Nobel Collection, Volume 2

Edited by
Idan Segev and Robert Knight

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The Nobel Collection, Volume 2

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Neuroscience and Psychology

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About this collection

This second Volume of our unique Nobel Collection brings you more articles by Nobel Prize winners (called Laureates), written specifically for young minds. These amazing research leaders explain their ground-breaking discoveries and how they achieved them, and also share their thoughts on making a career path in science with advice for becoming a successful researcher and having a happy life. Like everything Frontiers for Young Minds publishes, these articles have been reviewed and approved by kids like you!

What are the Nobel Prizes?

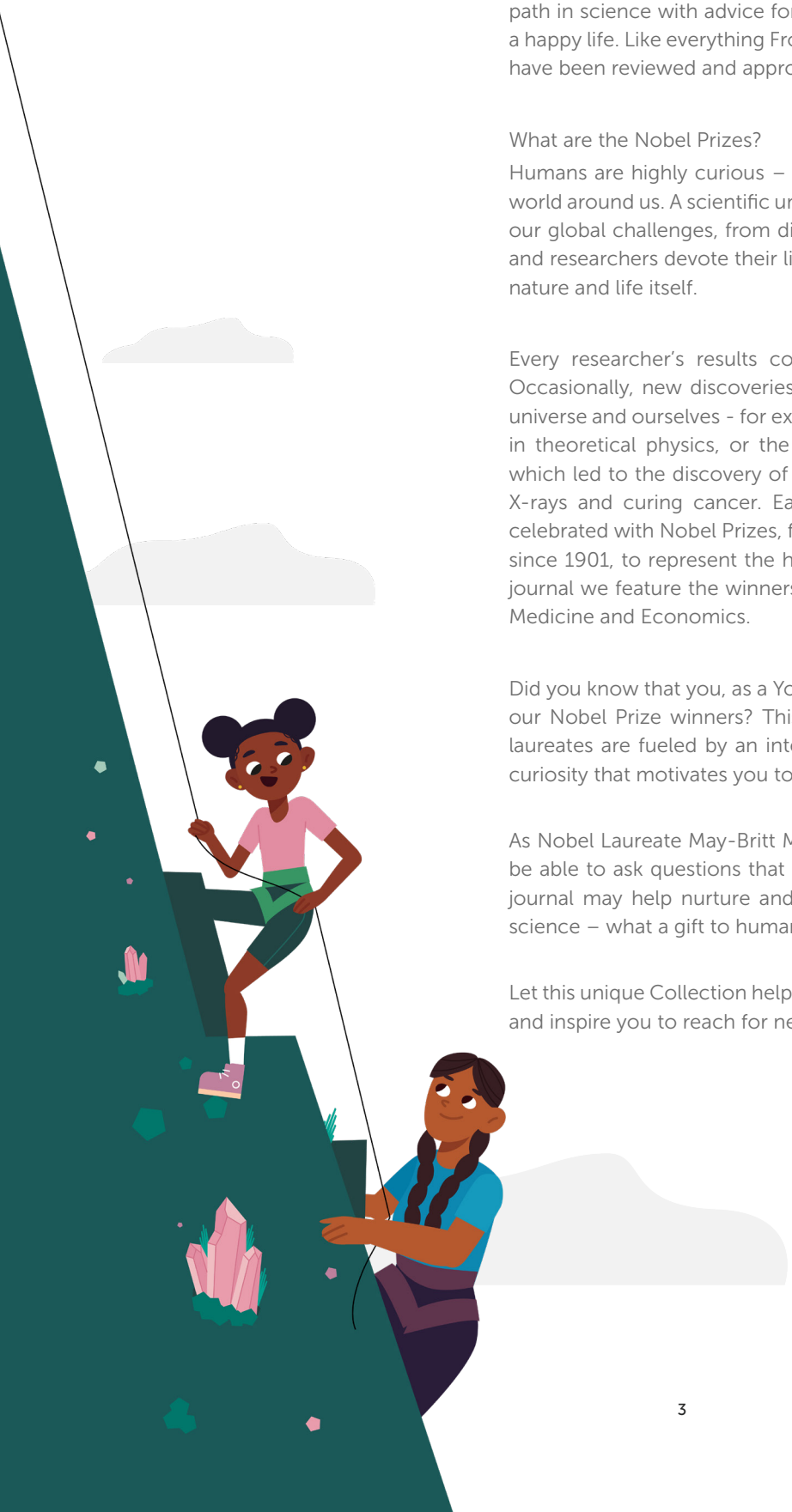
Humans are highly curious – we are eager to understand ourselves and the world around us. A scientific understanding is critical for finding solutions to all our global challenges, from diseases like Covid to climate change. Scientists and researchers devote their lives to exploring and understanding the laws of nature and life itself.

Every researcher's results contribute to our body of human knowledge. Occasionally, new discoveries totally transform the way we understand the universe and ourselves - for example, Albert Einstein's famous break-throughs in theoretical physics, or the pioneering work of Marie Skłodowska Curie, which led to the discovery of new elements and advanced treatments using X-rays and curing cancer. Each year, these transformative discoveries are celebrated with Nobel Prizes, founded by Alfred Nobel in his will and awarded since 1901, to represent the highest level of recognition for research. In our journal we feature the winners of prizes in Chemistry, Physics, Physiology or Medicine and Economics.

Did you know that you, as a Young Minds reader, share an important trait with our Nobel Prize winners? This is curiosity. The scientific journeys of Nobel laureates are fueled by an intense, life-long search for answers – the same curiosity that motivates you to read these articles.

As Nobel Laureate May-Britt Moser told us: "As a scientist, I feel privileged to be able to ask questions that I think are important. I hope the papers in this journal may help nurture and reinforce children's passion and curiosity for science – what a gift to humanity that would be!"

Let this unique Collection help you to develop your own curiosity and passion, and inspire you to reach for new discoveries in your own life!



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ASTRONOMY AND PHYSICS
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NEUTRINOS: THE GHOST PARTICLES THAT MAKE UP OUR UNIVERSE

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YOUNG REVIEWER:

RYAN

AGE: 15

In the field of particle astrophysics, scientists are trying to understand how the universe started and how it works at a very basic level. Using particles from astrophysics sources, we study the laws of physics at the smallest possible scale of matter and develop mathematical formulas that describe how elementary particles interact with each other to make up our universe. My colleagues and I have been studying neutrinos—one of the fundamental building blocks of the universe. That helps us understand how the universe has evolved since it began with the Big Bang some 13.8 billion years ago. In this article, I will tell you about the "ghost particles" called neutrinos—what they are, how we measure them, and why our discovery required a major change in our measurement methods. In this process, you will get to see how the most elusive elements around us are sometimes among the most important.

Prof. Art McDonald won the Nobel Prize in Physics in 2015, jointly with Takaaki Kajita, for the discovery of neutrino oscillations, which shows that neutrinos have mass.

NEUTRINOS: FUNDAMENTAL PARTICLES

What is the Universe made of and how has it evolved since the Big Bang. These are several of the most intriguing questions that we can ask ourselves. To answer them scientifically, we can use various approaches and methods. I come from the field of particle astrophysics—a relatively new field of research that studies the basic particles traveling through space, particularly those that reach the Earth. Particle physicists try to understand the basic particles that constitute matter and the forces that govern the interactions between those particles. In general, we try to develop experimental methods to find the smallest particles, called **fundamental particles—**particles that cannot be subdivided any further. Then, according to what we find, we generate what is called a theoretical model, which is a set of ideas and equations that explains how matter is created from these fundamental particles. We never say that our model is the best one, because each version of a model is based on the level at which we currently understand things, given the sensitivity or resolution of our current instruments. Over the years, instruments become progressively more sensitive and, consequently, we learn new and exciting things about the fundamental building blocks of matter and the universe we live in.

FUNDAMENTAL PARTICLES

The smallest particles that make up all other particles.

The long-standing model describing particles and the forces between them is called the **standard model** [1]. (To learn more about the standard model, see here.) According to the standard model, all matter, including the atoms that build our bodies, the air we breathe, and the light we receive from the Sun, is composed of fundamental particles. These particles were created during the big bang, some 13.8 billion years ago, and during subsequent evolution of the Universe.

STANDARD MODEL OF FUNDAMENTAL PARTICLES

A model for the fundamental particles and their interactions through the forces of nature.

Fundamental particles include electrons, quarks, and **neutrinos** (Figure 1A), as well as other particles you might have heard of, like photons, bosons, gluons, and Higgs particles. We will focus on neutrinos in this article. All the fundamental particles interact with each other through four fundamental forces, called the strong force, the weak force, the electromagnetic force, and the gravitational force. Quarks are the building blocks of both protons and neutrons. Neutrons and protons make up the nuclei of atoms, which are surrounded by electrons (Figure 1B).

NEUTRINOS

Fundamental particles that interact by gravity and the weak force.

Neutrinos are emitted by substances that are naturally **radioactive**, and during certain reactions that we can create in scientific devices called accelerators. However, neutrinos are most commonly generated by nuclear reactions in the Sun, in a process called nuclear fusion. In nuclear fusion, two atomic nuclei combine to form a single, heavier atom while releasing massive amounts of energy and particles including neutrinos. These neutrinos take 2 s to exit the sun and about 8 min to reach Earth. Their number is phenomenal—to give you an

RADIOACTIVITY

A spontaneous emission of energetic particles resulting from the breakdown of atomic nuclei.

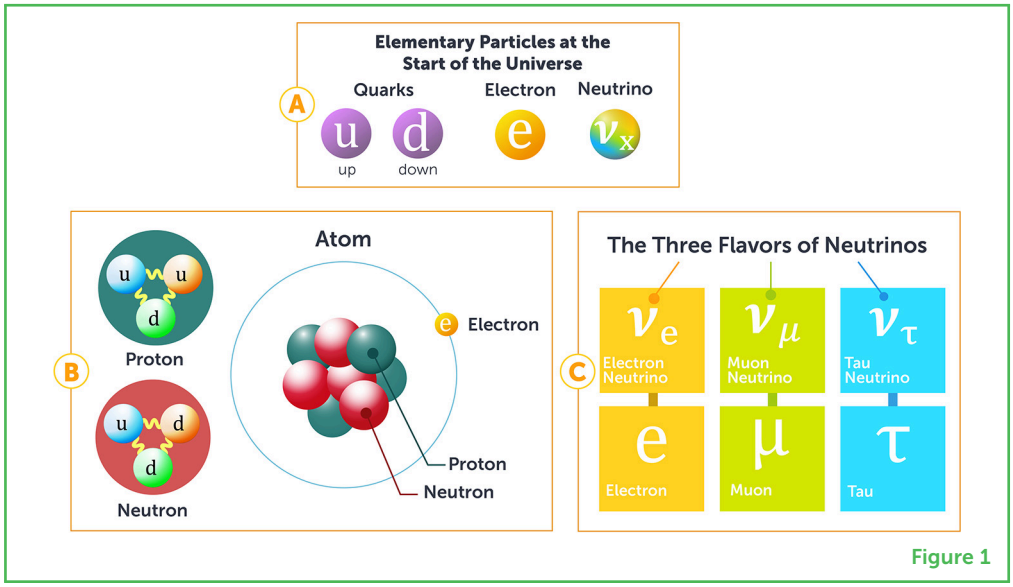

Figure 1

Figure 1

Elementary particles. **(A)** According to the standard model, the universe began with the formation of elementary particles called quarks, electrons, and neutrinos. There are several types of quarks, among them are up (u) quarks and down (d) quarks, and three types of neutrinos (ν_x, where ν designates neutrino and x stands for one of the three types). **(B)** Quarks are the building blocks of both protons and neutrons. Neutrons and protons make up the nuclei of atoms, and electrons circle around atomic nuclei. **(C)** Neutrinos come in three types, or flavors, and they interact with three elementary particles: the electron, the muon, and the tau.

idea, *every second*, each square centimeter of the Earth's surface is crossed by 65 billion solar neutrinos!

Neutrinos are unusual elementary particles because they interact with matter by only two of the four fundamental forces—gravity and the weak force (the weak force can enable a neutrino to change a neutron into a proton and an electron). Since neutrinos are nearly massless, the force of gravity they exert is extremely small and practically undetectable. As for the weak force, they must come extremely close to other protons, neutrons, or electrons to interact with them. This makes neutrinos extremely hard to detect [2]. Neutrinos can basically pass through ordinary matter as though it were almost transparent. In fact, neutrinos interact with matter only when they hit the nucleus of an atom or the electrons revolving around a nucleus head-on, and this happens quite rarely because atoms are mostly empty space. In all other cases, neutrinos pass through matter uninterrupted—including many billions of them that pass through our bodies every second! Because neutrinos only interact very weakly with our detectors, it is extremely difficult to see them and measure their properties. Due to their rare interactions with matter, some people call neutrinos "the ghosts of the universe."

Although elusive and hard to measure, neutrinos play a central role in the formation of the universe. They help to build structures like stars and galaxies. They also helped to generate some of the basic elements created at the start of the universe during the Big Bang.

Neutrinos come in three types, or **flavors**, called the electron neutrino, muon neutrino, and tau neutrino. Each flavor interacts with the corresponding elementary particle—electron, muon, and tau (Figure 1C) [3]. We do not know exactly why there are only three types of neutrinos, but these are the types we have found so far and they fit

NEUTRINO FLAVOR

A characteristic of neutrinos that defines their type. Neutrinos come in three distinct flavors—electron neutrino, muon neutrino, and tau neutrino.

the predictions of the standard model. As you will see below, our important discovery, for which I was awarded the Nobel Prize in Physics in 2015 jointly with Prof. Takaaki Kajita, is related to changes in the flavors of neutrinos as they travel through space, from the core of the Sun to the Earth.

HOW WE MEASURED NEUTRINOS

When we started our research on neutrinos, there was an unresolved problem in particle astrophysics called the solar neutrino problem [4]. To measure neutrinos, special detectors had been built, but these detectors showed that the number of observed electron neutrinos coming from the Sun was much lower than the expected number, based on very solid calculations of how the Sun burns. This discrepancy between the measured and expected number of neutrinos arriving from the Sun to the Earth meant one of two things: either we needed to update the standard model of elementary particles and alter the way we think about neutrinos, or we needed to change the way we calculate the number of neutrinos arriving from the Sun. Both possibilities had significant implications for our understanding of the universe and, therefore, many particle astrophysicists were on a collective mission to design an experiment that could solve the solar neutrino problem.

As mentioned previously, neutrinos cannot be measured by direct interaction with our detectors. Instead, neutrinos are normally measured *indirectly*, using effects that take place when fundamental particles are emitted in radioactive processes. For example, an electron neutrino can be measured using a radioactive process called beta decay, during which an electron is emitted. We can measure the energy of the emitted electrons, and scientists originally believed that only electrons are emitted in this process, so they expect to measure a single energy for all electrons emitted. Instead, they get a whole range of lower energies from the emitted electrons! To account for this range of energy release, they assumed that *another particle* (the electron neutrino) was also released. In this way, they indirectly measured electron neutrinos through the "missing energy" of electrons emitted during beta decay.

In our experiment at the Sudbury Neutrino Observatory (SNO), 2 km deep in the ground in Canada (Figure 2A and Appendix), we used a similar approach to indirectly measure neutrinos through their effect on a special type of water called **heavy water**. As you know, regular water (H_2O) is comprised of one atom of oxygen (O) and two atoms of hydrogen (H). Hydrogen has one proton in its nucleus. In contrast, heavy water (D_2O) contains one atom of oxygen but two atoms of deuterium (D). Deuterium has one proton and one neutron in its nucleus (in other words, it is a hydrogen atom with an additional neutron). This increases its weight by 10% but does not change its

HEAVY WATER

Water containing deuterium atoms instead of hydrogen atoms. Deuterium has one proton and one neutron in its nucleus, whereas hydrogen atom has only a proton. It behaves chemically like hydrogen.

chemical properties very much. Heavy water occurs naturally, such that 1 in every 6,400 molecules of water is D_2O.

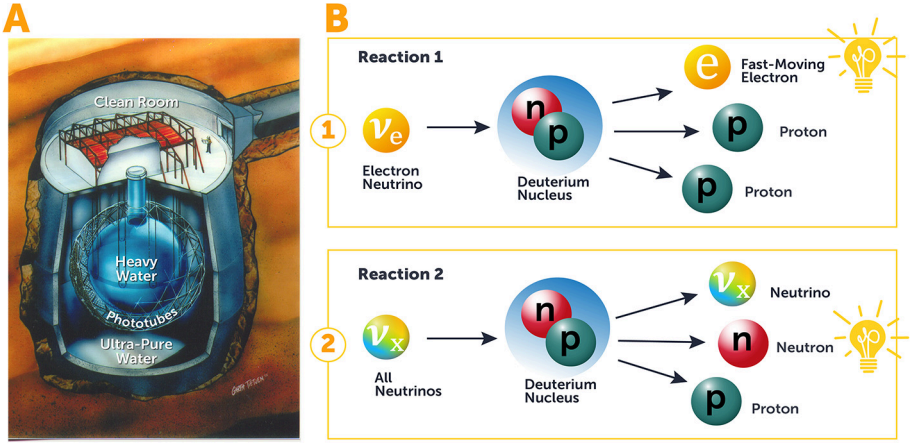

Figure 2

Figure 2

The underground Sudbury Neutrino Observatory for detecting neutrinos. **(A)** The SNO neutrino experiment was performed some 2,100 meters underground. It was designed to detect solar neutrinos through their interactions with heavy water. The observatory included a clean room from which scientists lower equipment into the measurement area, and a measurement area filled with ultra-pure water, to block radioactivity coming from the surrounding rock. The acrylic sphere in the center was filled with heavy water and surrounded by a sphere containing phototubes to measure the effects of neutrinos hitting the heavy water (Image credit: Prof. McDonald). **(B)** We measured two reactions: (1) Interactions of electron neutrinos with the deuterium nucleus, and (2) interactions of all three favors of neutrinos with the deuterium nucleus.

PHOTOTUBES

Light sensors that help us measure the light produced when neutrons interact with heavy water.

In our SNO experiment, we filled a big container with pure heavy water and measured the effects of collisions between neutrinos arriving from the Sun with that heavy water. Basically, we measured two reactions that occur when neutrinos collide with heavy water. In the first reaction, an electron neutrino interacts with a deuterium atom of the heavy water. This interaction changes the neutron in the atom's nucleus into a proton and a fast-moving electron that produces light (Figure 2B, Reaction 1), and we measured the light that this electron produces. In the second reaction, neutrinos of all three flavors (electron, muon, and tau) interact with a deuterium atom. In this interaction, the nucleus of the deuterium atom breaks into a proton and a free moving neutron. The free neutron moves through the heavy water and is detected in different ways in the three phases of the project. In the first phase, the neutron is captured by another deuterium atom, producing light with different properties than reaction 1 (Figure 2B, Reaction 2).

So, we had two light-producing reactions of neutrinos with heavy water that we could measure using our light sensors, called **phototubes**—therefore, we could indirectly measure the presence of neutrinos.

It took a great deal of effort to make sure that we were measuring only the effects of neutrinos and no other sources of radiation. We had to shield our detectors from the radioactivity coming from outer space, which is why we had to place the detectors some 2 kilometers underground, surrounded by rock (Figure 2A). We also had to make sure that we were not measuring radioactivity coming from the rock itself. Specifically, we had to shield our heavy water area from uranium and thorium—two radioactive elements present in rocks. To do so, we surrounded our heavy water container with ultra-clean water—billion

of times cleaner, in terms of radioactive elements, than tap water. This clean water captured the products of radioactivity from the rock. We also built the detector from materials carefully selected to be low in radioactivity and created ultra-clean air and ultra-clean workers who took showers and wore lint-free clothing.

To measure the light emitted when the neutrinos interacted with the heavy water, we placed many phototubes around the heavy water container. Creating this experimental setup was very challenging—it was both a major engineering task and a complex physics experiment. (To learn more about the engineering aspect of the project, see the Appendix.)

WHERE ARE THE MISSING NEUTRINOS?

As mentioned above, our challenge was to solve the solar neutrino problem, whereby the number of electron neutrinos measured as reaching Earth was about three times smaller than the expected number. Either the experiment or the theory (or both) could have been incorrect, *or* maybe the electron neutrinos from the sun were changing flavors and escaping detection in experiments that were solely or primarily sensitive to electron neutrinos.

In our experiment, we wanted to check whether flavor-changing was happening before the neutrinos reach the Earth. We knew that, in the core of the Sun, only electron neutrinos are produced (muon and tau particles are heavier than electrons and therefore producing them and their associated neutrinos requires more energy than is available in the Sun). This means that, if some of the neutrinos arriving from the Sun are not electron neutrinos, they must have changed flavor while traveling from the core of the Sun to the Earth. (Neutrinos change flavors in a periodic manner, through a quantum phenomenon called neutrino oscillations. You can read more about it here.) By tuning our detectors to a specific range of energy, we could detect the effects of neutrinos originating from the Sun, and not from other sources like the cosmic rays that emit neutrinos with higher energies. At the energies we studied, the Sun is by far the main producer of neutrinos reaching the earth.

In one measurement with our detector we observed *electron neutrinos* interacting with deuterium atoms and emitting a fast-moving, free electron, as described above. In a separate measurement, we observed neutrinos of all three flavors interacting with deuterium atoms and emitting a free-moving *neutron*. In other words, the first measurement told us how many electron neutrinos arrive from the Sun, while the second measurement told us the *total number* of all neutrinos coming from the Sun. Comparing the two, we found that only *one-third* of the total neutrinos arriving from the Sun are electron neutrinos. Therefore, two-thirds of the neutrinos changed

their flavor from electron neutrino to either muon neutrino or tau neutrino (Figure 3) [2, 5]. Our experiment showed that an electron neutrino can change flavors as it travels—this was the solution to the solar neutrino problem!

Figure 3

Neutrinos change flavors as they move from the core of the Sun to Earth.

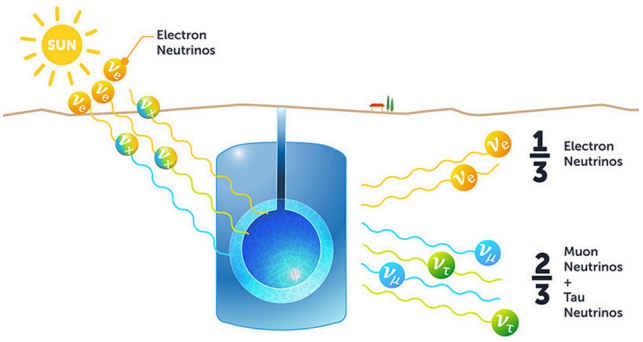

Figure 3

As part of the standard model for elementary particles, it was originally assumed that neutrinos have no mass and that they travel at the speed of light. The discovery that neutrinos oscillate implied—according to considerations resulting from Einstein's theory of relativity—that neutrinos *do* have mass. It is beyond the scope of this paper to explain in detail why the fact that neutrinos change flavor through space means that they have mass. But, in general, Einstein's theory of special relativity determines that this periodic change in flavor means that, from the point of view of neutrinos, time is passing. An experience of time implies that neutrinos move slower than the speed of light, and therefore have mass. Our experiment, along with measurements made at the Super-Kamiokande experiment in Japan with whom we shared the Nobel Prize, provided the first evidence for physics that goes *beyond* the standard model. The extension of the standard model will give us a more complete understanding of our universe at a very basic level. A large number of people worked for an extended period of time to make this great achievement possible. I am deeply grateful to everyone involved in this important project and I feel fortunate to have participated. Through being awarded the Nobel Prize, I see myself as representing all my highly skilled, dedicated colleagues who made this project successful.

RECOMMENDATION FOR YOUNG MINDS

I grew up in a very small, steel-manufacturing city in Canada. While people there appreciated the value of education, no one expected a resident to end up winning a Nobel Prize. This means that any one of you—if you work hard enough and find really good people to work with—can doing something really significant with your life, and perhaps win a prize like the Nobel Prize.

When it comes to choosing your career, I say pick a few things that you will be happy to do when you wake up in the morning, and then try them out. Then, see which ones you are good at—that is what I did! I believe it is a very good way to choose your career. After you choose something, just keep working at that career, and maintain positive, friendly relationships with the people around you—they are highly important for your success.

It is also very important to remain curious throughout your life, as the world as a whole, and science in particular, keep changing quickly. You might not believe it, but when I was in university in 1964, the university received its first computer. It was so large and heavy that it had to be lifted with a crane and lowered into the physics building through its roof! Nowadays, many of you probably have portable computers or even cell phones that are much more powerful and vastly smaller than that those early computers (Figure 4). This is one example of how much science has changed during my career, and I think this amazing pace will continue. Therefore, keep being curious, learn new things, and adapt to new advancements. Furthermore, remember that it is you, the young people, who are best at working with and developing new technologies—so you have a lot to contribute! Therefore, do not hesitate to learn as much as you can about the latest technologies, and try to pass that knowledge on and educate others—even your older colleagues.

Figure 4

Keep curious, as the world is changing rapidly. Technology has advanced rapidly since I was a student in the 1960s, and I believe this fast pace will continue into the future.

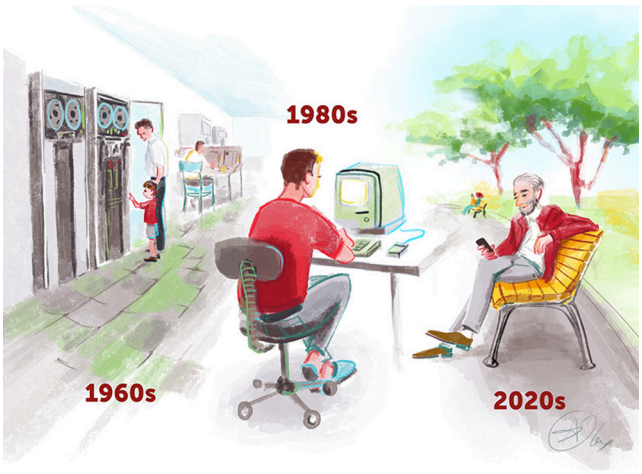

Figure 4

ADDITIONAL MATERIALS

Ain't no stopping them now with Art McDonald (Nature video).

ACKNOWLEDGMENTS

I wish to thank Noa Segev for conducting the interview which served as the basis for this paper, and for co-authoring the paper, and Alex Bernstein for providing Figures 1–4.

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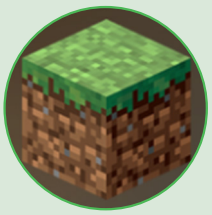
YOUNG REVIEWER



RYAN, AGE: 15

I really enjoy coding and I love Rubik's cubes. I also really love playing Minecraft.

AUTHOR

ART MCDONALD

Prof. Art McDonald is a Canadian astrophysicist born in 1943 in Sydney, Nova Scotia, Canada—a city of about 30,000 people on Cape Breton Island. Sydney was a great community—safe, social, and supportive, with many helpful teachers. Prof. McDonald particularly remembers Mr. Bob Chafe, who was his math teacher. As a teenager, Prof. McDonald belonged to a club that organized a community dance on Saturday nights at the YMCA. There, he met his future wife, Janet. Prof. McDonald earned his bachelor's and master's degrees in physics at Dalhousie University in Halifax, Nova Scotia, Canada, and his Ph.D. in physics at the California Institute of Technology (Caltech) in Pasadena, USA. After Caltech, he accepted a research position at the Atomic Energy of Canada (AECL) Chalk River Nuclear Laboratories, doing basic research at the accelerator facility. In 1982, Prof. McDonald moved to Princeton University in New Jersey, where he became a professor. During the 1980s, Prof. McDonald joined the project building the Sudbury Neutrino Observatory (SNO) in Ontario, Canada, to study the solar neutrino problem. In 1989, he became a professor at Queen's University in Kingston, Ontario, Canada, and he also became the director of the SNO facility. In 1999, the SNO observatory started measuring neutrinos, which led Prof. McDonald and his team to the conclusion that neutrinos change their flavor, implying that they also have a finite mass. This is in contrast to the prediction of the standard model. During his career, Prof. McDonald won numerous awards, including the Benjamin Franklin Medal (2007), Henry Marshall Tory Medal (2011), Nobel Prize in Physics (2015), and Breakthrough Prize in Fundamental Physics (2016). Currently, Prof. McDonald is a professor emeritus at Queen's University in Canada. He continues to be active in basic research on neutrinos and dark matter. During the COVID-19 pandemic in the spring of 2020, McDonald became one of the leaders of a project to mass-produce mechanical ventilators, which were in short supply, at low cost. Prof. McDonald and his wife Janet have four children and nine grandchildren, who are a great joy to them. *art@snolab.ca

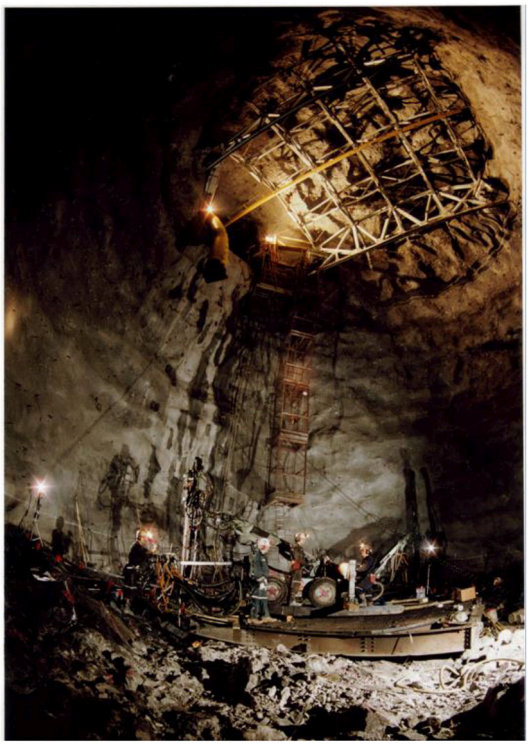
APPENDIX

Overview: The Sudbury Neutrino Observatory Experiment

The SNO experiment for measuring neutrinos and their flavors was a great collaborative effort. At any given moment, more than 150 people were working on the experiment, each responsible for a certain part. First, we had to excavate an enormous cavity, 2 km underground, in a former mine in Sudbury, Canada. The construction team had to drill holes in the floor of the cavern and place explosives there. They then had to lift all their equipment out of the cavity and set off the explosives to deepen and widen the cavity. After that, they had to remove the rubble created by the explosion. It took about 2.5 years and 8 sets of explosions to create this 34-meter high (the height of a 10-story building), 22-meter-wide cavity.

APPENDIX FIGURE 1

The construction team placing explosives to create the cavity for the SNO.



APPENDIX FIGURE 1

After creating the cavity, we had to build the acrylic sphere that would contain the heavy water. The sphere was constructed out of 120 pieces, each small enough that it could be lowered into the mine using the elevator.

Next, we had to construct a geodesic sphere around the acrylic sphere, where the photosensors would be placed to measure the effects of neutrinos reacting with heavy water. Overall, we installed 10,000 photosensors on the geodesic sphere, using lifts.

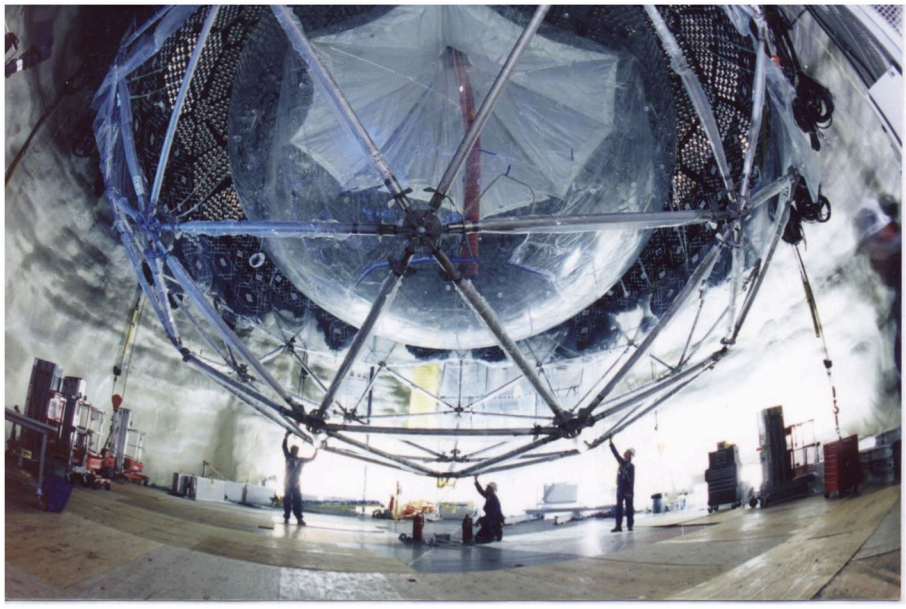
APPENDIX FIGURE 2

Placement of the top 60 (out of 120) pieces of the acrylic sphere that would contain the heavy water.

APPENDIX FIGURE 2

APPENDIX FIGURE 3

Construction of the geodesic dome around the acrylic sphere, before the installation of photosensors to detect the neutrinos.



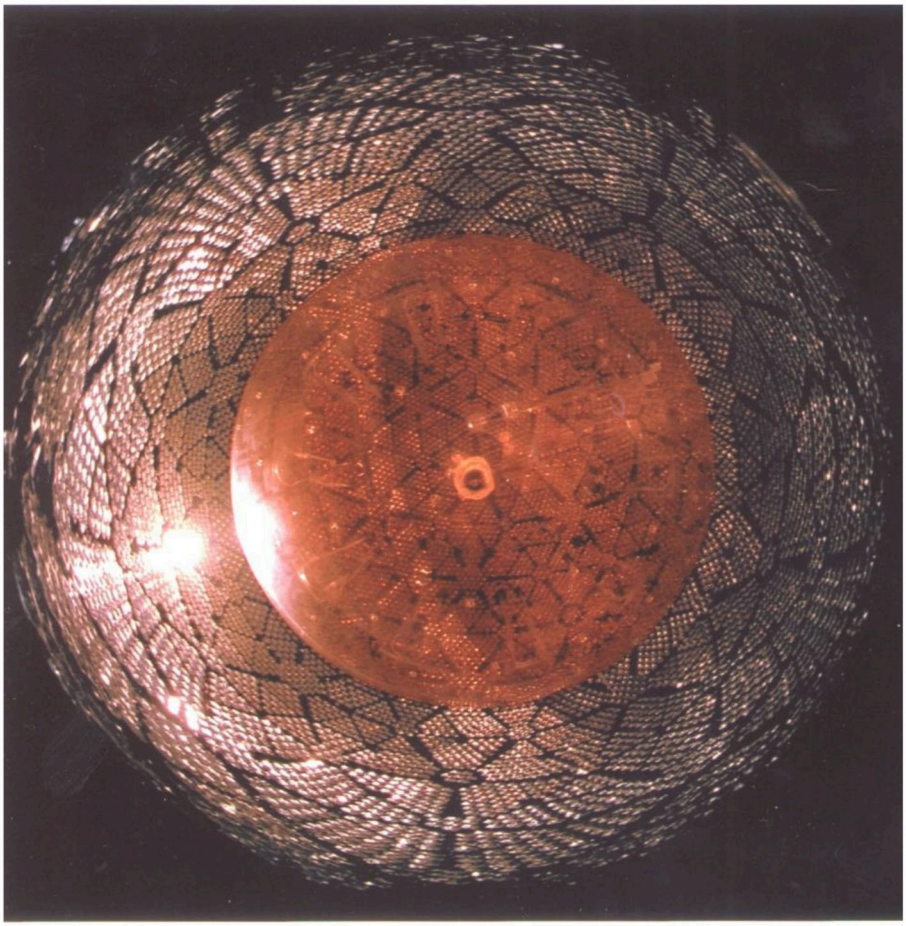
APPENDIX FIGURE 3

Eventually, we filled up the acrylic sphere with 1,000 tons of pure heavy water (D_2O). The water was so pure that we had less than one spontaneous radioactive decay per day per ton of water, which is a billion times purer than tap water. Even with such a huge amount of pure heavy water, we could measure the effect of only 1 neutrino arriving from the Sun per hour, because neutrinos rarely interact with matter.

As you can see, this project was both a complex engineering task *and* a fundamental physics experiment. Many skilled, dedicated people

APPENDIX FIGURE 4

A wide-angle shot looking up at the bottom of the acrylic sphere (red), surrounded by 10,000 photosensors used to detect the presence of neutrinos.



APPENDIX FIGURE 4

worked in collaboration toward a common goal that they felt was significant. We often had to choose how to go about the experiment and we did so by communicating with each other in detail about the alternatives, until it was clear that the group favored one alternative over the other. Fortunately, we were able to reach agreement after having good discussions. By working together in this collegial way, we made our experiment successful and, consequently, we learned something new and significant about the fundamental building blocks of our universe.

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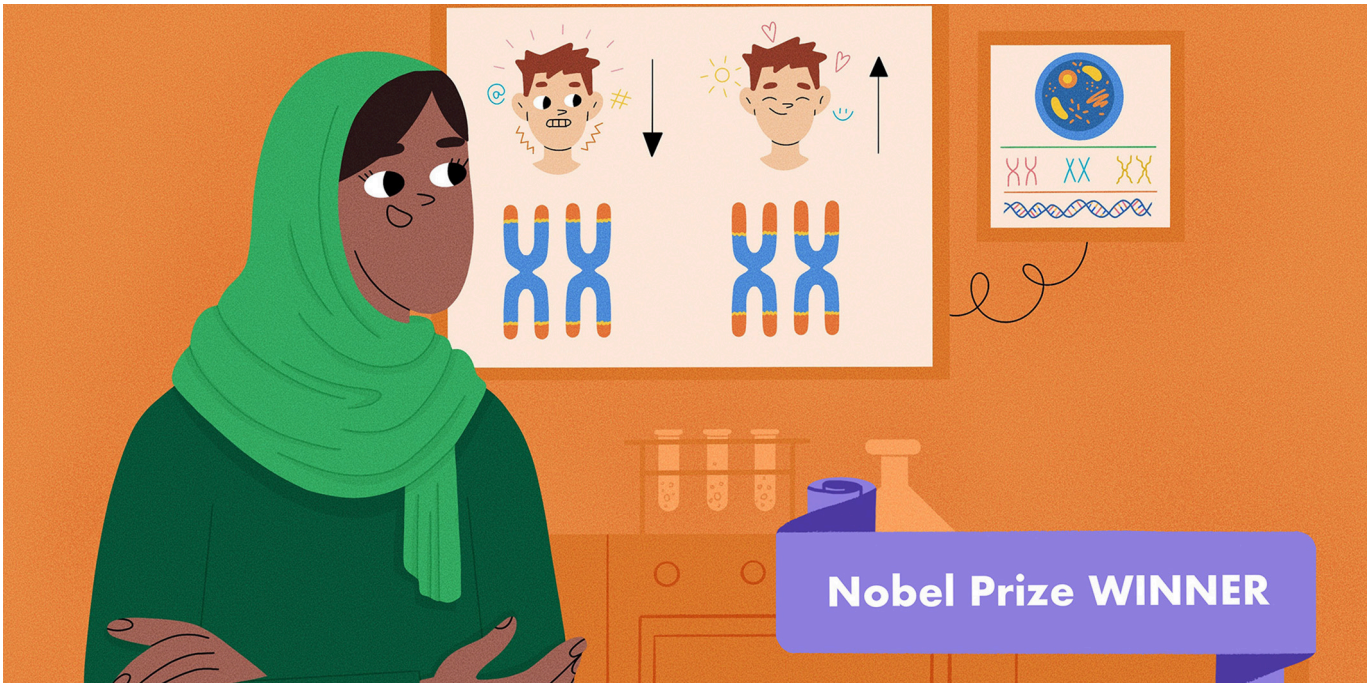

TELOMERE POWER: HOW TO LIVE LONGER AND HEALTHIER

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YOUNG REVIEWERS:


AMELIE
AGE: 14


AMITOJ
AGE: 14

Did you know that your daily choices, including how much you exercise, what you eat, and even how you think, can change the basic units that are present in your cells? In this article, I will tell you about telomeres, which are the protective tips of DNA molecules—the molecules where the organism's genes are stored. I will also introduce you to an enzyme that we discovered, called telomerase, which is responsible for the addition and maintenance of telomeres. After diving into the molecular details of telomeres and telomerase, I will reveal to you some very interesting connections between telomeres and human health. I hope, by the end of this article, you will be amazed by the way in which psychological, environmental, and societal factors can influence the fundamentals of our biology.

Professor Elizabeth Blackburn won the Nobel Prize in Physiology or Medicine in 2009, jointly with professor Carol Greider and professor Jack Szostak, for the discovery of how chromosomes are protected by telomeres and the enzyme telomerase.

PROTECTIVE TIPS ON THE ENDS OF DNA

Life, in all of its complexity, is a huge puzzle. Curious people like you and me are drawn to ask questions, like "What is this?," "What is going on here?," and "Why is this the case?". I chose to engage this unending curiosity through the study of biology—the science of life. Because biology is so complex, you always have to ask yourself: what are the things that I *can* understand, and what should I focus on in my research. Otherwise, you get overwhelmed immediately by all the details of the biological phenomenon you are studying. One avenue you may take in the study of biology is called molecular biology, which examines biological processes through the landscape of molecules and their interactions. Molecular biology is a very satisfying scientific field for me because, in many ways, it lets you answer specific and basic questions about the mysteries of life. In this article, I will tell you about the discoveries we have made, using molecular biology, about an important protection mechanism at the ends of the DNA molecules—the molecules that contain the genetic instructions (the code) that pass from parents to children. But first, we need to lay out the groundwork.

DNA, CHROMOSOMES, AND REPLICATION

CHROMOSOME

A structure of tightly packaged DNA inside cells.

DNA

The molecule that carries information about the appearance and function of living organisms.

EUKARYOTES

Organisms whose cells contain a nucleus.

PROKARYOTES

Organisms whose cells do not contain a nucleus.

Every living cell contains structures called **chromosomes**. Each chromosome contains a polymer (a very large molecule) called deoxyribonucleic acid, or **DNA**. Together, all this DNA is like a library of instructions that tell the cell itself, and any organism built from such cells, how to function. The DNA molecule comes in the form of a double helix which is composed of two linear strands that run opposite to each other and twist together forming the double helix (Figure 1). In chromosomes, DNA is tightly coiled and condensed inside the cells (Figure 1). In human cells, for example, there are 23 pairs of chromosomes that contain all of our DNA. These chromosomes are located in the cell's nucleus and are called *linear chromosomes*, as each of them has two ends. This holds true for all cells of **eukaryotes**, which are cells that have a nucleus. Organisms with cells containing a nucleus include all animals, plants, fungi, as well as most algae. In contrast, organisms which do not have nucleus in their cells, called **prokaryotes** (such as bacteria), have *circular chromosomes*, which have no end (like a circle).

When cells divide, their DNA must be replicated so that the new cells will also contain all the necessary instructions stored in the DNA. As you might know, the DNA polymer is a string of four basic chemical building blocks, called bases, that are symbolized by the letters A, T, G, and C (A stands for adenine, T for thymine, G for guanine, and C for cytosine). The sequence of these bases along the DNA polymer is the code that is used as the "instruction manual" for the cell. In the two

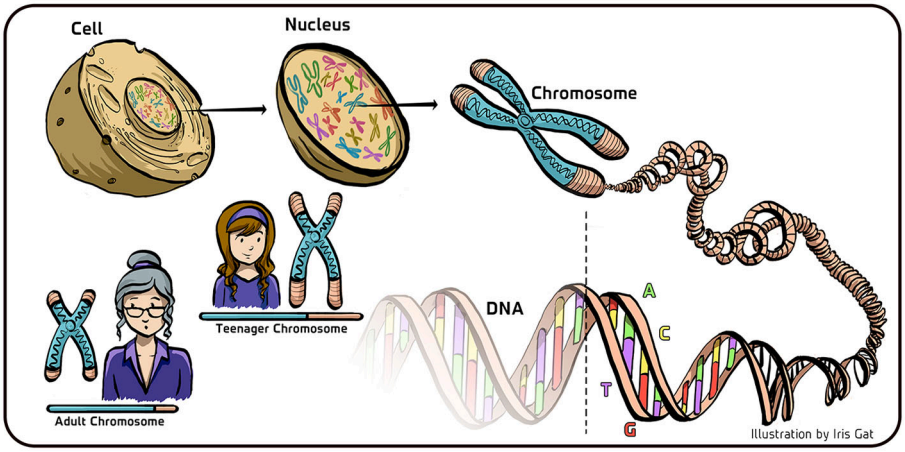

Figure 1

Figure 1

DNA and chromosomes in eukaryotic cells. In eukaryotes, the DNA is stored in the cell's nucleus, where it is coiled and condensed in structures called chromosomes. The DNA appears in the form of a double helix, made of four bases (A, T, G, and C) schematically denoted here by the four colors composing the DNA. When cells replicate, the DNA is copied to create two new double helices from the original double helix. The molecular machinery that copies the DNA does not copy the sequence of the DNA at the end of the chromosome (transparent part of the DNA; **bottom**). As a result, the DNA becomes shorter with aging **(lower left)**. To ensure a stable inheritance of the genetic material, a special mechanism is required to protect the end-part of the DNA sequence during replication.

strands composing the double helix, these bases always come in pairs, A-T and G-C, so that opposite to every A in one strand of the double helix there is a T in the other strand, and opposite to G there is a C and *vice versa* (Figure 1).

When DNA replication takes place in the nucleus, complex cellular machinery first separates the double helix into two single DNA strands. Then, each original strand serves as a template for the synthesis of its complementary strand. In this process, each base in each (by now separated) strand is matched by its respective pair base (T is complemented by A; A by T; G by C and C by G), until a whole new complementary strand is synthesized for each of the strands of the original DNA. At the end of this process, we obtain two new double helices that are identical to the original DNA.

So far, so good—we have a new double helix DNA ready to be used in a new eukaryotic cell following cell division. But it turns out that this complex machinery cannot copy the DNA strands up to their very ends (Figure 1). The sequence of base pairs at the ends of each DNA strand are not copied during cell division. This means that, following each replication, the original DNA will become shorter and shorter.

This is probably where your curious minds stop and ask—well, why does this happen? Why is the DNA not fully replicated during cell division? The truth is that we do not really know. This is one of those instances where we Biologists feel like archeologists—we try to decipher a historical turn of events using the fragmentary information of the artifacts that survived up until today. All that we do know is that the DNA is not fully copied during cell division (the "artifact"). We also surmise that the first cells in the evolution of life were prokaryotic (rather than eukaryotic) cells with circular chromosomes, where there are no free end to the DNA, and that eukaryotic cells, with their linear DNA—and thus DNA ends—developed later during evolution.

From such reasoning we think that the DNA replication machinery that operates in eukaryotes was originally developed in prokaryotes, where it worked well enough and did not have problems with the DNA ending, since there is no "ending" to a circular DNA? Does this then mean that a piece of the important coding genetic material contained in the DNA gets lost in case of the linear chromosomes of eukaryotic cells each time the cell replicates its genetic material—the DNA? Luckily, this is not the case, thanks to a protection mechanism that makes sure that none of the DNA important for its proper function in eukaryotes' cells will become lost.

TELOMERES—DNA PROTECTORS

As we saw in the previous section (Figure 1), in eukaryotes, DNA replication stops before the end of the DNA strands. If you were asked how to protect the important material encoded at the end part of the DNA, can you think of a solution to that puzzle? It turns out that, at the ends of linear chromosomes, there are special DNA sequences called **telomeres** (in Greek, "telo" means end and "mere" means part). The DNA at the telomeres is called a "non-coding DNA" and it ensures that the coding part of the DNA (which includes the instructions that are transferred from parents to offspring) will be properly transferred to the next generation.

TELOMERE

Protective DNA sequence (or a "cap") at the ends of linear chromosomes.

You can think of these telomeres like protective plastic tips at the ends of shoelaces. What actually happens is that the telomeres make up for the lack of DNA copying at the ends of chromosomes. Meaning that, to avoid the case whereby important (coding) parts at the end of the DNA will not be copied during cell division, now only parts of the telomeres (that are located at the very end of the chromosomes) are not being copied, but this does not result in any loss of meaningful (coding) parts of the DNA material. This is similar to the case where the plastic tips of shoelaces get partially worn out when you use them many times, but the shoelaces themselves remain protected. Even more excitingly, we discovered that, when a telomere shortens, it attracts a special **enzyme** that can add more telomeric DNA to the chromosome. Thus, the telomeres can be replenished. This is the beautiful solution that nature found to the problem of incomplete DNA replication at the ends of linear chromosomes.

ENZYMES

Protein structures that enhance chemical activity in living cells.

In the 1930, telomeres were identified by Muller [1] and McClintock [2] as "something" special at the ends of chromosomes that protected their ends. Later on, with the development of Molecular Biology, it was possible to characterize the molecular nature of the telomeres. In 1978, Joseph Gall and I identified the structure of telomeres at the end of the linear chromosomes in an interesting organism called Tetrahymena thermophila, commonly found in pond scum [3]. We found that telomeres of this pond scum organism are made of a specific pattern of DNA bases, namely the sequence TTGGGG

(Figure 2), which was repeated a different number of times (about 20–50) in different chromosomes within the population of cells. Soon after, similar repeating patterns were discovered in the telomeres of other organisms, such as ciliate Oxytricha (TTTTGGGG) and slime molds (TTAGGG) [4]. Human telomeres consist of a TTAGGG sequence, which repeats thousands of times at the ends of all of our chromosomes [4].

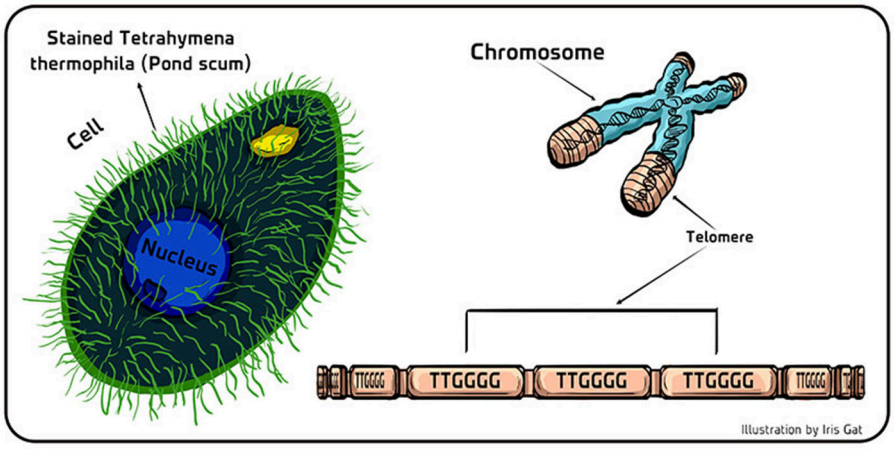

Figure 2

Figure 2

Telomeres in pond scum. **(Left)** Schematic of the single-celled eukaryotic organism *Tetrahymena thermophila* that lives in fresh water. The hundreds of hair-like projections (cilia) on the cell's surface act as tiny oars so it can swim around to hunt for food, or for a mate. **(Right)** Telomeres are like the protective tips of shoelaces that protect the genetic material stored in the coding part of the DNA (blue part of the chromosome). The telomeric (non-coding part) of the DNA (brown part of the chromosome) is comprised of repeating units of bases (TTGGGG in *Tetrahymena*; TTAGGG in us).

There are many interesting questions that could be posed at this point about telomeres and their repeating patterns. What I would like to focus on now is on the following question: how are telomeres added to the ends of chromosomes? And does this machinery supply protection in other situations, in addition to cell's multiplication? In the next sections, we will have a look at the wonderous mechanism that builds telomeres, and see what telomeres can teach us about human health and wellbeing.

EXTENDING THE LIFE OF *TETRAHYMENA*—THE DISCOVERY OF TELOMERASE

When I was studying Tetrahymena and its related species in the early 1980s, it was known that during their life-cycles, there is a stage where the original chromosomes are cut into smaller linear chromosomes, called minichromosomes. As we saw in the previous section for the whole chromosome, these minichromosomes also end with telomeric repeats of TTGGGG. When we found the structure of these DNA repeats in these pond scum cells, we tried to see if we could fit it into the known body of information at that time regarding how DNA bases are added to chromosomes. The only known mechanisms for DNA base addition at that time were (i) DNA replication and (ii) DNA recombination. Each of these mechanisms had very specific sets of rules for DNA addition, which were violated by the telomeric repeats that we had found (e.g., by the fact that telomeres of the pond scum

were heterogeneous in length, sometimes few and sometimes many repeats, and sometimes all the telomeres grew longer at once). These surprising behaviors meant that we could not fit our new findings about the structure of the telomeres into what, back then, were the only well-established principles and knowledge about DNA.

In these kinds of special crossroads in science, you have to think outside the box and entertain other, creative, possibilities in order to find the answer you are looking for. In this case, I tried to think which mechanism could be responsible for the addition of the telomeric repeats to the minichromosomes at the stage after they are cut from the long chromosomes. One possibility was the activity of an enzyme. To check this hypothesis, I put an extract of pond scum cells into a test tube and added various chemical substances to see whether any of the substances added telomeres to the minichromosomes. After some trial and error, I found that this extract *did* promote synthesis of telomeric repeats.

At this point, Carol Greider joined my lab as a Ph.D. student. Her challenge was to simplify the reaction in the test tube, so that we could find the specific enzyme activity responsible for the addition of the telomeric ends. After some more trials and errors, Carol simplified the assay to its bare essentials. We added synthetic repeats of TTGGGG, right after the chromosomes were chopped up into minichromosomes. At this stage, the telomeres were expected to be added. We added DNA building blocks into the test tube (two molecules called dGTP and TTP), along with some magnesium salt. We saw that TTGGGG repeats were indeed added to the ends of our synthetic DNA [5], which meant that we found a possible mechanism for the elongation of telomeres! Carol's fellow graduate student Claire Wyman came up with a name for the new enzyme that seemed to be responsible for the addition of telomeric repeats: **telomerase** [6].

TELOMERASE

An enzyme that adds telomeric DNA to chromosomes.

To validate our hypothesis regarding the function of telomerase in the elongation of the DNA in living cells (not just in the test tube), we performed some additional experiments. I will not go into the details here, but we found that telomerase had an **RNA** part, containing a short sequence that is the complement of the DNA sequence of the telomeres. This RNA acts as a template for the addition of the complementary telomeric sequence. In some of these experiments, we changed (or "mutated") the structure of telomerase to see whether mutations affected its capability to synthesize telomeric DNA and elongate telomeres. In mutations that allowed the telomerase to keep working but which had a mutation in the RNA template for telomeric DNA addition, we found that pond scum cells had alternative telomeric repeats—different than the original TTGGGG repeats and complementary to the base change we had put in the template [7].

RNA

A moveable copy of DNA which the cell uses to perform different actions, such as copying DNA.

Importantly, when we mutated telomerase so it did not function anymore, the telomeres of pond scum cells got shorter in each cell division, and finally after 20–25 divisions the cells stopped dividing and died [7] (Figure 3, left). This meant that the normally immortal pond scum cells (i.e., cells that multiply seemingly forever) became mortal (i.e., stop multiplying after a certain numbers of multiplications) when the activity of telomerase was damaged. All of these findings have led to the conclusion that telomerase is indeed responsible for the addition of telomeric DNA to the ends of linear chromosomes. It was that discovery for which Carol and I were awarded the Nobel Prize in Physiology or Medicine in 2009 (together with another collaborator, Jack Szostak, with whom I had explored telomere function in baker's yeast cells). It is important to note that later on, after the discovery of telomerase, it was found that its activity is important not only in the case of cell multiplication. It turned out that telomeric DNA is chemically quite susceptible to damage inside cells, and so there are different situations where it should be fixed—especially over long periods, such as the time frames of human lives. Therefore, telomerase is important even in cells which are not multiplying (Figure 3, right).

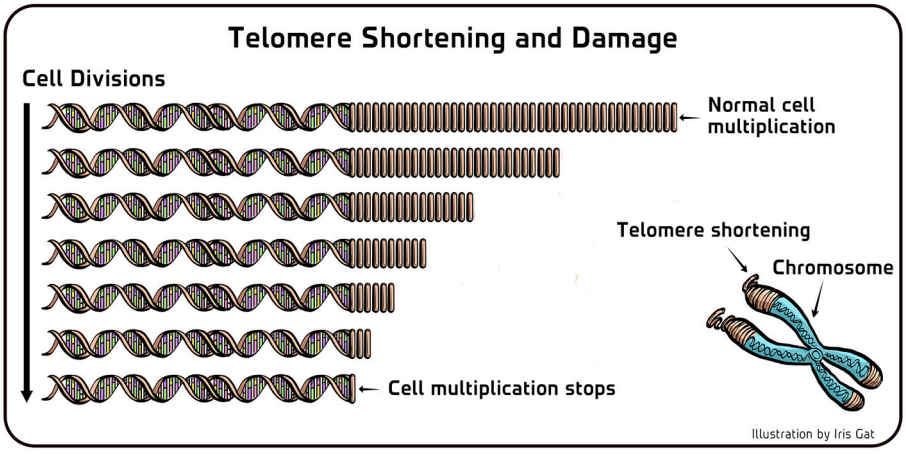

Figure 3

Telomere shortening and damage. **(Left)** In cells of the pond scum where telomerase does not work properly, the telomeric DNA (right repeating part of the DNA in this figure) gets shorter with every cell multiplication. When the telomeres become too short, the cell stops multiplying. The same holds true for human cells. **(Right)** Telomeric ends are chemically susceptible to damage inside cells. Therefore, the activity of telomerase is important also for the maintenance of telomeres in cells which are not dividing.

Now that you are acquainted with my work on telomeres and telomerase, I would like to present to you another line of research that developed later on along my scientific path. This line of research connected telomeres to human health in some very surprising ways.

LESSONS FROM TELOMERES—HOW TO IMPROVE HUMAN HEALTH

When I was working on telomere maintenance and telomerase in human cells at the University of California, San Francisco (UCSF), I was approached by a bright psychology researcher, Elissa Epel. Elissa, now

a professor in the Department of Psychiatry at UCSF, was then doing her post-doctoral studies on severe chronic stress. At that time, in the beginning of 2000s, it was known that people who are under severe chronic stress often exhibit physiological changes that mimic what we see when people get older naturally, only at a faster pace. In other words, chronic stress was related to accelerated human aging. From another viewpoint, by studying telomeres we knew that if you make a genetic mutation in the telomerase of pond scum or yeast cells that would make it stop working, the telomeres would become shorter and shorter in every multiplication until eventually they would get too short and that would send signals to the cell to stop multiplying (Figure 3). This brought up a new idea that was starting to get some traction in the field: that maybe telomere shortening is related to aging of mammals like us. It was not clear then what was happening in human cells during aging.

When Elissa came to me and asked whether chronic stress could possibly be related to telomere shortening, I thought that this was a very interesting question. She told me about a fascinating study that she was doing on mothers with children that had either developmental disorders or chronic illnesses. This group of mothers was under severe chronic stress, partly because there is often a lack of support for this kind of situation in the United States. In addition to the scientific interest that was sparked in me after hearing about Elissa's research and wondering about the possible relation of her findings to telomere shortening, I also had another, more personal reason for engaging in this research. At that time, my son was growing up and I found myself fairly often worried about him. That made me feel very empathic toward the women in Elissa's study, realizing how stressed out they could feel in their challenging caregiving situations.

So, we decided to launch a pilot study in which my group measured telomerase activity and another group measured telomere length in cells of mothers who were the main caregivers of children with chronic illnesses. We compared the findings to control parents, matched in all respects except that they did not have a child with a chronic illness. Our work was led by a post-doctoral researcher named Jue Lin, who was previously working on yeast telomeres and telomerase and was intrigued by this new line of research. Right away, in this first study, we received a surprising result—there was a significant, quantitative correlation between telomere length—in this case, telomere shortness—and both the chronicity of the caregiving and perceived psychological stress! (Figure 4). This was an amazing result, and it was the first indication that a psychological situation like chronic stress could be correlated with this very clear, physical change at the most basic molecular level!

As scientists, we do not rush to conclusions because we are aware of the human tendency of imposing what we want to see on reality and on our data. This tendency means we should be especially suspicious

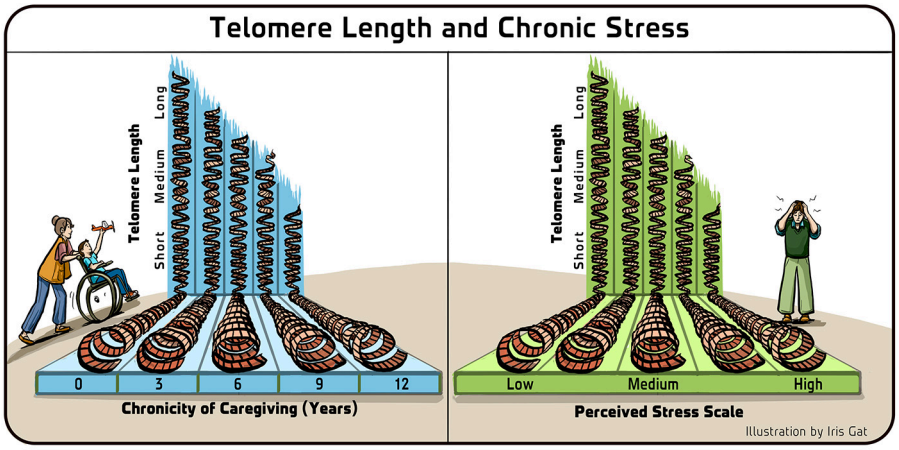

Figure 4

Telomere length and chronic stress. In the study that we first performed with mothers who were the main caregivers of children with chronic illnesses, we found that there was a statistically significant correlation between the shortness of the mothers' telomeres and both the number of years that they had been in that situation **(Left)**, and their perceived level of stress **(Right)**. Adapted from Epel et al. [8].

when the initial results we get match our "desired" hypothesis. Therefore, we decided to take additional actions to verify our initial results. One route that we took was to use different groups of people with similar chronic psychological stress of caregiving (such as caring for a family member with dementia) and see if the results on their telomere length would replicate. Additional research has involved checking for possible relations between telomere length and other parameters, such as environmental factors, educational parameters, and additional mental or psychological factors. Many such connections were found, and my group and others eventually concluded that that there are very significant relationships between telomere length and human health [9].

In 2017, Elissa and I co-authored a book for general readers that presents the heart and soul of our continuous work on telomeres and human health, called: *The Telomere Effect: A Revolutionary Approach to Living Younger, Healthier, Longer* [10] (see Additional Materials). Although I should mention that it was our publishers who insisted that we add "revolutionary" to this book's title, our book does in fact collect and present many interesting facts and conclusions. I would like to share two significant points. First, lifestyle and attitude matter! Meaning, the ways we sleep, eat, and exercise on a regular basis affect the lengths of our telomeres and, because of that, these activities can either promote or harm our long-term health and longevity. The same is true for habits of negative thinking, which are correlated with telomere shortening; as opposed to positive and resilient thinking, which enhance good telomere maintenance. Second, I want to emphasize the broader, social aspect of telomere length. Telomeres are affected by our environment! That means that when we make sure to support one another, on an individual and societal levels, we promote good telomere maintenance and overall human health. Let us remember, then, the important role we have in making sure that our telomeres, and the telomeres of our fellow humans, will stay long

and healthy. The choices that we make on a daily basis, as well as societal influences that we must all keep striving to improve, do matter, because they are reflected even in the most fundamental molecular biology of our cells.

RECOMMENDATION FOR YOUNG MINDS

There is a lot of advice that I can give you when it comes to doing science and being a scientist (Figure 5). I would like to start by emphasizing the power of persistence. If you find yourself interested in science, then you should know that you will have to persist because sometimes it will look quite daunting and complex. But, do not give up and you will find at some point that there is a wonderful time where you break through the challenge. Then you will feel very satisfied and know that your persistence was worthwhile. Also, for your long-term satisfaction, you have to be convinced that whatever you are doing is something of value. So, when you choose your way in science (or in any other profession), make sure to be engaged in things you believe are worthwhile doing. This way, there will be an inherent value in your work, and that will encourage you to persist even at times where it would be easier to give up. When you chose your particular path and persist in it, remember that everything, and especially knowledge and technology, can be used in different ways. Make sure to always keep in mind to use whatever you are engaged in for the good of humanity. And while you do so, also remember to always check your results rigorously and not let your personal preferences and wishes interfere with the way you collect and analyze data.

Figure 5

Recommendations for young minds.

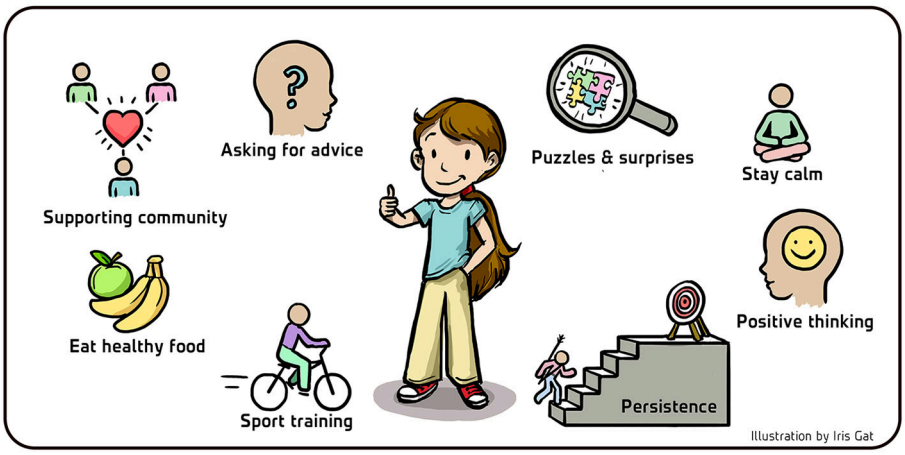

Figure 5

Another aspect that I want to stress is the importance of asking for advice. I learned that the hard way: early in my career, I was hesitant to ask for advice. I worried that people might think less of me if I seemed to be needing help, so I would refrain from asking for it. In hindsight, I see that this sometimes made my path more difficult than it had to be.

I say that, because as time progressed and specifically when my son was born and I had to find my way around being a young mother while being a full professor at the university, I opened up to the possibility of asking for advice. It turned out to be tremendously helpful—I was given all sorts of solutions I would never had thought about from people who already hacked the challenge I was facing, both personally and professionally. I realized that, in most cases, people like helping each other and actually respect you for your willingness to ask for advice. So I encourage you to ask for advice along your way instead of making your life unnecessarily hard. Also, please remember that there are many people who want you to succeed, so find these ones and keep them close, while keeping in perspective other people who are not helpful.

I also want to speak with you about puzzles and surprises. For me, science is full of puzzles—some are big puzzles, that you invest your whole career trying to solve, and some are smaller puzzles that you are faced with every day. My big puzzle is trying to understand how life itself works. That big puzzle breaks down into smaller puzzles each day when I analyze data and try to solve a particular question about a particular phenomenon. In the broad picture, science supplies for me both safety and stability, through an impersonal, rigorous way to get to a truth, and also surprises and thrills, through the unexpected discoveries that you make along the way. I call these surprises birthday present surprises, and I enjoy them very much. My advice to you, in that regard, is to fully enjoy the birthday present surprises that will cross your path. I know that some of you may be somewhat intimidated by surprises, but I can assure you that the kind of surprises you will meet in science are good surprises, if you approach them that way. The better the grasp you will have at your area of expertise, the freer you will feel to step out of your known territory and explore scientific birthday surprises.

Finally, I would like to direct some special words of encouragement to the future women scientists among you. As you can see from my example, women can have a successful, fulfilling, often joyful career in science. I do not know if you know, but in 2009 when Carol Greider and I were awarded the Nobel Prize in Physiology or Medicine, three other women won Nobel Prizes: in Chemistry, Economics, and Literature. I felt that this was sending an important signal to younger scientists, saying that a Nobel Laureate could just as well be a woman as it can be a man. Therefore, it is an honor for me to be a symbol for the future generation of women, and indeed all, scientists.

ADDITIONAL MATERIALS

1. The Telomere Effect: A Revolutionary Approach to Living Younger, Healthier, Longer—Amazon.

2. Women Who Changed Science—Elizabeth Blackburn.

3. Elizabeth Blackburn on the telomere effect—The Guardian.

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YOUNG REVIEWERS

AMELIE, AGE: 14

I love sciences and, in fact, I study physics, chemistry, and biology at school. However, I must admit that I have a passion for acting. I like to draw and practice judo in my free time. I am always over the moon when my parents and I go abroad as I am curious about new cultures and scenery! My favorite book genres are comedy, action and horror, and recently I developed a liking to manga. I enjoy reviewing interesting scientific articles!

AMITOJ, AGE: 14

My name is Amitoj and I am in 9th grade. My favorite subject in school is science. I play saxophone for my school band. I enjoy traveling and photography. I enjoy cooking and trying new foods. I like to play basketball, read books and spell words. I would like to go into the medical field when I grow older.

AUTHOR

ELIZABETH BLACKBURN

Prof. Elizabeth Blackburn was born in 1948 in a small city in Tasmania, Australia. She was a very curious child who loved animals and was attracted to biology from a young age. In the 1970s, Prof. Blackburn studied at the University of Melbourne, Australia, where she received bachelor's and master's degrees in biochemistry. She then continued with her Ph.D. studies in molecular biology at the University of Cambridge, England, where she used DNA sequencing to study the nucleic acid composition of a specific bacteriophage. In 1975, after finishing her Ph.D. in molecular biology, she began her postdoctoral studies in the laboratory of Prof. Joseph Gall at Yale University, United States. There, she investigated the chromosomes of *Tetrahymena*, commonly known as pond scum. She found that the telomeres of pond scum are composed of short, repeating patterns of the nucleotides thymine and guanine, in the form of TTGGGG. In 1978, Blackburn became an assistant professor of molecular biology at the University of California Berkeley, where she continued investigating the telomeres of pond scum. In 1985, along with her student Carol Greider, Prof. Blackburn identified the enzyme responsible for adding telomeric ends to linear chromosomes, which was

later named telomerase. For these discoveries Prof. Blackburn, along with Carol Greider and another telomere research collaborator, Jack Szostak, were awarded the 2009 Nobel Prize in Physiology or Medicine. In 1990, Prof. Blackburn left Berkeley and continued to investigate telomeres as a professor at the University of California San Francisco (UCSF). Together with psychology researcher Elissa Epel, she studied the relationships between telomeres and chronic stress. Their first study led to a whole series of studies connecting telomere length to human health in various ways. Findings arising from this prolonged collaboration were published in 2017 in a popular science book called *The Telomere Effect: A Revolutionary Approach to Living Younger, Healthier, Longer*. During her career, Prof. Blackburn has won numerous awards, including the NAS Award in Molecular Biology (1990), Australia Prize (1998), Harvey Prize (1999), Dickson Prize (2000), ASCB Public Service Award (2004), L'Oréal-UNESCO Award for Women in Science (2008), Nobel Prize in Physiology or Medicine (2009), and AIC Gold Medal (2012).
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THE OLFACTORY SYSTEM: IT SMELLS GOOD TO BE ALIVE

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YOUNG REVIEWER:

PELEG

AGE: 10

The world around us is filled with odors (smells), some pleasant, calming, or bringing back memories; others stimulating, scary, or disgusting. How many odors do you think you can recognize? You might be surprised to know that humans can recognize hundreds of thousands of different odors—not an easy task to accomplish. So, how do we do it? In this article, we will smell our way through the olfactory system, look at the connections between the nose and the brain, and see how odors are processed in the brain to evoke unique responses.

Professor Richard Axel won the Nobel Prize in Physiology or Medicine in 2004, jointly with professor Linda B. Buck, for their discoveries of odorant receptors and the organization of the olfactory system.

HOW DO WE SMELL THINGS?

When you see a beautiful bouquet of flowers or pass by a perfume store, you often lean in to smell them. Have you ever wondered

what it is, exactly, that you are smelling? And how do you recognize the smell? When you smell a flower, you inhale molecules that are released from the flower and then build an internal representation of the flower's odor, through the electrical activity that happens in the brain (Figure 1).

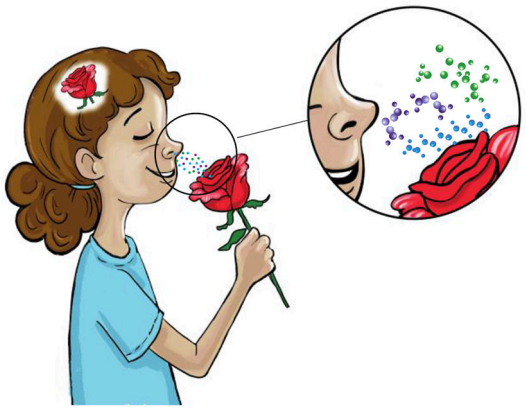

Figure 1

Representation of smelling. A variety of chemicals (odor molecules) are released from the rose to the air. These molecules reach the nose, where they activate electrical signals that are transmitted to the brain. In the brain, multiple regions are electrically activated. This activity enables us to identify a particular scent—in this case, that of a rose.

OLFACTORY SYSTEM

The sensory system responsible for smelling.

ODORANT

Odor molecules that are released from objects, travel through the air, and enter your nose.

NOSE EPITHELIUM

A tissue in the upper rear part of the nose involved in smelling.

RECEPTOR

A molecule on a cell that interacts very specifically with another molecule, like a lock and a key, and translates the interaction into a signal within the cell.

OLFACTORY SENSORY NEURONS (OSNs)

Nerve cells containing odor receptors that translate interaction with odorants into electrical signals which travel to the brain.

Before we dive into the complexities of smelling, let us look at how the **olfactory system** works. Odors are composed of molecules that are released from the object you smell (like an orange or a rose). The odor molecules, which are called **odorants**, travel through the air and enter your nose. Inside the nose, in the upper-rear part called the **nose epithelium**, there are cells that have special molecules called **receptors**. Each receptor has a unique shape, so that it "likes" certain odorants more than others and is more activated by their presence (Figure 2). These receptors are present on nerve cells called **olfactory sensory neurons (OSNs)**. The interaction between odor molecules and OSNs is translated by the OSNs into electrical signals, which then travel to the brain. Due to this brilliant design, each odorant (such as beta-ionone when you smell a rose, limonene when you smell a lemon, or benzyl acetate when you smell strawberries), activates a *unique combination* of OSNs [1] out of more than one thousand OSN types that you have, and this in turn causes a unique pattern of electrical activity that enables your perception of a specific odor. To sum up, the coding of odors in the brain is based on the activation of a unique subset of OSNs. Each OSN is activated electrically when its receptors interact with specific odorant molecules, but not with other molecules. This electrical activity then travels into various regions in the brain that process and represent smell information.

IDENTIFYING ODOR RECEPTOR GENES

When I started studying the olfactory system, it was known that animals can tell apart extremely large numbers of different odors, but it was not clear how. What *was* clearly implied was that there must

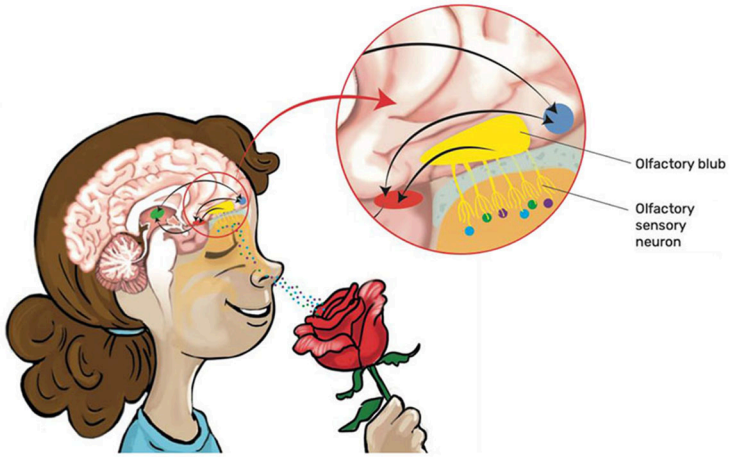

Figure 2

Smell receptors in the nose. At the inner, upper-rear part of the nose, called the nose epithelium, there are cells called olfactory sensory neurons (OSNs) that have protein molecules called odorant receptors. The receptors on OSNs interact with molecules that are floating around in the air, and the interaction of odorant molecules with OSNs generates an electrical signal that moves through nerve fibers (axons) to a brain area called the olfactory bulb. From there, the electrical activity continues on to additional regions in the brain (colorful circles) that process smell information.

be a brain mechanism that enables an animal to recognize this vast diversity of odor molecules. This led to the idea that there must be a very large number of genes that code for the odor receptors. Also, the OSNs, which translate the odorant receptors, must have a way to turn the odorant-receptor interaction into electrical signals.

In our research, we wanted to find the genes that code for (or dictate the nature of) odorant receptors. To do that, we made three assumptions that simplified our search: (1) there should be a large family of genes coding for odorant receptors; (2) odorant receptors have a mechanism for turning interactions with odor molecules into electrical signals; and (3) genes coding for odorant receptors are expressed *only* in OSNs in the nose epithelium. Using these assumptions, we were able to efficiently search for a family of genes that code for odorant receptors in mice. We isolated their OSNs and found a new gene family in the mouse DNA that consists of about 1,000 different receptor genes [2]. This was very exciting, since it was the first time that odorant receptor genes had been identified. About 23 years later, in 2004, this discovery earned me and my colleague Prof. Linda Buck a Nobel Prize in Physiology or Medicine [3].

After identifying odorant receptor genes, we could then use sophisticated techniques (including molecular genetics and neural imaging) to ask more complex questions about the organization and activity of OSNs in the nose and brain. For example, how many of the receptor genes does every OSN express? Does each OSN contain only one type of odorant receptor or *multiple* types of receptors? These two possibilities imply two totally different structures and functional mechanisms of the olfactory system. As it turned out, the first possibility was correct: each OSN expresses only 1 out of about 1,000 possible receptor genes.

NEURON

A nerve cell; the main cell type in the brain. Neurons generate electrical signals and transmit them to other nerve cells.

AXONS

Nerve fibers that carry electrical signals from one neuron to another.

OLFACTORY BULB

The first relay station in the brain involved in smelling. It receives information from OSNs and transmits information about odors to other areas of the brain.

GLOMERULUS

A region in the olfactory bulb at which all OSNs expressing a particular receptor converge.

ORGANIZATION OF OLFACTORY SENSORY NEURONS

Now let us look at how OSNs are organized in the nose and in the brain, where odor recognition occurs. In mice, there are 10 million OSNs in the nose and 1,000 different odor receptors. Since each OSN expresses only one receptor type, this means that each receptor type is expressed in 10,000 **neurons** (10 million/1,000 = 10,000). But how are the 10,000 neurons expressing the same odorant receptor organized in the nose epithelium? Are they spread out over a large area, or are they clustered close together? And what happens to the electrical information that they generate when they interact with their favorite odorant? Does the information for a specific odorant converge (or come together) to a specific region of the brain?

We found the answer to these questions by using an advanced technique that selectively colors neurons expressing the same receptor gene. In the nose epithelium, the OSNs are randomly distributed over a large area (Figure 3). The OSNs then send their extensions (fibers called **axons**) into the first relay station in the brain that processes smell, called the **olfactory bulb**. All the 10,000 OSNs expressing a particular receptor converge at a specific region in the olfactory bulb, called a **glomerulus** (Figure 3, right). Overall, there are 1,000 separate glomeruli in the olfactory bulb and each receives information from all the (10,000) OSNs expressing a specific receptor gene [4].

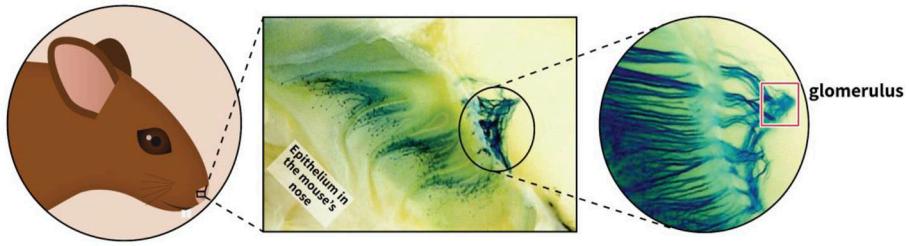

Figure 3

Organization of olfactory sensory neurons. In the mouse's nose, there are one million OSNs. Each OSN expresses only one specific odorant receptor, so each type of odorant receptor is expressed by ~10,000 OSNs spread throughout the nose epithelium (small blue dots in central image). Each OSN sends its electrical information *via* an axon (blue fibers) to a single location in the olfactory bulb, called a glomerulus (red square on the right). The fibers of all 10,000 OSNs expressing the same receptor converge in the same glomerulus. Sensory cells expressing different receptors converge in different glomeruli. (Image adapted from [4]).

ACTIVITY OF OLFACTORY SENSORY NEURONS

What happens when an animal is exposed to a specific odor (Box 1)? Odors are composed of many molecules (e.g., more than 400 in the case of a rose [6]). As we saw, each odorant molecule activates a specific group of OSNs (10,000 of them), which converge in and activate a specific glomerulus in the olfactory bulb. Smelling a rose activates a different group of glomeruli than smelling chocolate does, so specific smells create specific patterns (or "maps") of glomeruli activity in the brain.

Nowadays, we can look down on the olfactory bulb of rodents using neural imaging techniques, and "read" the spatially organized patterns

Box 1 | Olfactory systems of animals.

The ability to sense and differentiate between smells is very important to many animals, and olfaction was probably the earliest sense to evolve in organisms. There are many similarities between the olfactory systems of various animals. For example, the olfactory system of fruit flies, similar to that of humans and rodents, contains specific cells that each identify a relatively small number of odor molecules [5]. In fruit flies, the odor receptor cells (located on their two antennae) expressing the same receptor also converge in the same glomerulus. However, fruit flies have fewer glomeruli (about 60, compared to 1,000 in humans). The similarity between the olfactory systems of flies and humans allows scientists to draw important conclusions about the human olfactory system by studying fruit flies, which are easier to study than humans. There are also key differences between the olfaction systems of humans and flies, and smells that are considered pleasant or unpleasant for humans will not necessarily be experienced for the same way by flies, and vice versa.

(the "map") of neural activity, and decipher from this activity which odor was encountered. This is a great new method for scientists to recognize odors, but it is clearly not the way by which the animal recognizes odors as it does not have an imaging microscope in its olfactory bulb and cannot look from the outside on its own neural activity as we scientists do.

Although the fascinating ability of the brain to recognize odors is not yet fully understood, we do know that the neurons in the olfactory bulb project their axons to multiple brain regions (Figure 4). Some of these regions are responsible for automatic behaviors in response to odors. For example, when an animal encounters a specific odor that suggests the presence of danger, such as when a mouse encounters the odor of a cat, an automatic "run away!" response is activated. Other axons travel from the olfactory bulb to brain regions where learning takes place. There, an animal learns specific behavioral responses based on the odors it encounters [3].

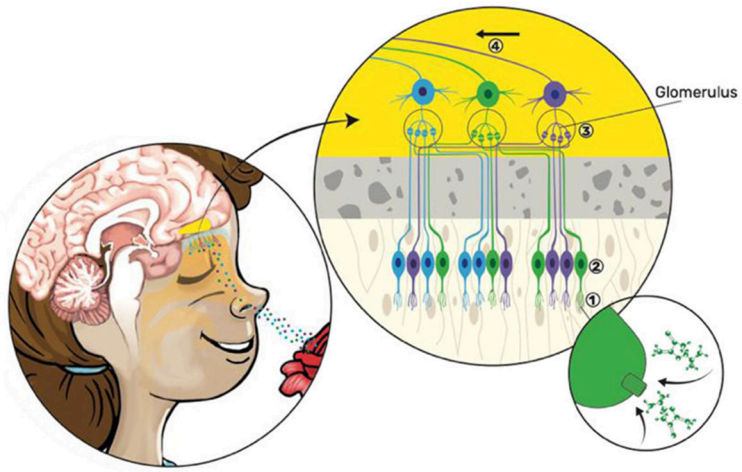

Figure 4

Figure 4

Anatomical and functional organization of the olfactory system. **(Left)** Odorant molecules enter the nose and bind to receptors on OSNs. Each ONS expresses only one type of olfactory receptor (differently colored "fingers"). OSNs' axons cross the nose bone and enter the first relay station of the olfactory system in the brain—the olfactory bulb (yellow). **(Right)** Close-up of the area linked from the arrow on the left. (1) OSNs expressing the same receptor bind only to certain odor molecules (enlarged example is shown for the "green" OSN). (2) OSNs expressing the same receptor (indicated by color) are spread throughout the nose epithelium. (3) OSNs expressing the same receptor send their axons to the same glomerulus. (4) Information travels from the olfactory bulb to other regions of the brain, responsible for either automatic or learned behavior (Image adapted from: The Nobel Prize).

The vast majority of human responses to odors are of the second type, learned rather than automatic. People impose learned meanings upon specific odors, and those personal meanings affect their responses to the odors. For example, someone who has a romantic first date that includes wine could learn to associate the smell of that wine with the feeling of love. Afterwards, when they smell wine, they feel "excitement butterflies" and want to reach out to their loved one.

This means that individuals may have unique behavioral responses to a specific odor, depending on their past experiences with that odor (Box 2). For some of us, smelling a rose is associated with a beautiful emotional experience (like love), whereas for others a rose might be associated with the color red, which might be associated with blood and fear. But if our brains respond differently to the same odor molecule, then do we actually experience the same smell when we smell a particular odor?

Box 2 | Olfaction and age.

Olfaction tends to weaken as we get older: our ability to detect faint smells or to differentiate between smells decreases. Several factors lead to this, including decreasing numbers of odorant receptors and decreased function of certain brain regions. Interestingly, recent studies have shown that losing your sense of smell is a precursor to Alzheimer's disease, and can help diagnose the disease more than 10 years before memory-related symptoms.

DOES MY ORANGE SMELL LIKE YOUR ORANGE?

Imagine that someone who has never seen nor smelled an orange asks you to describe what an orange smells like. Could you put it into words? Probably not—an orange just smells like an orange, and you learn to know and recognize that smell by association. When you see an orange, you smell it at the same time; then, even if you smell it in the dark, you know that it is an orange by associating the smell with the image of an orange, or with the name "orange." In this sense, olfaction is fundamentally different from vision. If someone has never seen an orange before and asks you what an orange looks like, you could say that it is round, has an orange color, is about the size of a baseball, has a smooth surface, etc. You can create an internal image of an object in your brain, but you cannot really create an internal image of an odor in your brain.

If we cannot describe odors using language, and cannot even build an internal image of odors, how do we know that you and I smell the same odor when we smell an orange? The answer is that we do not know! As we mentioned, it is very likely that, when you and I smell an orange for the first time, we are activating different patterns of neural activity in our individual brains—but both of us are associating that odor with the same fruit, because we are both seeing an orange. Apart from

associating the odor with the object "orange," are we actually having a similar experience of that odor? Maybe, but the odors we perceive could be *relative to everything else* we have smelled in our lives. For example, an orange smells more like a lemon than it smells like coffee, and that is true for all of us. This means that the similarities between the way individuals perceive odors might be purely *relative*—simply, that we all agree that a specific object smells more like some objects than others. This is a good reminder that our perception of odors is not absolute—unlike our perception of the color red, for example, which is based on the unchanging frequency of light.

THE RIDDLE OF PERCEPTION—AN OPEN QUESTION FOR FUTURE SCIENTISTS

There is one very important and complex question about perception that science has not yet answered. This question is valid for olfaction and all other senses and so is very fundamental—asking how *interpretation* of sensory information happens.

As we discussed, when the brain processes information from the senses, a specific pattern of electrical activity is generated in a particular set of neurons in the brain, representing the physical world in the brain through patterns of neural activity. These patterns of activity can vary in time (when they occur) and space (where in the brain they occur). So, the richness and variety of the whole physical world is somehow represented by the firing of specific groups of neurons at specific times and places in the brain.

For scientists, this implies two things: first, that physical reality is *abstracted* by the brain and, second, that the brain must *interpret* this abstract information to give it a meaning. For example, an object in the outside world, like an orange, is translated into a specific pattern of electrical activity that represents it in the brain, and then the brain "figures out" the meaning of this electrical activity (that there is an orange out there in the world) by interpreting and imposing meaning on this activity. But the brain must somehow associate this pattern of activity with a meaning like "this is the smell of an orange; it makes me feel good because it reminds me of the orchard I visited a few years ago…". Currently, this surprising "jump" from electrical activity in the brain to the interpretation and meaning we place on it is a true mystery—we do not yet understand how it happens. I believe that this "magical" step is the next big riddle that future neuroscientists should address. Perhaps you will be one of them?

RECOMMENDATIONS FOR YOUNG MINDS

In my view, there is a very simple way to choose what to do in life. It does not matter what you choose—whether it is science or

construction. But whatever it is, make sure to choose an area that you love, devote yourself to it, and work on it with intensity and passion. That is all! You must be passionate about what you are doing. This passion, fed by skill and knowledge, will drive you forward to excellence. So, you must discover your field of interest and then learn as much as you can about this field. When passion and knowledge are tied together, it often leads to creativity and happiness.

ADDITIONAL MATERIALS

1. Ted-Ed: How do we smell?

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CONFLICT OF INTEREST: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

YOUNG REVIEWER

PELEG, AGE: 10

I play tennis. I like to swim. I play the piano and basketball. I play a lot in my computer. I really like seeing movies and I like to play with my family and friends.

AUTHOR

RICHARD AXEL

Prof. Richard Axel is a molecular biologist in the Department of Neuroscience at Columbia University (New York, United States). He was born in 1946 in Brooklyn, New York, and being tall, he played basketball in his teens. He then went on to study literature at Columbia University, where he was exposed to the field of molecular biology and became a research assistant. Prof. Axel attended medical school at Johns Hopkins University (Maryland, United States), and became an MD in 1971. Later, he returned to Columbia University to pursue his passion for molecular biology and became a professor there in 1978. He developed gene-transfer techniques that enable the introduction of foreign DNA into any cell, permitting the production of a large number of clinically important proteins, and leading to the isolation of the gene for CD4, the cellular receptor for the AIDS virus, HIV. He then applied molecular biology to neuroscience, revealing over a thousand genes involved in perception of odors. During his scientific career, Prof. Axel won numerous awards and honors, among which are the Nobel Prize in Physiology or Medicine (2004), the Golden Plate Award from the American Academy of Achievement (2005), and the Double Helix Medal (2007). He has two sons, Adam and Jonathan, and is married to Prof. Cori Bargmann, a behavioral geneticist at Rockefeller University.
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DEFYING GRAVITY? ON THE MAGIC TRICKS OF SUPERFLUIDS

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YOUNG REVIEWERS:


RANJAI
AGE: 13


RANVIR
AGE: 13


YARDEN
AGE: 14

Physics is one of the best tools that we have for solving puzzles in our world. These puzzles can range from questions about common phenomena that you see around you—like the wind blowing through a tree's branches, to questions about very rare and mysterious phenomena that happen only under specific conditions. My journey with physics led me to one very special phenomenon, in which a normal fluid is cooled down and suddenly changes its fundamental properties to become what is called a superfluid. In this article, I will walk you through the fascinating world of superfluids, present some of the interesting things they do, and explain how these materials tie in with the discovery that led me to winning a Nobel Prize in Physics in 2016.

Professor Michael Kosterlitz won the Nobel Prize in Physics in 2016, jointly with professor David Thouless and professor Duncan Haldane, for theoretical discoveries of topological phase transitions and topological phases of matter.

TOPOLOGY: A MATHEMATICAL LANGUAGE OF SHAPES

TOPOLOGY

A branch of mathematics that deals with describing shapes of objects.

Topology is a mathematical field that discusses the shapes of things and divides objects into classes according to their shapes. One key parameter of any shape is the number of holes that is has in it (for a nice demonstration of topology with pastries, click here). So, for example, a sphere has no holes, whereas a doughnut has one hole (Figure 1A). Therefore, a sphere and a doughnut belong to two separate topological classes. This means that you cannot turn a sphere into a doughnut in a smooth way, because you would have to poke a hole in the sphere and therefore tear the material. In topology, you can distort the material as much as you want but you cannot poke holes or glue pieces together. Thus, you can distort a sphere into a soup bowl so that they are topologically the same. This may seem very strange but the ideas can be useful.

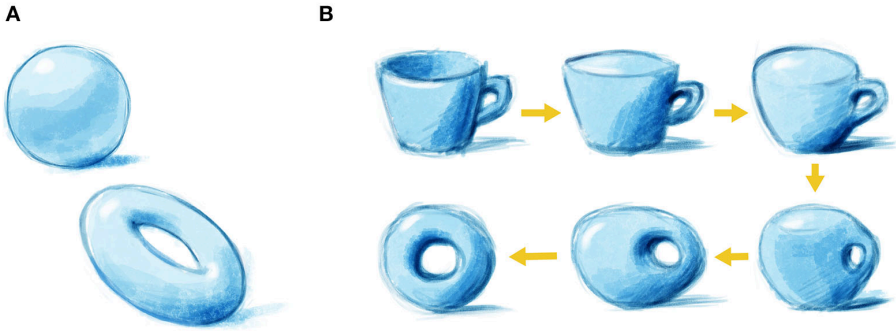

Figure 1

Topology and shapes. **(A)** A sphere has no holes, and a doughnut has one hole—therefore, they belong to two separate topological classes. **(B)** A doughnut and a coffee mug both have one hole and are therefore topologically equivalent. This means we can turn one into the other in a smooth way, without tearing the material or gluing the hole shut, both of which are forbidden in topology. If this happens in the physics, topological ideas are relevant and may be useful.

Now, how about a doughnut and a coffee mug with a handle? They might look different at first, but if you look closely, you will find that they both have one hole. In the eyes of topology, this means that a doughnut and a coffee mug are equivalent. Using the technical term, they have topological equivalence. Therefore, you can transform them into each other in a smooth and continuous way (Figure 1B). So, in this case, the number of holes is called a topological invariant—it stays the same, or is preserved (invariant) with respect to the donut and the coffee mug, even when these objects go through a manipulation that changes their outer appearance.

TOPOLOGICAL MATERIALS

Materials whose properties are described using topology.

The language of topology can be useful for describing the properties of certain materials, which are therefore called **topological materials**. In the next section, we will glimpse how topology helps us identify the differences between materials, and how it also helps us to explain certain unusual and exciting phenomena, like fluids that appear to defy gravity.

TOPOLOGICAL MATERIALS: FROM PLAIN TO EXOTIC

As we mentioned, topology is a convenient way to describe certain differences that we observe between materials. One family of materials that we all know very well is called insulators. An insulator is a material, such as rubber or plastic, that does not easily conduct electricity. This property is determined by the energy characteristics of the material, meaning the levels of energy that are created by the electrons present in that material. Usually, materials are characterized by the structure of their energy bands—the levels of energy that can be occupied by electrons inside that material. For an insulator, there is an "energy gap" between two energy bands that electrons cannot usually cross, so their movement is limited. For conductors, there is no energy gap, so electrons are free to move between energy levels within the material (to learn more about the energy bands of insulators and conductors, see here). The energy landscape of an insulating system can be classified according to topological invariants—topological properties that are preserved even when the system changes its state. This means that we can spot and classify specific insulators based on the topological properties of their energy states.

One specific group of insulators has attracted a lot of interest over the past 15 years or so. These materials are called **topological insulators** [1] because they can be classified and described using topological invariants. Topological insulators are special because they are both conducting and insulating at the same time. How can that be? In the middle part of these materials, which is called the bulk, electrons move in small, close loops, and do not travel around (Figure 2C). Therefore, the bulk of topological materials is insulating, much like plastic or rubber (Figure 2A). But, at the surface of these materials, special states form in which electrons can move along the edge (Figure 2C). This means that the surfaces of topological insulators are conducting, much like metals (Figure 2B). You might be thinking to yourself, "Ok, this is cool. But is it useful in any way?" This question occupies many physicists and computer engineers today. Let us have a peek at one possible answer.

TOPOLOGICAL INSULATORS

Materials that exhibit both insulating properties in their bulk and conducting properties on their surfaces.

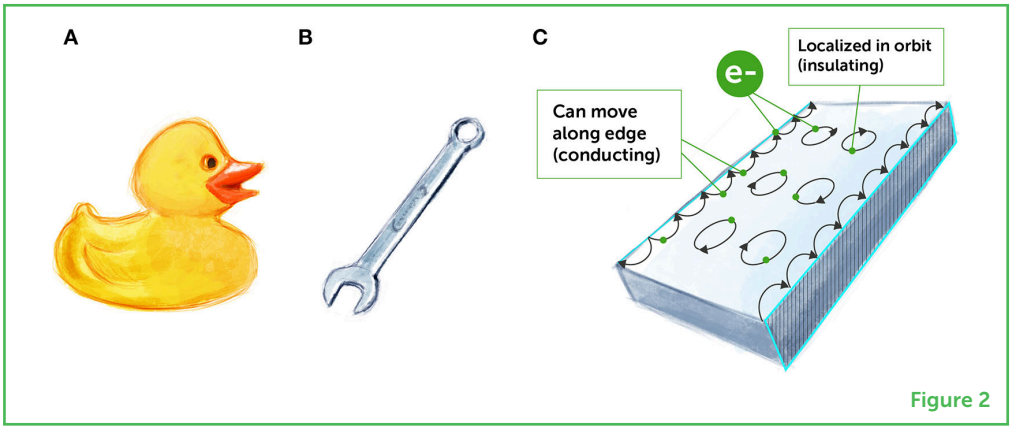

Figure 2

Insulators and conductors. **(A)** Rubber is an electrical insulator, so it does not conduct electricity easily. **(B)** Metals are electrical conductors, so electricity easily flows through them. **(C)** Topological insulators are unique materials in terms of their conducting properties. In their bulk, their electron move in closed circles ("localized") and they behave like insulators. On their surfaces, their electron move freely and they act like conductors ("hopping" on the edges).

ARE TOPOLOGICAL INSULATORS USEFUL?

It turns out that the conducting states formed on the surfaces of topological insulators are very stable—they are resilient to defects and perturbations of the material. A major reason that these states are resilient and stable is that their characteristics tend to rely on the entire system—not just on a small part of it or on a few atoms in a specific location. You can think about it like a collective phenomenon of the material as a whole. This means that even if something small—like a local imperfection in the material—is present, it still does not significantly affect the system as a whole, and therefore it does not change the topological state of the system [2].

How can this be useful? The robustness of a topological insulator could be useful for computer applications, as it creates stability. Stability is the most fundamental requirement of a computing element (an element in a computer that performs calculations), since we want these elements to give us consistent results with as few errors as possible. Therefore, topological insulators have an enormous potential for improving computing elements in the future. However, there are major technical challenges involved in this process, so we are quite a long way from using topological insulators in computers—but it might be possible in the future.

I will now take you one step deeper into the enchanted world of topological materials, and present to you my contribution to an explanation of one of the most exotic phenomena in physics, called superfluidity.

A FLYING FLUID: THE STORY OF COLD HELIUM

SUPERFLUIDS

Fluids that flow without dissipation.

Did you know that there are fluids that can defy gravity and climb glass walls? These fluids are called **superfluids**, and they behave very strangely at extremely low temperatures (the temperature at which normal helium becomes superfluid helium is called the Lambda Transition temperature, which is 2.17 K at a pressure of one atmosphere). Due to their exotic nature, superfluids are of great interest to scientists. They allow us to study exceptional physical phenomena that we do not encounter in daily life. The most common example of a superfluid is liquid helium, ^{4}He. You may be familiar with helium as the gas that fills up balloons and makes people's voices sound funny when they inhale it, but it can exist as a liquid, too at extremely low temperatures close to absolute zero or −273° Celsius.

In 1972, three physicists published a brilliant experiment dealing with thin films of helium [3]. They took a quartz crystal in an atmosphere of Helium gas. By adjusting the pressure of this gas they changed the total amount of Helium adsorbed on the surface of the quartz

crystal which would form a layer two or three atoms thick. The quartz crystal has its natural resonant vibration frequency which depends on the total mass of the vibrating crystal. When a thin layer of Helium atoms is stuck to the crystal surface, one naturally expects that these atoms will move with the crystal surface so that their only effect will be to increase the mass of the vibrating body and slightly decrease its resonant frequency. When the physicists looked at the oscillation frequency of the helium covered crystal at low pressure and very low coverage they measured the expected decrease in resonant frequency. However, when the gas pressure and helium coverage was increased, the resonant frequency ceased to follow the expected decrease (Figure 3A) and remained different from the expected value as if the extra Helium was decoupled from the motion of the crystal.

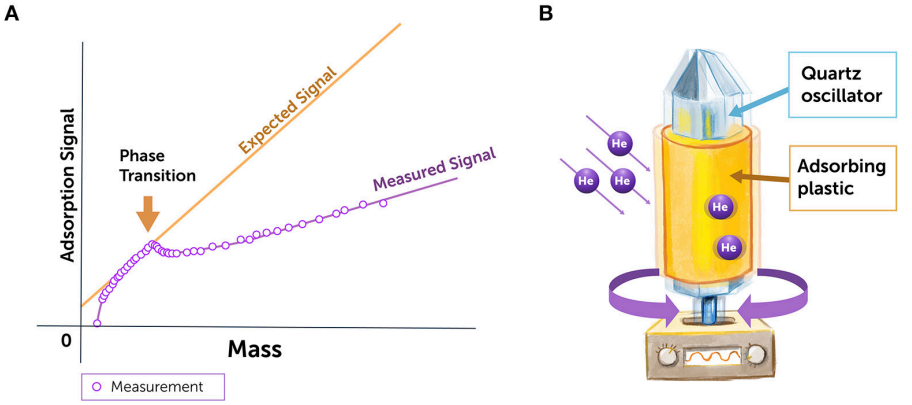

Figure 3

A later experiment took a strip of plastic and wrapped it around an oscillating rod made of quartz (Figure 3B). When you vibrate a crystal-like quartz, it has a natural frequency at which it moves, called its oscillation frequency. So, the first thing the physicists did was to measure the natural **oscillation frequency** of the rod with the roll of plastic around it. Then they increased the pressure of the Helium gas surrounding the oscillating rod and measured the oscillation frequency of the quartz rod again. When helium atoms meet the surface of the adsorbing plastic, they normally adsorb (lock onto) it, creating a thin film around the rod and increasing its mass. As a result, there is a slight reduction in the natural frequency of oscillation, because heavier crystals oscillate at a lower frequency (move more slowly) than light ones.

The easiest way to interpret this result was that some of the helium film was no longer sticking to the oscillator once it became a superfluid. The difference between normal and superfluid helium has to do with the way they flow. Normal helium gets attached to whatever it tries to flows on, due to a property called **dissipation**. Superfluid helium, on the other hand, flows freely with no dissipation, and therefore seems

Figure 3

Superfluid helium experiment. **(A)** The measured oscillation frequency of the quartz crystal differed from its expected oscillation frequency when a few thin layers of cold helium were adsorbed. The adsorption signal represents the oscillation frequency, and the mass represents the amount of Helium adsorbed on the crystal surface. Helium in its normal state increases the oscillating mass, and decreases its oscillation frequency. But if some of the helium becomes superfluid, it does not increase the oscillator's mass the same way, so the oscillation frequency is reduced less than it would be with normal helium (Adapted from Chester et al. [3]). **(B)** In a later experiment [4] which involved much lower frequency oscillations, a plastic Mylar sheet was wrapped round a quartz torsional oscillator rod, ^{4}He gas adsorbed on the Mylar sheet and the resonant frequency and dissipation measured. The principle of this experiment was the same but much more accurate and detailed results were obtained.

OSCILLATION FREQUENCY

The frequency at which an object, called an oscillator, vibrates.

DISSIPATION

Loss of energy that cannot be reversed without adding external energy.

to "fly," or hover, above the material it flows on! You can watch some interesting demonstrations with superfluid helium here and here.

This was a pioneering experiment, showing that thin films of helium become superfluid at low temperatures. The problem was, at that time, there was no theory that could explain this change in behavior in thin-film helium, which is called a **phase transition**, from normal to superfluid. In fact, a common theory at the time even predicted that such a phase transition should *not* occur under these conditions and that superfluidity was impossible in a two-dimensional film. In fact, this experiment contradicted a widely accepted tenet of the nature of the low temperature phase of any system. There was a rigorous mathematical theorem which stated that the low temperature phase of the system could not have long range order at any temperature which, according to widely accepted wisdom, meant that there could be no superfluidity in our two-dimensional film. Now there was a major conflict between a rigorous theory which seemed to say that superfluidity in a thin film was impossible while experimental observation said the exact opposite. Clearly, either experiment or theory must be wrong or misinterpreted because experiment showed unambiguously that a thin film of ^{4}He is superfluid and has a phase transition. This is where my then supervisor, Prof. David Thouless, and I came into the picture: we developed a new theory that explains the phase transition of thin films of helium from superfluid to normal fluid and resolved the contradiction between experiment and theory.

PHASE TRANSITION

An abrupt switch between two states of a system, in which the properties of the system change. For example, the transition of liquid water into solid ice.

VORTICES: "BEHIND THE SCENES" OF SUPERFLUID HELIUM

As I mentioned, liquid helium has two phases. In its normal phase, it flows with dissipation, meaning that it interacts with the surface it meets, exchanges energy with that surface, and gets stuck to it. In its superfluid phase, liquid helium flows freely with no dissipation, and acts like it is hovering over the surface it meets. To understand the phase transition between normal and superfluid helium, we had to figure out the mechanism responsible for dissipation. As it turns out, the answer lies in peculiar configurations called vortices (Figure 4), which for quantum mechanical reasons, are the *only* excitations which can dissipate the flow of a superfluid and explains why the very messy surface of Mylar on which the helium is flowing has no effect on the theory or on the experiment. The only effect of the substrate is on the friction between it and the vortices but it has no effect on the superfluid. For simplicity, you can think of a vortex as a fluid circling around, like when you pull the plug out of a bath and the water swirls around as it goes down the drain. To understand this you will have to learn a lot of physics so just remember that these vortices in the superfluid are the only excitations it is necessary to think about and that, in two dimensions, these vortices interact with each other exactly like little electrically charged particles and these

particles can appear and disappear as they like but the total charge of the system must remain zero. These vortices form in neutral pairs with one vortex with counterclockwise and the other with clockwise rotation at very low temperatures, but at higher temperatures these pairs unbind into two free vortices that drift to the edges of the fluid and then vanish there thus reducing the uniform superfluid flow by a small amount (Figure 4B). This is the dissipation seen in the flow of the normal fluid. Since the two states of liquid helium's flow can be defined as two topological states, liquid helium is also considered to be a topological material—much like the topological insulators we discussed previously (To learn more about topological materials and vortices, see here).

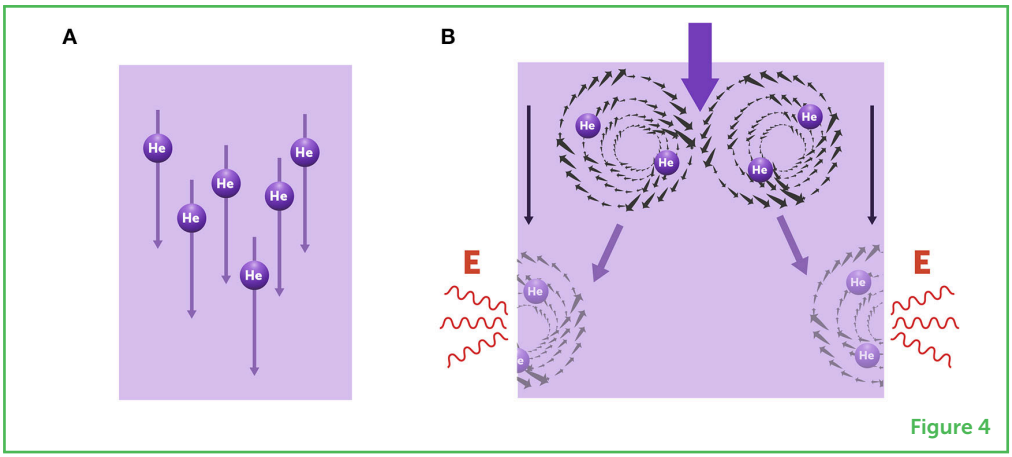

Figure 4

Phase transition mechanism in liquid helium. **(A)** In superfluid helium there are no vortices, so the fluid flows freely without dissipation. **(B)** In normal helium, pairs of vortices are formed (top) and drift to opposite edges of the fluid, where they vanish and release energy (bottom). This process creates dissipation and results in a slower flow with more dissipation.

After discovering that the essential physics of the superfluid system involves the interactions of vortices, we developed a mathematical model to explain the phase transition of liquid helium, and other phase transitions in similar systems, with very high precision [4–7]. This was an important development that took us one big step forward in understanding some of the amazing characteristics of topological materials.

I would like to finish with a few personal notes for young readers about my love for mathematics and physics, and my recommendations for how to live a happy life.

RECOMMENDATIONS FOR YOUNG MINDS

Lovely Symbols: The Beauty of Mathematics and Physics

When I was introduced to algebra in school, I thought to myself "Wow, this is a great way of doing things—much better than arithmetic!," because algebra allowed me to do lots of mathematical things I could not easily do before. It was like switching on a bright light that suddenly made all sorts of things possible! I immediately loved symbols and the fact that mathematical symbols eliminated a lot of confusion and kept things very simple. I know that this is not the case for everyone because

it depends on the way each individual thinks. But for me, working with symbols and equations is fun and exciting, and I enjoy it up to this day. In a way, for me, doing physics is similar to rock climbing (another passion of mine)—you are out in the unknown, on your own, completely responsible for your own actions, trying to navigate your way forward (Figure 5). The advantage with physics is that the penalty for making a mistake is less serious than with rock climbing!

Figure 5

Recommendations for Young Minds.
(A) Working with symbols and equations is similar to rock climbing. You are out exploring the unknown, completely responsible for your own actions, while trying to navigate your way. I find it very exciting.

Figure 5

How to Choose Your Profession

You should do what you love and what you are good at. It is important to be good at whatever you do, and if you are good at it, you are probably going to enjoy it. I also think you should have fun with what you are doing, because if you do not have fun and enjoy your work, it is not worth doing. So, that is a piece of advice I can offer to young readers—have fun in life, because you only have one life, and if you do not have fun, life is not worth living.

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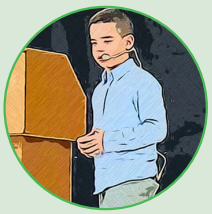
YOUNG REVIEWERS

RANJAI, AGE: 13

My name is Ranjai and I am super interested in chemistry and astronomy. In my free time I read books, listen to songs (almost all the time!). My favorite subjects are maths and science. I play tennis, table tennis, and sometimes cricket and football. I also watch Naruto on TV.

RANVIR, AGE: 13

My name is Ranvir and I am in class eight. I like learning about reptiles especially snakes and I am interested in herpetology. When I was younger, I started catching skinks, and found them fascinating. I like to get my friends interested in going for hikes and finding insects, worms, we even found a Microhylid frog, and a snake, a *Lycodon capucinus*! Besides herpetology, I also like doing origami, not modular though. And these days I read Greek mythology.



YARDEN, AGE: 14

I was born and raised in Israel. My main hobbis are KAMI (israely martial art) and rhetoric. I have a brown belt in KAMI and I won second place in the Israeli "young speaker" competition. I am also in the scouts and I like to sing.

AUTHOR

MICHAEL KOSTERLITZ

Prof. Michael Kosterlitz is a British-American physicist, born to a family of Jewish immigrants in Aberdeen, Scotland. His father, Hans Kosterlitz, was a neuropharmacologist known as one of the key discoverers of endorphins. Prof. Kosterlitz received his Bachelor of Arts degree, subsequently converted to a M.A. degree, at Gonville and Caius College, Cambridge, England. In 1969, he earned a Ph.D. in physics from the University of Oxford and it was there that he met his wife Berit. After his graduation, Prof. Kosterlitz had a fellowship at the Istituto di Fisica Teorica in Turin, Italy, and was a research fellow at the University of Birmingham, England from 1970 to 1973. There, he studied phase transitions in two-dimensional materials, together with Prof. Thouless (with whom he shared the Nobel Prize in Physics in 2016). After a few postdoctoral positions, including at the University of Birmingham, and Cornell University (USA), he was appointed to the faculty of the University of Birmingham in 1974. In 1982, Prof. Kosterlitz became a professor of physics at Brown University, Rhode Island (USA), where he currently works. He won several prizes, including the Maxwell Medal and Prize in 1981, the Lars Onsager Prize in theoretical statistical physics in 2000, and Nobel Prize in Physics in 2016, for his work on the topological phase transition of liquid helium. Kosterlitz was a pioneer in Alpine climbing in the 1960s, known for establishing routes in the UK, Italian Alps, and Yosemite. There is route bearing his name in the Orco Valley of the Italian Alps, named Fessura Kosterlitz. Michael and Berit have three children, Karin, Jonathan, and Elisabeth. *j_kosterlitz@brown.edu

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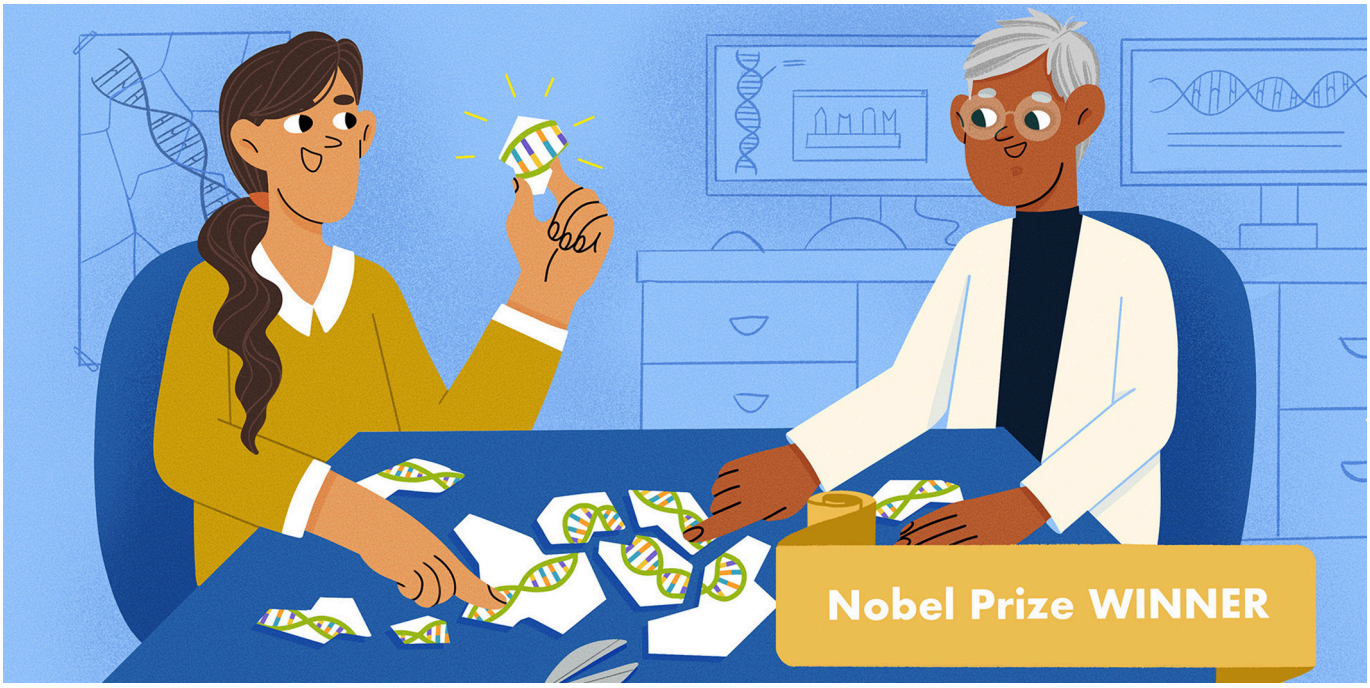

RNA SPLICING—CUTTING AND PASTING GENES

Phillip A. Sharp [1,2*]

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YOUNG REVIEWERS:


ANASTASIA
AGE: 14


KENZO
AGE: 10


MAXIME
AGE: 10


NOURA
AGE: 15


SAIF
AGE: 15


YOUNIS
AGE: 15

Science in general, and specifically the science of life, offers an intriguing path to walk along. As you deepen your understanding of a particular topic, you become aware of things you did not see at all when you started. Sometimes, this new seeing even drives you to reconsider and redefine very basic concepts that you learned along the way. This is exactly what happened after we discovered a process called RNA splicing. In RNA splicing, pieces of genetic instructions are cut and pasted together to form the final instructions for producing proteins. The discovery of RNA splicing has driven us to rethink what we previously believed about genes, which are the most fundamental units of information in biology. In this article, I will tell you what we discovered about RNA splicing, how it influenced our ideas about genes, and how we now use this knowledge to significantly improve people's lives.

Prof. Phillip Sharp won the Nobel Prize in Physiology or Medicine in 1993, jointly with Prof. Richard Roberts, for their discoveries of split genes.

FROM GENES TO PROTEINS—HOW DNA DIRECTS CELL FUNCTIONS

One of the most fundamental processes of life involves reading the genetic information, or "instructions" stored in cells in the form of **DNA**, and turning those instructions into the structures and functions of a living organism (Figure 1). The instructions within the DNA code for the production of **proteins**—tiny biological machines that perform many crucial functions in the body. The creation of proteins from DNA requires a middle step, called **transcription**. In transcription, a set of instructions from the DNA sequence (called a **gene**) is made into a movable copy that can travel to the protein-producing factory in the cell. This copy of the DNA that drives the creation of proteins is called **messenger RNA (mRNA)**. **Translation** is the name of the process by which proteins are produced based on instructions in mRNA.

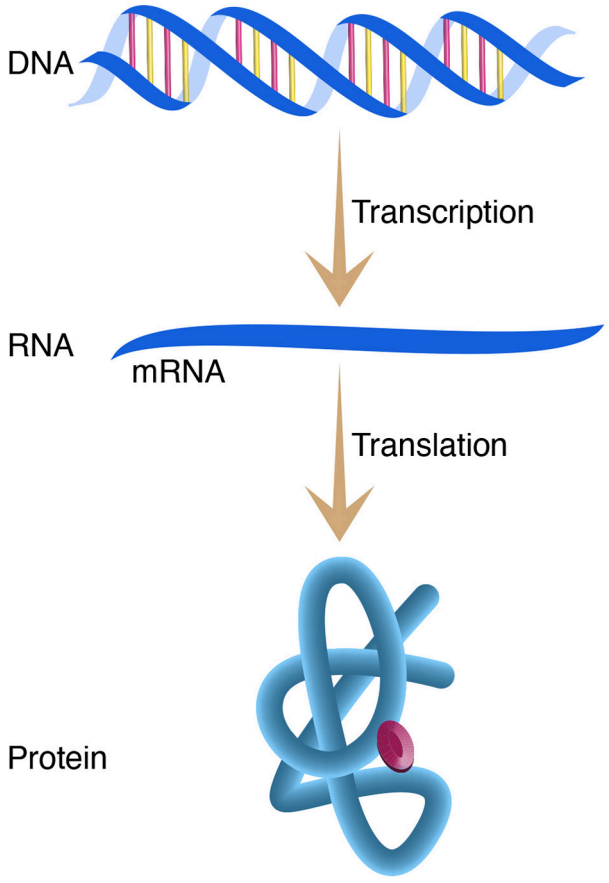

Figure 1

Over the course of evolution, the process of preparing mRNA from DNA became more complex. A completely new intermediate stage emerged between transcription and translation, called *RNA splicing*. In this stage, separate pieces of an mRNA are cut and pasted together to produce the final version of the mRNA. In the next sections, we will explain RNA splicing, how we discovered it, what are its

DNA

Genetic information stored in all cells.

PROTEINS

Tiny biological machines that participate in many crucial functions in the body, such as muscle movement, digestion, and immunity.

TRANSCRIPTION

The process by which DNA is copied into mRNA.

Figure 1

DNA contains the information to make proteins. Living cells use the genetic information in DNA to produce proteins, through two main steps. First, the information in the DNA is copied in a process called transcription, to create a movable mRNA copy of the instructions for a particular protein. The mRNA then travels to the protein-production factory of the cell, where the specific protein is made in a process called translation.

GENE

A piece, or several pieces, of DNA that contain instructions for the production of proteins.

MESSENGER RNA (mRNA)

RNA that is used to produce proteins.

TRANSLATION

The process by which a protein is produced based on instructions from mRNA.

benefits, and how this knowledge can be used to help people with certain diseases.

FOR RNA SPLICING, NUCLEI MATTER!

PROKARYOTE

An organism, such as bacteria, whose cells do not have nuclei.

EUKARYOTE

An organism, such as humans and other mammals, whose cells have nuclei.

The most ancient species that developed on earth had only one cell and no nucleus [1], so its genetic material was not separated by a membrane from the rest of the cell's content. Cells developed nuclei only after about 1–1.5 billion years of evolution. Nucleus-free organisms are called **prokaryotes**, and organisms that have nuclei in their cells are called **eukaryotes**. Bacteria are a well-known example of prokaryotes. In contrast, all mammals, including humans, are eukaryotes.

The process of protein production was first discovered in bacteria. Researchers found that an mRNA copy is made from a continuous piece of DNA (a gene) and is then translated into a specific protein (Figure 2, left) [2]. At that time, most researchers believed that this process was similar in eukaryotic cells. But, some years later, we discovered that an additional step is added before translation and after transcription in eukaryotic cells [3]. In this step, the mRNA produced through transcription is spliced (cut and pasted) to produce the final mRNA that participates in translation. The initial DNA copy is called pre-mRNA, and the final version, after RNA splicing, is called mature mRNA (Figure 2, right).

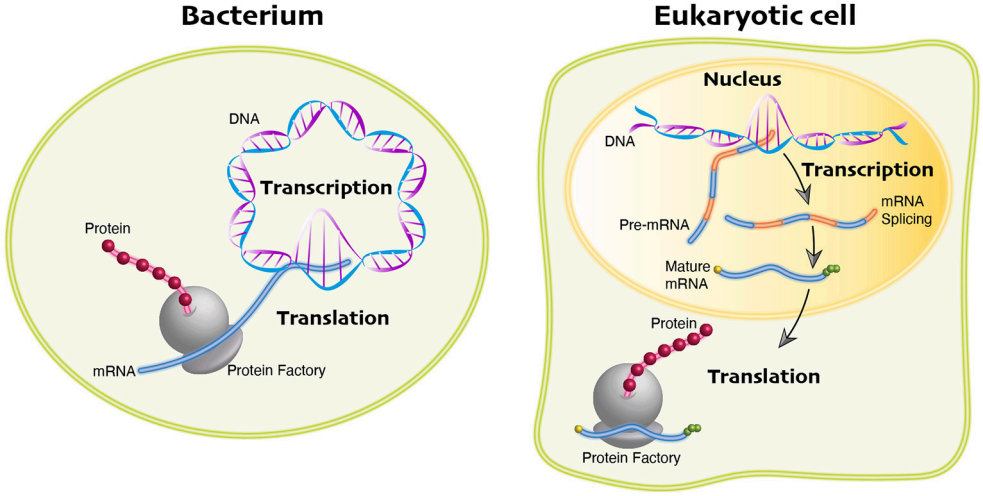

Figure 2

Figure 2

Protein production in prokaryotic and eukaryotic cells. **(Left)** In prokaryotic cells like bacteria, which do not have nuclei, mRNA is produced from DNA by transcription and is then directly translated into a specific protein. **(Right)** In eukaryotic cells, a pre-mRNA is made by transcription in the cell's nucleus. Then, the pre-mRNA goes through an additional processing stage called RNA splicing. Only then does the mRNA leave the nucleus and travel to the protein-production factory, where translation occurs (Image adapted from Khan Academy).

SPLICING—CUTTING AND PASTING RNA

You can think of the RNA splicing process, by which pre-mRNA becomes mature mRNA, like editing a book. Imagine you have a book in which there are stretches of a few words that make sense together,

EXON

A "sense" gene segment that is used in the production of a protein.

INTRON

A "nonsense" gene segment that is removed from pre-mRNA to produce mature mRNA.

ALTERNATIVE SPLICING

Using different combinations of exons to create multiple proteins from the same gene.

then a lot of gibberish (non-sense) words, and then a few more words that made sense together. To make the book readable, you must edit out the gibberish and join the pieces that make sense. The joined pieces create a sentence that has a function, or makes sense, to the reader. Returning to mRNA, it turns out that pre-mRNA is created from both sense and non-sense DNA sequences. The sense sequences are called **exons**, and the non-sense sequences are called **introns**. When a pre-mRNA molecule is spliced, the sense pieces are brought together and the non-sense pieces are removed and destroyed. This "cutting-and-pasting" process produces the mature mRNA that is used to produce proteins.

But why do eukaryotes have these non-sense introns in the DNA in the first place? Well, scientists are also wondering about that—we do not have a definite answer yet. We know that humans have about 23,000 genes, and almost all of them are made of multiple exons that are spliced together in different combinations in different cells, or at different times in some cells. So this means that multiple proteins (and therefore multiple functions) can be created from the same gene, by selecting which exons are joined together. This is called **alternative splicing** (Figure 3). Some scientists propose that alternative splicing is what allowed the evolution of complex organisms like humans. Alternative splicing allows the DNA to be used efficiently—organisms that use alternative splicing can make complex proteins and perform complex functions using fewer genes.

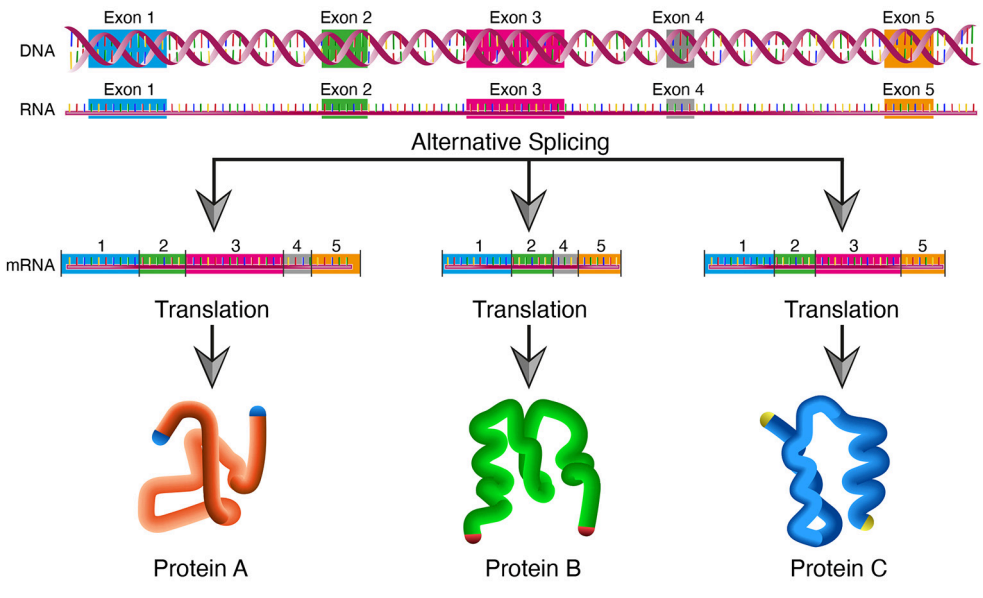

Figure 3

Alternative splicing. In alternative splicing, exons are joined together in different combinations, creating different mRNAs, and therefore different proteins with complex functions, from the same gene. This could be the evolutionary advantage that allowed complex organisms like humans to evolve (Image adapted from Wikipedia).

VIRUSES HELPED US DISCOVER RNA SPLICING

To study mRNA splicing in our lab, we used a virus called adenovirus type 2 [3]. This virus has a relatively short DNA, and it uses animal

cells to reproduce its DNA very rapidly. These two facts mean that this adenovirus is relatively easy to use in scientific studies, since it is a simple system that naturally produces many copies of itself.

After choosing adenovirus type 2 as our system of study, we wanted to compare its DNA to its mRNA molecules. If an mRNA exactly matches a specific piece of DNA, that suggests that the mRNA is copied directly from the DNA, without splicing—the way it happens in bacteria. But if the mRNA does *not* match the specific DNA piece, that suggests that splicing is happening to create the mature mRNA.

For our DNA-mRNA comparison, we chose the most common mRNA found in adenovirus two, which codes for a protein called a hexon. When we compared this mRNA with the relevant part of the DNA, we found two areas that did not match between the mRNA and the DNA. One area is called the 3′ ("three prime") end of the mRNA strand (Figure 4, green circle), and we already knew that this area is a special "tail" that is added to the mRNA to protect it as it travels through the cell. The other non-matching area was at the other end of the mRNA strand, called the 5′ ("five prime") end (Figure 4, blue circle). This surprised us because the 5′ end of the mRNA molecule contained a long piece of mRNA that did not match the specific section of DNA, and we did not know where it came from.

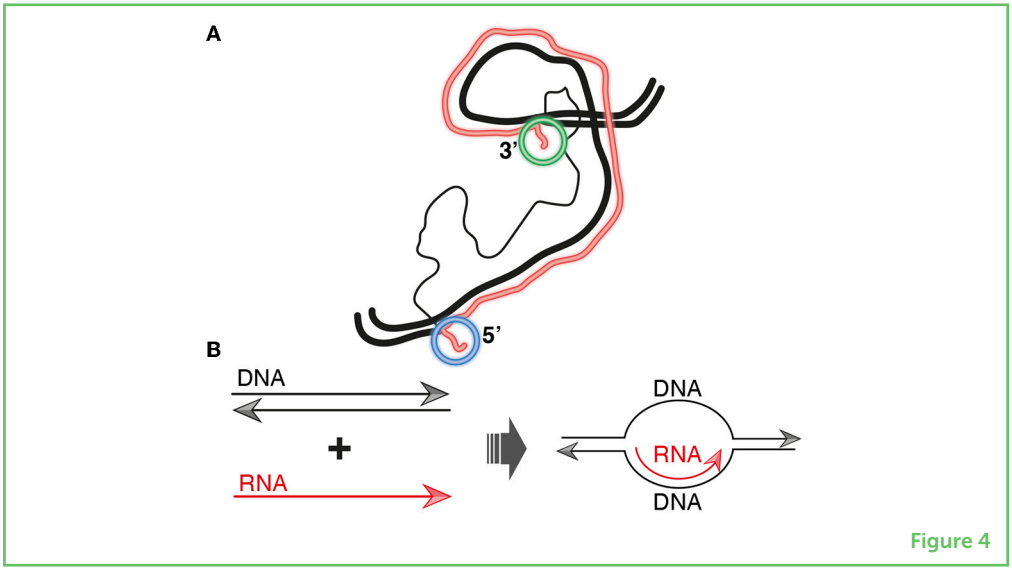

Figure 4

Figure 4

Comparing adenovirus DNA and mRNA helped us discover RNA splicing. **(A)** In our study, we used a virus called adenovirus to look for mRNA splicing in eukaryotic cells. When we compared the relevant segment of DNA (thick black line; thin black line is the other DNA strand that separated) with the mRNA (red line) that codes for the hexon protein, we discovered two non-matching areas: the 3′ and 5′ ends of the mRNA (green and blue circles). The finding that a long piece at the 5′ end of the mRNA did not bind to the DNA was surprising, and it suggested that another process was involved in making mRNA. **(B)** A schematic figure showing how a strand of RNA binds to a strand of DNA, when the two strands of DNA are separated in experiments [Image Adapted from Berk [4]].

To solve the riddle, we had to find out where the non-matching area at the 5′ end of the mRNA came from. After many discussions, we came up with the idea that the non-matched piece could have come from a different place in the DNA. This would mean that there is one continuous piece of DNA that encodes *most* of the hexon mRNA, and a different piece *somewhere else* in the DNA that encodes the 5′ end. To check this idea, we compared the hexon mRNA to another section of DNA, located near the section that matched most of the hexon mRNA in our first experiment. What we found was absolutely amazing: the

5′ end of the hexon mRNA was attached to the DNA in four *separate segments*, and between those segments there were three DNA loops (Figure 5). This meant that the 5′ end was spliced from four separate exons, which were separated by three introns.

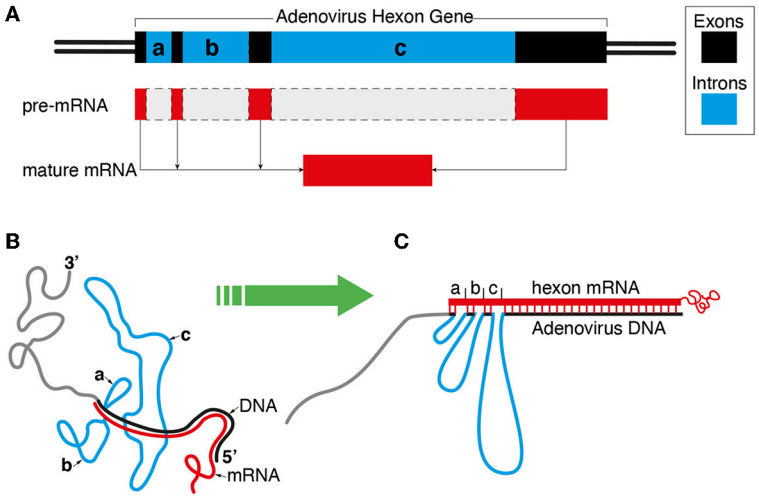

Figure 5

Figure 5

Splicing of hexon mRNA. **(A)** Part of the hexon gene (DNA) contains four exons and three introns, from which the 5′ end of the hexon mRNA is spliced. The pre-mRNA is a direct copy of the DNA, but the mature mRNA has been spliced to remove introns. **(B)** In our experiment, some parts of the adenovirus DNA were attached to the 5′ end of the hexon mRNA (red), while other parts of the DNA were not attached and formed three loops called a, b, and c. The attached parts are exons and the loops are introns. **(C)** The complete spliced hexon mRNA bound to the adenovirus DNA [Image credits: **(A,B)** adapted from Berget et al. [3]; **(C)** Phillip A. Sharp].

This was a truly novel discovery, since no one else had ever suggested that mRNA could be cut and pasted from separate DNA segments. This discovery of RNA splicing changed the way we think about genes!

RETHINKING THE MEANING OF "GENE"

Before we knew about RNA splicing, we thought of a gene as a continuous piece of DNA that encodes a specific protein. But the discovery of RNA splicing taught us that many genes are split genes, meaning that they are combined from different, non-continuous pieces of DNA (exons). Moreover, we know that these pieces can be "mixed and matched" to create not only one, but many different proteins. There are even examples of one specific group of exons coding for tens of thousands of different proteins [5]!

So, if a gene is not one continuous DNA sequence that encodes one protein, what exactly *is* a gene? We still do not know the full answer. As often happens in science, we are faced with incredible complexity, and perhaps we will never have all the answers. But, nevertheless, we always try to expand our knowledge and make the most out of the knowledge that we already have. As you will see in the next section, our knowledge of RNA splicing is being used to help improve the lives of sick people, including children your age.

RNA SPLICING FOR THE GOOD OF HUMANITY

RNA splicing is a fundamental process for all living things, including humans. RNA splicing allows an organism to turn certain genes "on" or "off", and it therefore helps organisms to carry out many of the complex processes needed for life. As with every important biological process, when something goes wrong, diseases can result. To treat these diseases, we must understand how the damaged biological process works, and then figure out how to fix it.

Some very exciting medical developments are based on RNA splicing. Only a couple of years ago, for the first time in history, we were able to successfully treat children who had a genetic disease called spinal muscular atrophy. This disease is caused by a mutation in the DNA that inactivates the RNA splicing of a particular gene such that an important exon is left out. This mutation causes patients to slowly lose cells in their spinal cord that control their muscles. As the spinal cells and muscles deteriorate, there is progressive loss of muscle function creating severe disabilities and reducing quality of life. Before the discovery of RNA splicing, spinal muscular atrophy was a deadly disease. Now, with our knowledge of RNA splicing, we can manipulate the splicing process so that the missing exon is included in the mature mRNA. This allows a properly functioning protein to be produced and enables individuals with spinal muscular atrophy to develop more normally, and to lead reasonably normal lives.

This is only one example of how our knowledge of RNA splicing can help to improve people's lives. I have also started two companies that are using knowledge of RNA splicing to develop important medical applications. These companies are called Biogen and Alnylam Pharmaceuticals, and you can learn more about them by following the links.

It has been extremely exciting to discover RNA splicing, to study the whole splicing process, to think about what it means and how it could be used, and then, 30–40 years later, to see the science turned into a treatment that improves the lives of young children. This is common in science, and it is one of the things that makes doing science, particularly biomedical science, so fulfilling. Not only are scientists discovering deep secrets about biological systems, but occasionally those insights lead to ways of helping others. One of the most gratifying things a person can do in life is to help others, including helping them to understand more about the world, who they are, and their relationship to others. Such understanding is what makes humans unique and interesting.

RECOMMENDATIONS FOR YOUNG MINDS

I want share with you what I learned as I was growing up, going to school, and figuring out what I wanted to do for a career. I found that, if I followed my interests and passions, I was motivated to learn as much as I could about those topics, which allowed me to make important contributions to society. If you try to be too practical in life and do not spend some time dreaming of the future, you might not see enough of the future to fulfill your dreams. However, if you are too day-dreamy, you may never bring yourself to solve the problems you will face as you pursue your goals. So, follow your curiosity and, if it leads you to something you are passionate about, give yourself to it. You do not know what the world will be like 20 or 30 years from now; just do what motivates you to learn and take the time to have fun while you are doing it.

It is also good to remember that life is not a straight path—it often does not advance in predictable steps, but rather in many possible branches. At certain times in your life, you will come to points when you will need to make decisions. One decision will take you one way, and another decision will take you another way. These paths could be quite different from one another, particularly when making decisions that have very long implications, but that is OK. So, when you come to one of those forks in the road, take one! And remember to enjoy it and follow your passion while you are doing so.

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ADDITIONAL MATERIALS

RNA Splicing: What is a Gene?—Phillip A. Sharp.

Nobel Lecture: Split Genes and RNA Splicing—Phillip A. Sharp.

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YOUNG REVIEWERS

ANASTASIA, AGE: 14
I am Anastasia, a year 10 student captivated by science! I am very passionate about learning and discovering new opportunities. My dream is to study medicine, as I am very interested in how our body works and how it can be affected. Outside of my studies, I love painting, drawing, and crafting, as well as many other extracurricular clubs. But most of all, I love cooking deserts (I have a sweet tooth)!

KENZO, AGE: 10
Hi I am Kenzo, I am 10 years old, always excited and super friendly. I have a lot of friends and make new friends easily. I like listening to songs and playing video games. I also really like fighting and self defense. My favorite hobby is parkour. At school, I enjoy sports, arts, math, and the breaks. I often express my thoughts and talk while the teacher explains so time goes faster ☺. I love reading comics.

MAXIME, AGE: 10

My name is Maxime, I love sports, music, and science, especially space. I am very inquisitive and enjoy problem-solving situations. I just got into coding and I am loving it.

NOURA, AGE: 15

I am Noura, I have many interests such as building robots and playing the piano, but science has a special place in my heart and I have always been looking for the latest scientific research and projects.

SAIF, AGE: 15

Hi! My name is Saif. I am 15 years old. I have always been passionate about science, particularly biology and chemistry. I love to read science books and biographies about fascinating people such as Steve Jobs. I also participate in programs and competitions that enhance and improve my passion for science, such as wining the best group project at the National Science Fair in 2020. I also enjoy doing experiments with my science teacher.

YOUNIS, AGE: 15

Hi! My name is Younis, and I am 15 years old. I have always been attracted to science subjects as they are very fascinating, especially environmental management, geography, geology, and space. And through Frontiers for Young Minds I hope to learn more about the world we live in.

AUTHORS

PHILLIP A. SHARP

Prof. Phillip Allen Sharp an American professor of molecular biology, Prof. Sharp is a member of the Department of Biology and the Koch Institute for Integrative Cancer Research at the Massachusetts Institute of Technology (MIT), Massachusetts, United States. Prof. Sharp studied chemistry and mathematics at Union College and completed his Ph.D. in chemistry at the University of Illinois at Urbana-Champaign in 1969. After his Ph.D., Prof. Sharp did his postdoctoral training at the California Institute of Technology, and then studied gene expression in human cells at Cold Spring Harbor Laboratory. In 1974, Prof. Sharp went to MIT, where he joined the Center for Cancer Research (now the Koch Institute for Integrative Cancer Research) and conducted experiments that led to the discovery of RNA splicing. During his years at MIT, Prof. Sharp was the director of the Center for Cancer Research (1985–1991), served as head of the biology department from (1991 to 1999), and founded and directed the McGovern Institute for Brain Research (2000–2004). Prof. Sharp won numerous awards and prizes, including the NAS Award in Molecular Biology (1980), the Louisa Gross Horwitz Prize (1998), the Dickson Prize (1991), the Nobel Prize in Physiology or Medicine (1993), and the National Medal of Science (2004). Prof. Sharp started two successful biomedical companies with knowledge of RNA splicing for medical applications. *kids@frontiersin.org

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TURNING RNA INTO DNA: THE DISCOVERY THAT REVOLUTIONIZED BIOLOGY AND BIOTECHNOLOGY

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YOUNG REVIEWERS:


KRISH
AGE: 13


MEHRANEH
AGE: 15


MOHAMMAD
AGE: 12

Viruses are unique biological systems. They are parasites that use the cells of other organisms, called hosts, to multiply, often causing disease to the host. One of the most interesting features of viruses is that some of them contain RNA as their genetic material—all other known organisms use DNA. In the beginning of my career I worked on RNA viruses, trying to understand their basic behaviors and processes. When I focused on RNA viruses that are known to cause cancer, I discovered that they can make DNA from their RNA genomes, in a process called reverse transcription. That was a great discovery that changed the prevailing way of thinking and had profound implications in the fields of biology, medicine, and biotechnology. In this article, I will tell you about viruses, walk you through the discovery of reverse transcription, and describe some major implications of our findings in terms of improving or even saving many human lives.

Professor David Baltimore won the Nobel Prize in Physiology or Medicine in 1975, jointly with Prof. Renato Dulbecco and

Prof. Howard M. Temin, for their discoveries concerning the interaction between tumor viruses and the genetic material of the cell.

THE FASCINATING WORLD OF VIRUSES

VIRUS

A tiny particle that infects living cells and uses the cells' machinery to make more viruses. Viruses can infect all life forms.

Viruses are tiny particles that infect cells and sometimes cause disease. Viruses exist in uncountable numbers, and every living animal and even every bacterium has its own set of viruses. More than a million different viruses have been identified! You are probably familiar with some viruses, such as the influenza viruses that cause flu; SARS-CoV-2, which causes COVID-19; or varicella-zoster virus, which causes chickenpox. Maybe you have heard of the human immunodeficiency virus (HIV), which causes AIDS, or the Ebola virus. Viruses vary dramatically in their structures (Figure 1), in how many species they can infect (whether they infect only a particular species or several species), and how dangerous they are to the organisms they infect, which are called the hosts.

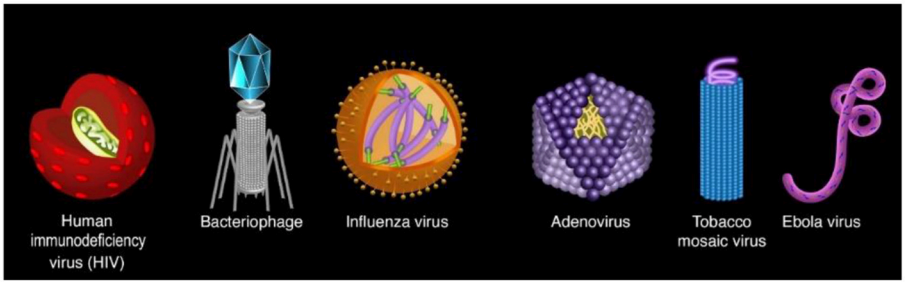

Figure 1

The variety of viruses. Viruses come in many different shapes. Every animal and bacterium has its own set of viruses (Image adapted from here).

Viruses multiply by penetrating a host cell and inserting their genetic material, which the host then treats as its own. This way, viruses "enslave" the host cell, tricking it into producing many copies of the virus. Viruses multiply extremely quickly—in as little as 20–30 min in bacteria and a few hours in mammals, including humans. They spread by moving from one host to another. For example, some viruses can move between humans through sneezing or when someone touches a surface that was previously touched by an infected person. We can defend ourselves from some viruses using vaccination, and viruses that infect only humans are easier to handle.

As you might know, DNA is the molecule that carries the genetic information in living systems. DNA has a relative called RNA, which serves as a moveable copy of the information in DNA and enables the production of proteins (To learn more about DNA, RNA, and proteins, see this Nobel Collection article about protein degradation and this Nobel Collection article about RNA splicing.). All organisms in the animal kingdom have DNA as their genetic material. Viruses are unique in that some of them, called RNA viruses, use RNA as their genetic

material (It is believed that viruses are remnants of an earlier world, in which RNA was used as the genetic information. To read more about this early RNA world, read this article.). DNA and RNA viruses have various ways of using their genetic material to make a specific type of RNA called **messenger RNA (mRNA)** [1], which is used to make proteins. I created a classification system for viruses, called the Baltimore Classification, which classifies viruses based on the way they make mRNA. Within this classification, there are two types of DNA viruses that use only DNA to make mRNA (groups I, II), three types of RNA viruses that use only RNA to make mRNA (groups III, IV, V), and two groups of viruses that use both DNA and RNA to make mRNA (groups VI, VII) [1, 2].

MESSENGER RNA (mRNA)

A type of RNA that carries the instructions for making proteins and moves from the nucleus to the protein factory of the cell (ribosome).

STUDYING RNA VIRUSES

When I started my scientific career in the 1960s, I wanted to work on the fundamental chemistry of life. It seemed to me that viruses offer the best opportunity to do that because they are the simplest organisms in the world. We could study viruses and understand their operation in detail—all the way down to the molecular level.

In the 1960s, we knew very little about how RNA viruses replicate. At first, I worked on a polio-like RNA virus that grows in mice (group IV according to the Baltimore Classification, quite similar to SARS-CoV-2), trying to understand how this virus multiplies and how it affects the life of its host. I deciphered the replication mechanism of this polio-like virus and then extended the findings to other RNA viruses. In this process, I discovered several important proteins called **enzymes** that make DNA and RNA [3, 4].

ENZYMES

Proteins that control the speed of chemical reactions in living cells.

Around 1970, I became interested in whether there were other, undiscovered ways that RNA viruses replicate themselves. I was particularly interested in RNA viruses that cause cancer, called **RNA tumor viruses**. When I started to study these viruses, I had no idea that a great surprise was awaiting me.

RNA TUMOR VIRUSES

RNA viruses that cause tumor by integrating their genome into the host genome.

REVERSE TRANSCRIPTION

In the 1960s, a colleague of mine named Howard Temin suggested that RNA tumor viruses could copy their RNA into DNA. Nobody had clear evidence that this was true and many people did not believe it, since the prevailing belief (called the "central dogma") was that RNA was made from DNA (in a process called transcription), and not the other way around (Figure 2). Nonetheless, there was nothing *impossible* about copying RNA into DNA, because RNA and DNA are very similar molecules that are reproduced using similar mechanisms. In 1970, I decided to check the hypothesis that RNA might be copied "back" into DNA. To do that, I opened up RNA tumor viruses and added radioactive

DNA precursors (Box 1). These are building blocks that allow us to detect the presence of any DNA made in a sample, because that DNA becomes radioactive. Within several days of experiments, I could show that the sample of RNA tumor viruses could make DNA [4].

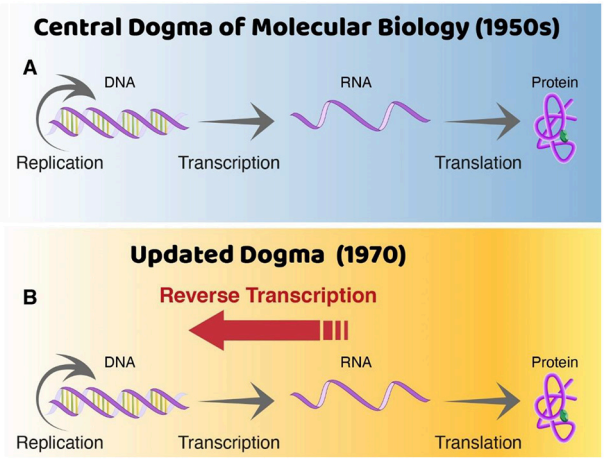

Figure 2

Figure 2

A change in dogma. **(A)** Prior to the discovery of reverse transcription, it was believed that RNA could be made from DNA through the process of transcription, but scientists generally did not believe that DNA could be made from RNA. **(B)** My discovery in 1970 showed that DNA *can* be made from RNA, by a process called reverse transcription. This finding changed one of the most basic ideas (dogma) in molecular biology. DNA replication, the process of making two identical DNA molecules from an original DNA molecule.

Box 1 | Finding DNA within RNA tumor viruses.

The process by which I used radioactive precursors to discover DNA went as follows: I bought ready-made nucleotides (the building blocks of DNA—A, T, C, and G), that were labeled with radioactive hydrogen. I put the virus and the labeled nucleotides in a test tube and used a detergent to break up the fatty membrane that covers the virus. The labeled nucleotides then contacted the RNA of the virus and the **reverse transcriptase** enzyme that copies RNA into DNA. I added some magnesium, which is necessary for the enzyme, and placed it in a 37°C bath. The enzyme built radioactive DNA from the labeled nucleotides. I used a strainer to separate the long DNA molecules from the remnants of the labeled nucleotides and, using a radiation detector, I found that the DNA molecules were radioactive! To prove that the molecule was indeed DNA, I used an enzyme called DNase that breaks DNA apart. When I added DNase to the reaction products and filtered it again using a strainer, I got no radioactive signal. That proved that the material I measured in the original reaction was definitely DNA.

REVERSE TRANSCRIPTASE

An enzyme that performs reverse transcription.

REVERSE TRANSCRIPTION

The process by which DNA is copied from RNA—the "reverse" of normal transcription, in which RNA is copied from DNA.

My findings meant that RNA tumor viruses could make DNA out of their RNA genomes, because there was no other possible source of DNA in the experiment. I also showed that, if we eliminated the RNA from the samples, no DNA was found in them. This was a huge discovery of what is now called **reverse transcription**—a discovery for which I won, together with Renato Dulbecco and Howard Temin, a Nobel Prize in Physiology or Medicine in 1975—only 5 years after my experiments.

A NEW ENZYME THAT CONVERTS RNA TO DNA

When I discovered reverse transcription, it was known that RNA and DNA are copied by enzymes, so I knew that there was an enzyme

in the virus particles. At that time, we did not know which enzyme converts RNA to DNA, nor did we understand the process used by that enzyme. My colleagues and I worked for 10 more years to discover the enzyme involved in reverse transcription and to decipher the complex mechanism by which it copied RNA into DNA. To do so, we developed a novel system, in which we could add known RNA molecules and examine what was made from them. This system allowed us to look at chemical reactions that no one had ever seen before. We found the enzyme that copies RNA to DNA and called it reverse transcriptase [5]. Several years after we found this enzyme, scientists from other research groups figured out its structure using an imaging method called X-ray crystallography (To learn more about the history of X-ray crystallography, see this Nobel Collection article.). Those scientists found that reverse transcriptase has a hand-like structure with "fingers," a moveable "thumb" that can open and close, and a central area called the active site, where DNA is made from RNA (Figure 3).

Figure 3

The structure of reverse transcriptase. Reverse transcriptase has a hand-like structure with "fingers" and a moveable "thumb" that can open and close. In its central area, it has an active site where RNA is made into DNA [Adapted from [6]].

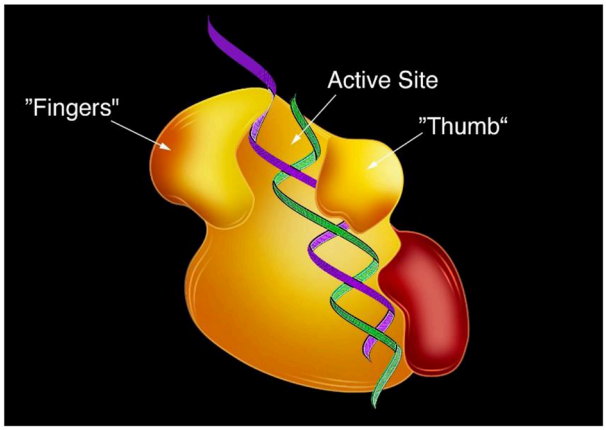

Figure 3

NEW TREATMENTS FOR VIRAL INFECTIONS AND CANCER

RETROVIRUSES

Viruses that make DNA by copying their RNA genome using reverse transcription.

Our discovery of reverse transcription and reverse transcriptase had major implications—both for our understanding of basic molecular processes in cells and for treatment of diseases. First, our discovery paved the way to understanding a type of viruses called **retroviruses**. Retroviruses are RNA viruses that use reverse transcription to create viral DNA from viral RNA. This viral DNA is then integrated (inserted) into the host cell's DNA (using another viral enzyme called integrase), making it part of the host cell's genetic material (Figure 4). After the viral DNA is integrated into the host's DNA, the host produces viral proteins that assemble to form new virus particles.

HIV, which causes AIDS, is one well-known and very problematic retrovirus (To learn more about HIV and AIDS, see

Figure 4

Life cycle of a retrovirus. **(1)** A retrovirus enters the host cell and sheds its outer envelope. **(2)** The retrovirus uses reverse transcription to create viral DNA from its RNA genome. The viral DNA is then integrated into the host cell's genome, becoming part of the host's DNA. **(3)** After integration, the host transcribes the viral DNA into mRNA and then translates the viral mRNA to produce viral proteins that are then assembled into new virus particles. **(4)** The new viruses go on to infect other cells (Image adapted from David Baltimore).

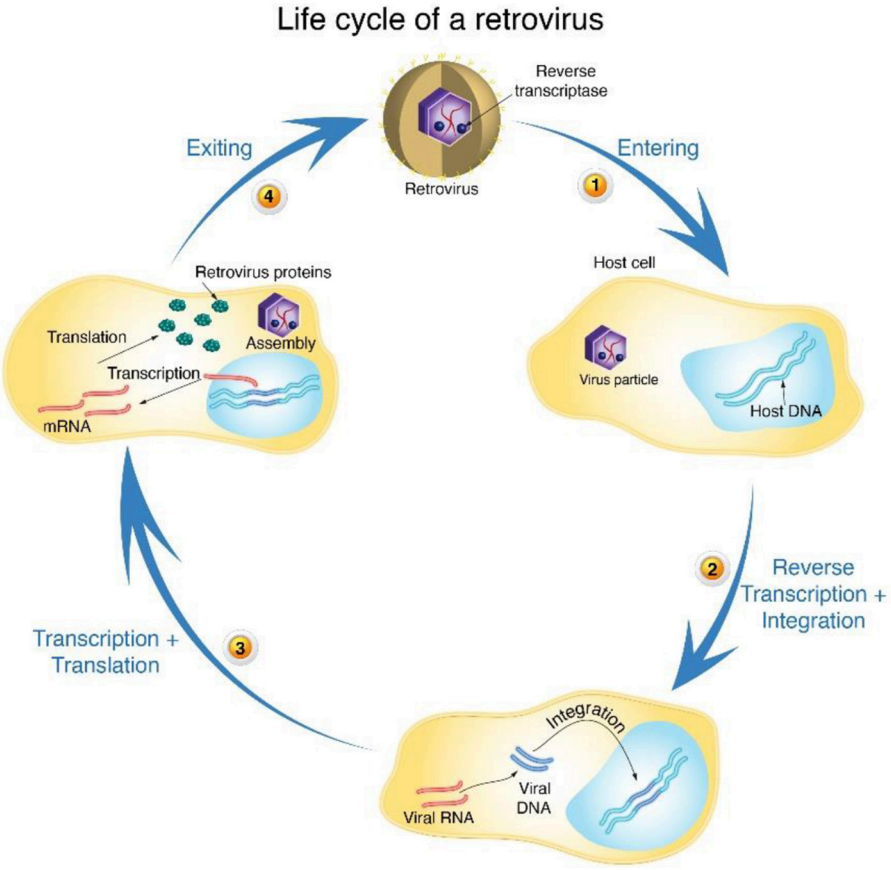

Figure 4

this Nobel Collection article.). HIV was detected in 1983, about 2 years after AIDS became a global pandemic. HIV was detected based on its reverse transcriptase, and drugs were developed to treat AIDS. Had we not discovered reverse transcriptase in 1970, some 10 years before the emergence of AIDS, it would probably not have been possible to find the virus, and we would have spent a long time trying to understand why AIDS occurs. The relatively rapid discovery of HIV saved and improved the lives of many people who would have been less fortunate if AIDS had emerged before the discovery of reverse transcription.

Our discovery also played a key role in cancer treatment. Prior to our discovery, the way that RNA viruses cause cancer was a puzzle. In cancer, cells change from growing in a controlled way to growing out of control, sometimes into large masses called tumors in the body's tissues or as rapidly growing cells in the blood, as in the case of leukemia. Since RNA is generally an unstable molecule, it did not make sense that RNA could cause a permanent change in a cell's behavior. DNA, however, is a very stable molecule, and RNA tumor viruses were found to perform reverse transcription, copying their RNA into DNA, and basically turning themselves into genes of the cells they infect. The viruses then bring new genes into the cell and these genes make

proteins. The viral proteins can override the host genes and force the cell to grow and divide continuously, making the infected cell a cancerous cell.

The connection between cancer and genes, which we discovered by studying RNA tumor viruses, turned out to be a very important process in the development of cancer. Our discovery provided one possibility of what goes wrong in cancerous cells, and it turned out to be true for multiple kinds of cancers, not only those caused by viruses. Our idea that cancer could be a genetic problem expanded the field of cancer research and triggered the discovery of life-saving drugs, including a "miracle drug" called Gleevec that blocks certain protein that signal cells to grow. The development of these drugs was based on the understanding that a specific gene caused a specific type of cancer. When we can inhibit the activity of a specific protein that is produced from that gene, we can inhibit the cancer.

USE IN BIOTECHNOLOGY AND GENE THERAPY

BIOTECHNOLOGY

An industrial field that uses biological processes to develop products.

Our discovery also helped to advance **biotechnology**, which often involves creating desired proteins for various applications, including drugs. One of the first things we asked after we discovered reverse transcriptase was: can it copy *any* RNA, or can it only copy viral RNA? It turned out that reverse transcriptase can copy *any* RNA into DNA, if we give it a little piece of DNA that is complementary to the RNA we want to copy, as a "starter." So, this meant that we could turn any mRNA—the template for making a protein—into DNA, effectively making it into a gene. Once the mRNA was in the form of a gene, we could put that gene into cells (like bacteria) that could make lots of mRNA and then proteins from that gene. This ability to turn any mRNA into DNA and then make many copies of a desired protein was revolutionary for the biotechnology industry and led to the development of many new drugs.

Retroviruses are commonly used in gene therapy, as a tool for curing genetic diseases [7]. One very successful example of retroviral gene therapy is for the treatment of bubble baby disease, officially called severe combined immunodeficiency (SCID). These babies have no functioning immune system, so any infection is lethal for them. In the past, these babies had to live in plastic bubbles that separated them from the outside environment so they would not get sick. Nowadays, novel retroviral gene therapies that replace the babies' damaged genes with functioning genes can restore their immune systems and allow them to live normal lives.

I was not originally focused on studying diseases and trying to cure people. I was initially interested only in the basic science. I was curious about viruses and wanted to understand them and how they affected their hosts. But the way it turned out, the new knowledge I helped

uncover had, and still has, great implications for biotechnology and certain areas of medicine. This is one example of a recurring theme in science: life-improving and even lifesaving applications often spring from new scientific knowledge.

RECOMMENDATIONS FOR YOUNG MINDS

When I work with students, I encourage them to be as independent as possible—to think independently about problems and solutions and to work on those problems in labs that support them in their quest to be independent. It is often difficult for young students to work independently, but they must do this because science is based on the work and knowledge of individual scientists. Nowadays, we are very focused on cooperation and collaborative work, and that is very important. But ultimately, it is the imagination, knowledge, and hard work of individual scientists that lead to discoveries like reverse transcriptase and so many others that are made every day. So, I encourage my students and I encourage you to choose a career path that gives you independence as early as possible, and that allows you to find your own way in science (Figure 5). That means you do not just mimic the ways that your supervisors and advisors do science, but instead you find your unique way of doing things. To conduct a successful study, you need an in-depth understanding of the topic you are focusing on, such as a particular organism or disease. When you first start out in biology, where things are complicated and require many different skills—you need to have in-depth understanding and focus only on one or two defined problems, because that will allow you to deepen your knowledge. Later in your career, you might choose

Figure 5

Recommendations for young minds. I encourage all of you who are interested in a career in science to be independent and find your own way.

to take a broader look at what is going in other fields of biology and other areas in science but, in the earliest stages of your career, focus and depth are very important.

My greatest enjoyment as a scientist comes from discovering new things through trying to solve biological problems. I think that is the most rewarding life a person can possibly live, and I encourage people to move in that direction, if their minds work that way. Many people do not want to spend their time solving problems and that is fine. The most important thing is to figure out what gives you pleasure and then go into it full-time. It is not easy being a scientist, nor is it easy doing anything else with full commitment and enormous depth. But, once you get into that depth, it gives you rewards that you may never achieve any other way.

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YOUNG REVIEWERS

KRISH, AGE: 13
Krish is a 7th Grader and has a passion toward scientific research and scientific phenomenona. Krish is very active in scientific discussions and he enjoys talking about scientific discoveries with his classmates, friends, cousins, teachers, and parents. Krish loves playing soccer and he is a professional swimmer.

MEHRANEH, AGE: 15
Hi my name is Mehraneh. I like reading, baking and drawing. I also love traveling. I want to be a lawyer someday.

MOHAMMAD, AGE: 12
Hi my name is Mohammad. I like legos, building and playing sports. I want to be an engineer someday.

AUTHORS

DAVID BALTIMORE
Prof. David Baltimore is an American virologist and Judge Shirley Hufstedler Professor of biology at the California Institute of Technology (Caltech, California, United States). Prof. Baltimore earned his bachelor's degree in chemistry at Swarthmore College (Pennsylvania, United States). He then studied for 1 year at the Massachusetts Institute of Technology (MIT, Massachusetts, United States), and continued his studies at Rockefeller University (New York, United States), where he received his Ph.D. in animal virology. Between 1963 and 1964, Prof. Baltimore served as a postdoctoral fellow in biophysics at MIT. Then, he decided to change direction and studied animal viruses at Albert Einstein College of Medicine (New York, United States). In 1965, Prof. Baltimore received his first independent position at the

Salk Institute in La Jolla (California, United States). In 1968, he returned to MIT as a faculty member, where he presently works, and focused his research on the problem of cancer. From 1997 to 2006, Prof. Baltimore was president of Caltech. During this period, he was also the president of the American Association for the Advancement of Science. During his career, Prof. Baltimore won numerous awards, including the NAS Award in Molecular Biology (1974), the Nobel Prize in Physiology or Medicine (1975), the Sir Hans Krebs Medal (1997), the National Medal of Science (1999), and the Lasker Award (2021). *baltimo@caltech.edu

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THE ECONOMY: MUCH MORE THAN MONEY

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YOUNG REVIEWERS:


MATEO
AGE: 10


RYKA
AGE: 14

The economy is what keeps the world as we know it functioning. Our daily lives are heavily affected by the economy, both locally and globally. Some people think that the economy is mostly concerned with money, but in fact it is much broader than money. The economy relates to very fundamental issues concerning human life, such as human wellbeing and equality between people and groups. In this article, I will give you a taste of the ways in which economists view human wellbeing. I will then explain why, when we study the economy, it is not enough to look only at individuals or at groups of people—we need to do both. Finally, we will discuss the future of the economy, and I will share some tips that I have learned during my scientific career.

Professor Angus Deaton won the Nobel Prize in Economics in 2015 for his analysis of consumption, poverty, and welfare.

WHAT IS THE ECONOMY

The economy is one of the pillars around which our world revolves, that affects us individually and collectively. The economy was not

GLOBALIZATION

The increasing influence that people and companies that are far apart (even across the globe) have on one another.

ECONOMICS

A social science that focuses on human wellbeing, focusing to a large extent on the production, distribution, and consumption of goods and services, and that analyzes the choices individuals, businesses, governments, and nations make regarding their resources. It is also concerned with distribution between people, and on poverty.

MICROECONOMICS

The study of the economic behavior of individuals, such as consumers, companies, and industries.

MACROECONOMICS

The study of the entire economy, including the general behavior of prices and the total amount of products and services present.

designed by someone for a certain purpose—it is a complex, dynamic phenomenon that is generated by the activity of individuals trying to make themselves better off. The economy changes over time and does so quite rapidly, especially in the last 20–30 years. Current and ongoing advances in technology, along with increased **globalization**, profoundly change the ways in which the economy operates. All these factors make **economics** a complex field of study (to learn more about economics, see here).

Our job as economists is to uncover some basic principles that influence economic activity (human greed is one of them!). We try to identify relationships between various aspects of the economy, such as relationships between how much money people make, how much products cost, which kinds of products are being purchased and how much of them, and how much money people are saving. In **microeconomics** we ask questions about the individual economic choices that people make. In parallel, we can also ask questions on a larger scale about how economic choices of large groups (such as countries) affect the economic state of the whole group. These broad questions are dealt with in the field of **macroeconomics**.

Ideally, our understandings of both micro- and macro- economics are developed into useful policies and regulations that make people better off. Luckily, economics has become a much more data-driven science over the last few decades, so economists can now use the huge amount of data they have collected to gain new insights about various economic processes that were previously difficult to understand or impossible to study.

As you will see throughout this article, economics is not just about money—it deals with fundamental issues of human wellbeing, inequality, and poverty. The ways that we view and act upon these issues can influence the welfare of individuals and of society as a whole. I have dedicated my career to studying these critical issues, and I now invite you on a journey that will give you a glimpse into some of my important findings.

ECONOMY AND HUMAN WELLBEING

Economists have been accused of being interested only in money and in how financially well-off people are, but that is only a small part of economics. Many economists think about human happiness and wellbeing. Amartya Sen, an Indian economist who is a hero of mine, likes to think about economic wellbeing by asking what kinds of things people are capable of doing, given their circumstances, including their money. According to Sen, a person's quality of life and wellbeing have to do with how able are they are to do the things they would like to do to—things that make life worth living [1]. This capability is influenced by many life conditions, including a person's health and where they live. Poverty is broader than simply not having enough money—it is

the inability of a person or group to achieve the level of functioning that they value. Poverty is therefore concerned with health, education, jobs, and protection from violence, among others.

What if we think about a successful economy as one that increases human happiness? Jeremy Bentham was an influential economist who believed in that approach. But, simply asking people how happy they are is problematic because there are different kinds of happiness. A study I did with Prof. Daniel Kahneman, a fellow Nobel Laureate in economics, revealed that overall **life satisfaction** is different from feeling happiness in a given moment [2]. Imagine yourself having a great time with your friends at the movies. If I were to ask you how happy you are, you might say that you are very happy. But if I were to ask you how your life is going, you might say that it is not going so well, because you are having trouble at school and you do not like where you are currently living. Does that mean that you are happy or not? Or, if you have been intensely studying for an important exam all week, you might say that you are not so happy right now. But, if I were to ask you how your life is going overall, you might say that it is going very well, and that you are enjoying your studies and your social life.

LIFE SATISFACTION

A subjective measure of how your life is going.

Our study showed that above a certain yearly income (about $75,000 U.S. in 2010), an increase in income does not increase happiness (Figure 1). We believe this is so because beyond this income, the ability of individuals to do what matters most to their emotional wellbeing does not increase. On the other hand, life evaluation (satisfaction) keeps rising with increasing income. In other words, people feel more satisfied with their lives as their income increases, such that every doubling of income results in the same increase in their life satisfaction. Therefore, in economics it is important to distinguish between types of happiness to take them all into account.

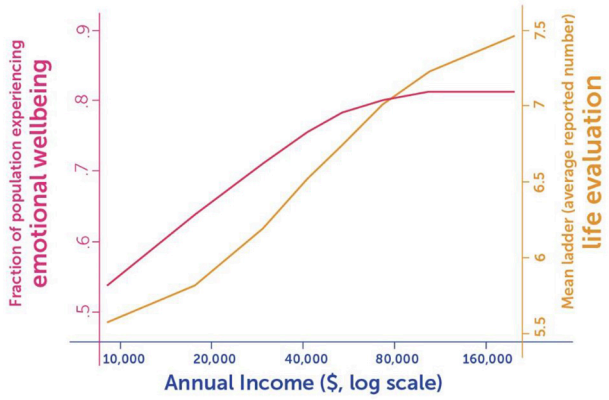

Figure 1

Figure 1

Momentary happiness and life satisfaction are different. Momentary happiness, represented here as a measure of emotional wellbeing (pink line), stops increasing at a certain income level (around $75,000 U.S. in 2010). Life satisfaction, represented here as a measure of life evaluation (yellow line), keeps rising as annual income increases. This shows that there are multiple aspects to happiness, and that they act differently in response to life events (figure adapted from Gotoh and Dumouchel [3]).

The topic of human wellbeing is complex—it is challenging to define it, measure it, and turn our results into effective economic policies and regulations. With time, I believe we will gain a clearer understanding of the aspects that contribute to human wellbeing, which will help us direct the economy to maximize human wellbeing.

WELLBEING—INDIVIDUALS VERSUS LARGE GROUPS

The average economic behavior of groups of people is very different from the behavior of the individuals who make up these groups (Figure 2). The interactions *between* people (and other economic players, such as companies) are important. An understanding of only the way people (or other players) work as *individuals* may not explain how they act when they form groups.

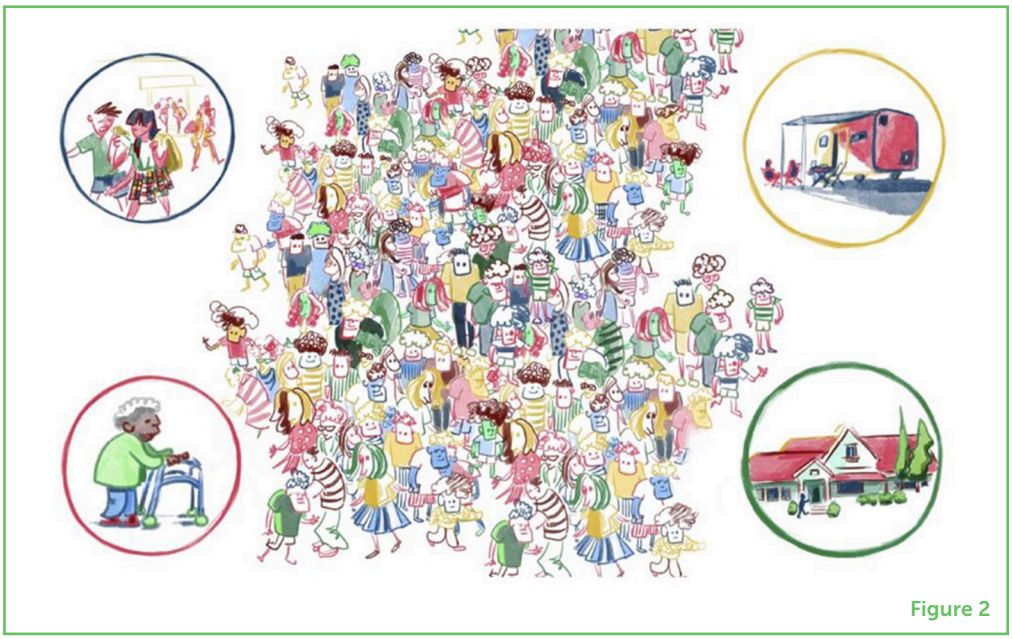

Figure 2

Figure 2

The economic behavior of groups of people is different than that of individuals. When we want to see the full economic picture, we must consider both the average economic behavior of groups of people (middle), and the economic situation of individuals, or sub-groups, within the larger group (four surrounding circles).

As an example, let us say that I am a farmer and I have a really good crop this year. When I bring my harvest to the market, I think "Wow, this is great! I am going to be rich this year!" But it turns out that many other farmers had great crops too, and, as a result, the price of the crop drops so much that I actually become poorer (Figure 3). This is a simple example of what happens when we look at the combined result of many individual actions—we often see something very different from what we see at the individual level.

GROSS DOMESTIC PRODUCT (GDP)

A measure of how a whole country is doing financially. It is the total value of the products and services produced in a country over 1 year.

On the other hand, it is not enough to look only at what is happening on average—we also need to look "under the hood" at what is happening at the individual level and for specific groups of people. For example, my colleague Anne Case and I showed that almost all the gains in the **gross domestic product** (GDP) in the United States since 1970 have gone to only one third of the American population—people

Figure 3

The economic picture for individuals can be different from that of large groups. **(A)** When there is a good year of corn crops, individual farmers expect a large profit. **(B)** However, many other farmers also experienced good corn crops. **(C)** Because there is so much corn available, the price of corn actually goes *down* and the farmers will get *less* money for the same amount, and might even finish up making less money in total, in spite of their larger crop.

who have at least 4-year college degrees [4]. The other two thirds of the population—people without college degrees—have not benefited from gains in GDP. This means that to know if Americans are better off following an increase in GDP, we must "zoom in" on specific groups of people, and even down to individual people, to figure out how well they are doing.

In summary, to understand economics in general, and human wellbeing in particular—we must look both at the individual level and the aggregate level. Only the integration of both perspectives can give us a complete picture of any given situation. As you saw, the economy deals not just with money, but with much broader questions about how to make people better off and improve their overall quality of life.

RECOMMENDATION FOR YOUNG MINDS

My first piece of advice to the young scientists among you is: do not be afraid to go off in a different direction from everyone else. Part of conducting great science relies on each scientist contributing their unique perspective and way of thinking. Even if your peers and colleagues do not accept your views, stay true to your personal way, and know that good things might come out of it in the future.

When it comes to choosing an occupation, it is good to follow your passions—but within reason. Choose something that is both important for you personally but that benefits others as well. For example, devoting your life to dealing with climate change seems to me like a reasonable thing to do in today's world. Although such a path will not always be pleasant and easy, you will be satisfied and pleased with yourself when you learn something new about the world and implement it to help your environment.

For those who will choose an academic career, I recommend that you first gain a strong academic background in one selected discipline, before exploring other useful disciplines. Be aware that mathematics is important for many career choices. It helps scientists and economists develop models and theories and, on a more basic level, it helps to ensure that we are thinking straight and avoiding unnecessary errors.

Finally, kids of your generation should hold us—the grown-ups—accountable for the kind of world we will leave for you. Do not tolerate receiving a destroyed planet (Figure 4). If we adults deplete the planet through our irresponsible behavior, you and your kids will have a more difficult future. There are already many things we can do to save our planet from further damage, and we must find ways to implement those steps as soon as possible. The choices we make now will influence the generations of the future. Your role is to drive these actions forward—help the older generation to make the right decisions *today*, to make sure that your generation and those that follow will be able to live a good life on this planet.

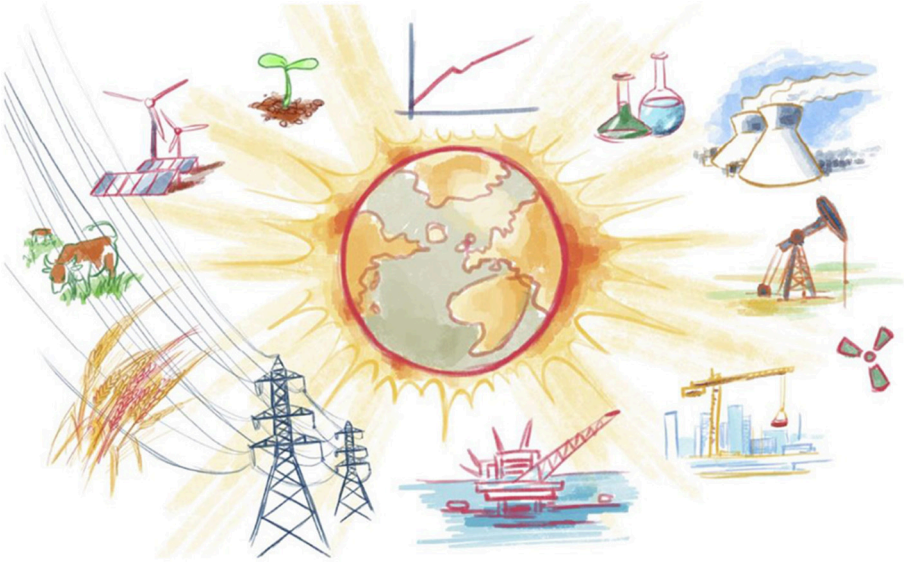

Figure 4

Figure 4

The planet's future is in our hands. The choices we make in our everyday lives about the energy sources we use, how we use our land, how we produce our food, and the processes we employ in our industry and agriculture, profoundly affect our present and future lives on this planet. Young people should hold grown-ups accountable for the condition of the world they leave behind and help adults make choices that will lead to a better future for the generations to come.

ACKNOWLEDGMENTS

I wish to thank Noa Segev for conducting the interview which served as the basis for this paper and for co-authoring the paper, and Alex Bernstein for the illustrations.

ADDITIONAL MATERIALS

- The Great Escape: Health, Wealth, and the Origins of Inequality—a book by Prof. Angus Deaton on the history of economic

development and how it influences our health and living standards.

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CONFLICT OF INTEREST: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

YOUNG REVIEWERS

MATEO, AGE: 10
I am a fourth grade student. I love Pokémon, Roblox, and Legos. I want to be a computer scientist when I grow up. My favorite book is Harry Potter and the Sorcerer's Stone.

RYKA, AGE: 14
Ryka is an upcoming young scientist, aged 14, who loves doing research in computational linguistics and medicine. She enjoys music and is getting formal training as a composer and pianist. One of her recent projects looks at the application

of music to reduce opioid addiction. Her compositions has also been performed in stage by a Grammy nominee! Beyond computer science and music, Ryka also enjoys crime shows. Her favorite game is Unsolved Case Files, which lets her play a real life detective.

AUTHORS

ANGUS DEATON

Sir Angus Stewart Deaton is a British American economist. Professor Deaton earned his B.A., M.A., and Ph.D. degrees in economics at the University of Cambridge, United Kingdom. Between 1976 and 1983, he worked as a professor of econometrics at the University of Bristol (Bristol, England). In 1983, Prof. Deaton became a permanent member of the faculty at Princeton University, New Jersey, United States. In his years at Princeton University, Prof. Deaton served as the Dwight D. Eisenhower Professor of International Affairs and as a professor of economics and international affairs at the School of Public and International Affairs and the Department of Economics. During this time, he was also a member of the Chief Economist's Advisory Council of the World Bank, a senior research scientist for the Gallup Organization, and the president of the American Economic Association. During his career, Prof. Deaton studied and contributed to various important topics in economics, including consumer demand, consumer savings, and measurement of economic wellbeing and poverty. Prof. Deaton won numerous awards and prizes for his work, including the Frisch Medal (1978), the BBVA Foundation Frontiers of Knowledge Award (2011), and the Nobel Prize in Economic Sciences (2015). *deaton@princeton.edu

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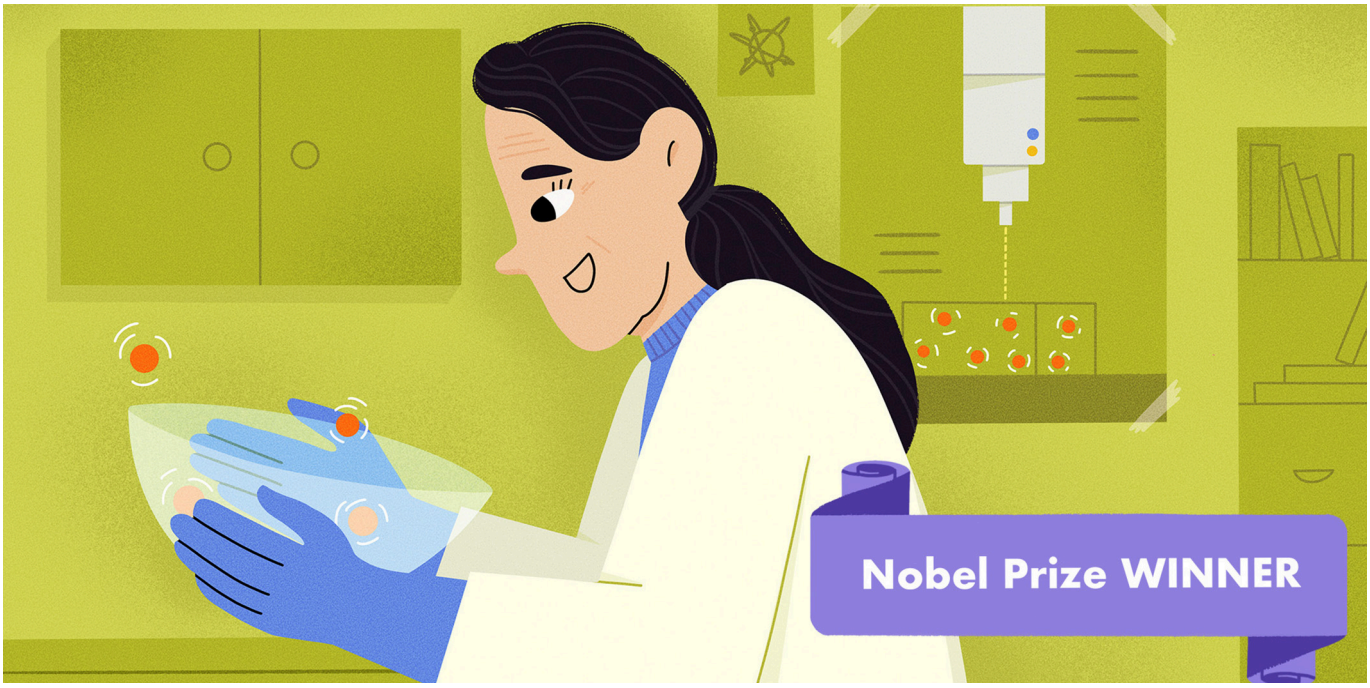

HOW TO CATCH AN ATOM: TALES ON TIME-TELLING AND FUTURE APPLICATIONS

Noa Segev[1*] *and David Wineland*[2*]

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YOUNG REVIEWERS:

RYAN
AGE: 15

YARDEN
AGE: 13

This article is based on an interview between the two authors.

Small particles, such as single photons, electrons, atoms or charged atoms (called ions), can experience a very different world from that which we usually perceive. While in our daily life, things seem to be reasonably predictable, continuous, and well-defined, in the "quantum" world of single or small numbers of particles, there are surprises and many unexpected "non-classical" behaviors. In addition to its complexity, the world of small particles opens up some very interesting possibilities for applications to practical problems. To take advantage of the amazing properties of small particles, scientists and other researchers have developed various techniques for holding and isolating photons, electrons, atoms, and ions and manipulating their behavior. In this article, we will try to give you a glance into the fascinating lives of small particles, tell you about techniques for working with them, and mention exciting new potential applications that take advantage of their unique behaviors.

Prof. David Wineland shared the 2012 Nobel Prize in Physics with Prof. Serge Haroche, Collège de France, Paris "for ground-breaking experimental methods that enable measuring and manipulation of individual quantum systems".

THE LIVES OF SMALL PARTICLES

The world of atoms and subatomic particles is extremely rich and fascinating. In it, we encounter many peculiar phenomena and find that our daily intuition about how things work does not apply in the atomic and subatomic world. One interesting feature of this world, which is often called the quantum world, is its apparent discreteness. Unlike our daily world, the world of particles appears to not be continuous, as if there are sudden jumps between different conditions. For example, we know that electrons in atoms can occupy only specific regions around the nucleus, called atomic orbitals. (In quantum mechanics, we learn that the electrons do not act like point particles orbiting the nucleus (like planets orbiting the sun); rather, they are described by "wavefunctions" where, in effect, their position is spread out in space.). In each of these atomic orbitals, electrons have a certain amount of energy, called their **energy level**. When an atom releases energy by emitting a light particle called a photon, the energy of an electron inside the atom appears to instantaneously jump from one energy level to another, lower energy level. Similarly, when an atom gains energy by absorbing a photon, an electron appears to suddenly jump from an initial orbital to a final orbital with a higher energy level. In fact, the "jumps" are not instantaneous but in some cases, they take only a very short time, on the order of 1 billionth of a second.

ENERGY LEVEL

Specific discrete energy value that a quantum system can have such as those of electrons in an atom.

The theory in physics that best explains the wonderous world of atoms and subatomic particles is called **quantum mechanics**. Although the foundations of quantum mechanics were laid almost a century ago, there are still some puzzles that we do not yet fully understand about the fundamental behavior of particles, which are the building blocks of the material world. However, many techniques have been developed that help us to better understand and control the behavior of particles. Next, we will briefly tell you about two such techniques—one for trapping particles (even a single particle) in a specific location, and the other for slowing down their motion, or cooling them.

QUANTUM MECHANICS

A theory in physics describing the behavior and properties of atoms and other particles as well as more macroscopic systems like the vibrations of miniature mechanical oscillators.

TRAPPING MANY PARTICLES

Particles typically move around a lot. When we work with particles, we often want them to be confined in a specific location. We often study **electrons** and atomic ions, which are affected by electric fields. By

ELECTRONS

Fundamental particles in atoms which have a negative charge.

ELECTRODES

Typically metal structures that conduct electricity and can be used to create electric fields.

arranging **electrodes** in a specific geometry, and applying voltage to them, we can produce electric fields that trap our electrons or ions in a specific location [1, 2]. An analogy is to think about marbles in a bowl: our particles are the marbles and the electric fields effectively provide the bowl (Figure 1A). The center of the bowl is like the center of the electric field "trap": if the particles move in any direction away from the bottom of the trap (or bowl) they will experience a "push" back toward the center. Much like gravity keeps marbles in the bottom of the bowl, the electric field keeps the particles confined—near the center of the trap. Professors Wolfgang Paul and Hans Dehmelt shared half of the 1989 Nobel Prize in physics for their development of traps for ions and electrons [1, 2].

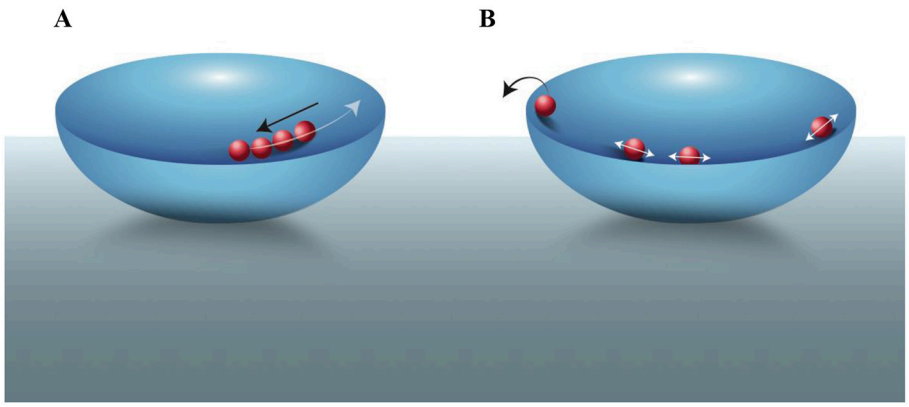

Figure 1

Figure 1

Trapping particles–the bowl-and-marbles analogy. Electrons and ions moving in an electric field "trap" can be viewed as marbles in a bowl. **(A)** When particles move away from the center of the electric field bowl (white arrow), they are pushed back toward the center (black arrow), keeping them trapped inside the bowl. **(B)** If we want to trap only a single particle, we can for example, first trap multiple particles and, by applying oscillating electric fields and increasing the movement of particles, we can eliminate particles one-by-one, by "evaporating" them out of the bowl (black arrow), until only a single particle is left [3].

TRAPPING A SINGLE PARTICLE

Sometimes we need to control particles very precisely. Working with groups, or "ensembles," of particles is sometimes more convenient, both because it is easier to trap many particles at once and because it is easier to measure the larger signals (the electric currents induced in the electrodes by the movement of the charges) generated by many particles together compared to the small signals of a single particle. But when working with many particles, it is harder to control them as precisely as we can control one particle. Think of this like trying to keep an eye on one kid in a class compared to keeping an eye on many kids at once—you can imagine how much harder the second case is.

We *can* control the speed of one particle with high precision, including bringing the particle to nearly a complete stop, but it is more difficult to control the speeds of many individual particles in a group with the same precision (When particles in a group collide, it can perturb their internal energy levels in an uncontrolled way.). Therefore, if we need very high control and precision (as we need for atomic clocks, as you will see below), we sometimes need to work with single particles to

finely control the particle's motion and minimize errors that occur when working with many particles [3].

To trap a single charged particle, we can first trap several particles as in Figure 1A. Then, we apply an oscillating electric field to the particles, so that occasionally a particle will "fly out" of the trap. In our bowl-and-marbles analogy, you can think about this as increasing the motion of the marbles inside the bowl, until a marble "jumps over" the edge of the bowl (Figure 1B). Each time a particle jumps out of the bowl, we can measure a sudden, discrete reduction in the total oscillating electrical current induced in the electrodes (as in [3]). We repeat this process until the current of the system is equal to the current of a single particle so that we know we are left with only one trapped particle [1]. Then, we can either study its properties, and/or use its known properties for specific applications [1, 2]. When working with certain atomic ions we can scatter laser light from them; the total observed scattering is proportional to the number of ions, which enables us to tell when we have a single ion in the trap.

COOLING ATOMS WITH LASER BEAMS

Another important technique for controlling particles is slowing or cooling them to very low temperatures using lasers, so that they are barely moving. This is called **laser cooling**. As you have learned, electrons move around the nucleus only in specific energy levels. When a photon approaches an atom, it is absorbed by the atom only if it has exactly the right amount of energy to transfer electrons from one energy level to another; otherwise, the light just passes through the atom. As you might know, the energy that **photons** carry is directly related to another property of light called frequency (the number of cycles that a wave completes in 1 s), such that photons with higher energy have higher frequencies, and *vice versa* (to learn more about frequency and energy, see here).

LASER COOLING

A technique that uses laser beams for slowing down and cooling atoms and ions.

PHOTONS

Particles of light carrying a specific, discrete amount of energy proportional to their frequency. This was Max Planck's idea and was followed subsequently by Einstein.

MOMENTUM

A physical quantity defined as the product of the mass of a particle and its velocity. The higher a particle's momentum is, the stronger the force it can impart on other particles.

When an atom moves against the direction of light such as that in a laser beam, the frequency of the light experienced by the atom has higher frequency and therefore is "more energetic," compared to the case when the atom moves away from the light source (Figure 2). This is called the Doppler effect. Therefore, if we tune the laser frequency slightly below the frequency (or energy) required for the transition between two electron orbits when the atom is at rest, then when the atom moves toward the laser, it will experience it as having a higher frequency and will absorb the light (red atom in Figure 2). Absorbing the light will slow down the atom due to the photon **momentum** imparted to the atom which reduces the atom's momentum thereby reducing its speed. Think of it like two rugby players running toward each other, slowing down after they bump into each other. On the other hand, if the atom moves away from the laser (green atom in Figure 2), the laser beam frequency experienced by

the atom will be shifted low and the probability that the laser beam photon will be absorbed by the atom will be reduced. Consequently, the atom will keep moving at approximately the same speed (to learn more about laser cooling, see this video). This differential effect between the atom moving toward vs. away from the laser means that we have a way to slow down the motion of an atom moving in a *specific* direction (toward the laser). Combining several lasers projecting from different directions, we can slow the atoms that are moving in all directions.

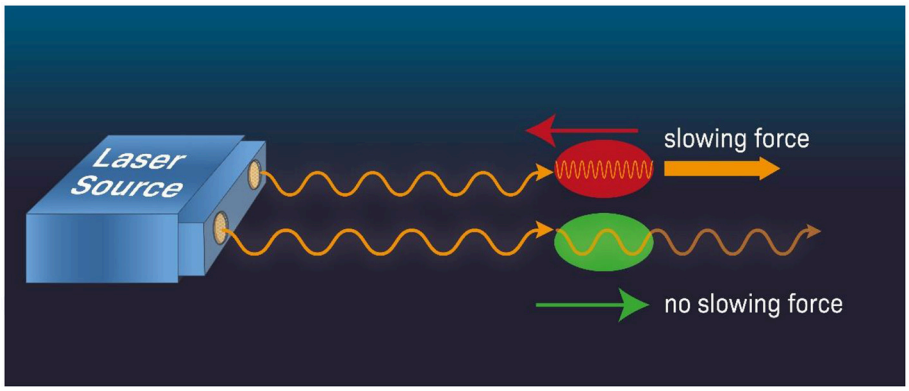

Figure 2

Figure 2

Laser cooling. When an atom moves against a laser beam (red) it experiences higher beam frequency (that is, photons of a higher frequency). If we tune the laser's frequency slightly below the specific frequency that the atom absorbs when it is at rest, then the atom moving against the beam direction will experience, through the Doppler effect, photons of a higher frequency and absorb the laser's light and slow down (think of the laser photon as if it is a hard object moving toward the atom and when they collide, the atom slows down). In contrast, an atom moving in the same direction as the laser beam (green) will only weakly absorb the laser photons, as the photon frequency is lower than the frequency for maximum absorption by the atom. Therefore, the atom will continue moving without its speed changing appreciably. Combining a few laser beams that project from different directions, atoms can be slowed down to very low speeds in all directions.

ATOMIC CLOCKS: TELLING TIME ACCURATELY

Clocks are such a common part of our daily lives that we rarely stop to think about fundamental questions, such as how time is measured and what limits the accuracy of telling time. For scientists and engineers at laboratories like the Time and Frequency Division of the US National Institute of Standards and Technology (NIST), this is what they think about all day long! Their mission is to keep improving the accuracy of clocks, and to measure time more and more precisely. As for most experimental physicists, these scientists act like detectives, carefully identifying all the important factors and environmental effects that limit the accuracy of telling time. They then try to reduce these effects as much as possible to continually improve the accuracy of measuring time. These clock scientists have been working on this task since the 1950s when the first atomic clocks were demonstrated (to learn more about the history and operation of atomic clocks, see this article).

In general, to measure time intervals, we actually count the number of cycles of a reference frequency source, such as the oscillations of a mechanical pendulum or a piezoelectric quartz crystal oscillator (a device found in cell phones whose mechanical oscillations are driven by the electrical voltage applied on it.). If we know the frequency of our frequency source, we know how much time has passed by counting how many cycles were completed in a certain time interval (i.e., duration between two points in time). For example, if we know

that the frequency of our source is 100 Hz (cycles per second), then we know that the duration of each cycle is 1/100 (or 0.01) second. The higher the frequency of the source, the more precisely we can define time intervals.

We can measure time internals very accurately using atomic clocks as our frequency source. This means that instead of using the low frequency of a mechanical pendulum, or the frequency of quartz crystal oscillator, we can use the very high frequency that corresponds to the frequency of photons that cause transitions between discrete energy levels of atoms. For example, we could shine a laser beam on atoms that have first been placed in their lowest energy electronic state and we observe the amount of absorption of the laser beam. When the absorption is maximized, we know that the laser beam frequency matches the frequency of photons that correspond to the energy difference between the two atomic energy levels. If the laser beam is not maximally absorbed, we change its frequency a little bit until the absorption is maximized, and satisfy this condition. Then, by counting the number of cycles of the laser oscillation we can precisely determine time intervals (Figure 3).

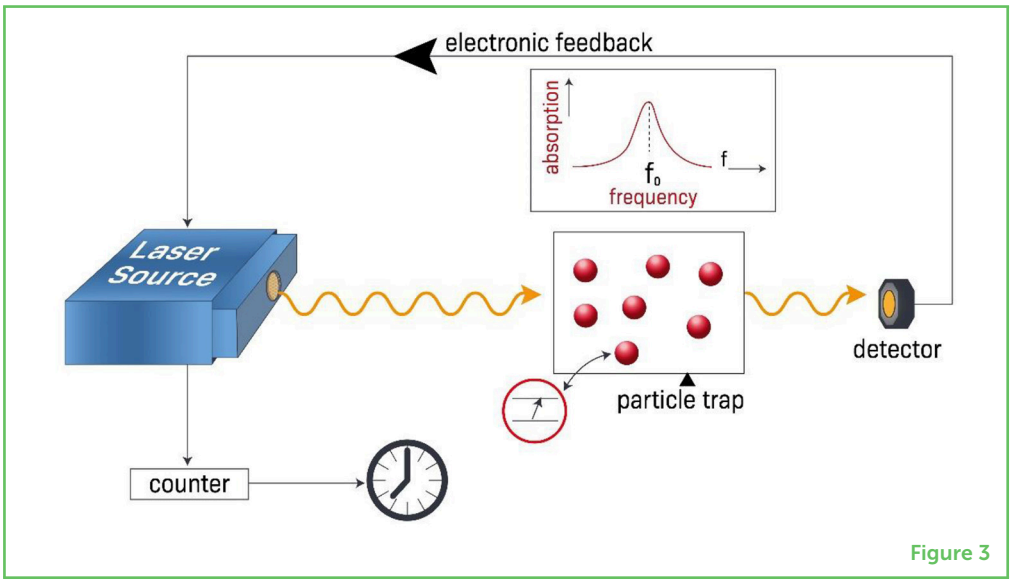

Figure 3

Figure 3

Principles of atomic clocks. When a laser beam is maximally absorbed by trapped and cooled atoms (red balls), it means that the laser's frequency equals the frequency of photons required for electrons to "jump" from a lower energy level to a higher energy level (schematic in red circle). We tune the laser frequency using an electronic feedback system until the laser beam is maximally absorbed by the atoms. We then use a device count how many cycles the laser beam makes, which we then use together with the atom's transition frequency to calculate how much time has passed. Because the laser has a very high frequency, the time for each oscillation cycle is very short and we can measure time intervals with very high precision.

Atomic clocks are used in satellites to detect your location using the GPS in your smartphone, for example. Knowing the speed of light and using synchronized atomic clocks to measure the time it takes for light to travel from the satellite to your smartphone enables the software to accurately compute your distance from the satellite. Using a network of time-synchronized satellites, your three-dimensional location can be determined. The atomic clocks in satellites must be very accurate, since very small errors in their time measurement, even on the scale of one millionth of a second, result in large errors of hundreds of meters in determining your location using GPS.

For many years, the best atomic clocks were based on a particular transition in a specific element (the "hyperfine" microwave transition in neutral atomic cesium which has a frequency of about 9.2 GHz, or about 9.2 x 10^9 Hz.). But for the last few years the most precise frequency standards are based on transitions that have frequencies near those of light waves corresponding to the colors of light we see with our eyes) around 10^{15} cycles per second [4] (To learn more about optical atomic clocks, see this article). Uncertainties in these frequencies due to environmental perturbations are at around 1 part in 10^{18} which implies that clocks based on these transitions would be uncertain to less than a second over the age of the universe (~13.7 billion years).

An important potential application that can utilize advanced techniques of laser cooling is called quantum computation. Quantum computation uses the quantum characteristics of atoms and ions or more macroscopic devices to perform certain complex computations much more efficiently than classic digital computers. For a brief introduction, see the Appendix.

RECOMMENDATIONS FOR YOUNG MINDS

We feel that the work we do is more like a hobby because we would probably be interested in the same things even if they were not part of our profession. That is something that we wish for you, too. We believe that you should find something that you really like, and if you like it, you will be willing to work hard and spend a lot of time on it, and then you are likely to be successful. Even if you change your mind about what you like, or what is interesting for you, that is fine. You obviously do not want to spend your time on something too far off from what you like to do anyway. Of course we also, think it is important to keep your eyes open and course-correct your decisions when needed.

For those of you who chose a career in science, it is also important to know that patience and perseverance will be required. In science, and specifically in scientific research, the fruits of your efforts are often not immediate. It takes time to develop the knowledge and skills required to perform high-quality research and gain new insights about the world. You must be able to endure some difficulty and persevere even when things do not go your way. If you do, you will eventually enjoy the fruits of your efforts and enjoy the wonder of discovery.

We want to also emphasize that, in our opinion, choosing a career or a path based on making money is a mistake. You are not likely to be very satisfied or successful if you focus only on supporting yourself financially. On a similar note, if you chase after prizes and awards, that would most likely not be a successful path either. We advise you to choose something you like and invest the hard work needed to

progress toward a meaningful goal, instead of focusing on salary of social recognition.

Finally, we have some advice for those of you who intend to go to college. When you go to graduate school, you will be assigned to work on a particular project. From our experience, it is always useful not only to just focus on the exact topic that you are working on, but also to branch out a little bit and read some broader, related materials. This is exactly how David got the idea for laser cooling—by reading additional papers on topics not directly related to his project at that time. This eventually became a major milestone in his scientific career.

APPENDIX: FUTURE ADVANCES AND APPLICATIONS

The performance of atomic clocks will continue to improve. Frequency shifts due to many environmental perturbations on the atoms such as stray local electric and magnetic fields must be accounted for with increased precision. Two additional effects that must be included in clock comparisons come from Einstein's theory of relativity and are separate forms of what is called "time dilation"—the slowing of time in one reference frame relative to another.

First, Einstein taught us that in a reference frame that is moving relative to us, say the frame attached to a moving atom or ion, time runs slower compared to us, as stationary observers in a lab. This shift is proportional to the average energy of motion of the ions, so that one of the benefits of laser cooling is that we can reduce the shift by about a factor of a million compared to room-temperature ions or atoms.

The second kind of time-dilation that Einstein taught us is that time runs slower in the presence of gravitation [the so-called "gravitational potential red shift" [5–7]]. This is not a big effect in our normal daily experience as can be illustrated by the following example: Suppose you and a twin sibling were separated at birth. You live at sea level; your twin has lived 1.6 km above sea level (for example, in Boulder, Colorado). After 80 years, your twin will only be about 0.001 s older than you.

This is of course a negligible effect in terms of typical human activities, but it can be observed with accurate clocks and needs to be taken into account when comparing clocks at different locations as in navigation via GPS.

As a simple demonstration of the effect, two separate clocks based on the same atomic transition in an ion were compared at the National Institute of Standards and Technology in Boulder, Colorado [5]. Initially the two clocks were at the same height but separated laterally by a few meters. The frequency ratio of the two clocks was unity to about

1 part in 10^{18}. One of the clocks was then raised by 33 cm and the ratio of the frequencies of the two clocks was measured again. The frequency of the raised lock increased by about 4 parts in 10^{17}, close to the expected result.

Even more dramatic demonstrations of the gravitational potential red shift were recently demonstrated by two groups using neutral atoms where the gravitational red shift was observed at millimeter scale [6, 7].

In addition to improved clocks, another important potential application based on controlling and manipulating individual quantum systems, is quantum information processing, which includes quantum computation (computer calculations performed using quantum elements) and quantum simulation (computer simulations that use quantum effects to understand physical phenomena). Although this topic is beyond the scope of this paper, we can give you an idea of this important field and where it is heading.

To do so, we first need to explain another peculiar phenomenon in the world of quantum particles, called *superposition*. Superposition refers to the fact that particles can represent two different energy levels at the same time. Consider the example of a single trapped ion being like a marble in a bowl. We can excite the ion's motion with an oscillating electric field and create a classical-like condition where the marble rolls back and forth say between the left side and right side of the bowl. However, with our quantum tools we can also make a situation where at certain times the marble is simultaneously on the left and right side of the bowl in a "superposition" state. This is very counterintuitive and makes no sense in our everyday classical world, but it is the world quantum scientists live in.

Extending this idea to the energy levels of a single atom, we can make a superposition state where the atom is simultaneously in its lower and higher energy state. In practice, this is relatively easy to do. Previously, we spoke about a single atomic ion absorbing a single photon and making a transition from its lower to higher energy level. It turns out that if our laser beam is composed of many photons that are spread out in space in all directions perpendicular to the direction of the laser beam and we apply the laser for a particular duration, we can realize a situation where the atom is excited only "half-way." That is, after the laser beam is switched off, the atom is in a superposition of its lower electron energy level and its higher energy level. So, superposition means a particle can simultaneously exist in multiple states (two in the above example) at any given moment.

The field of quantum computation is based in part on superposition of two states of a quantum system, atomic ions in the above example. As you might know, a normal computer is composed of basic units called "bits," that can be in one of two states, which we call "0" and "1."

This two-state system, when combined with other similar two-state systems, can perform all the calculations of a conventional computer. The idea of quantum computation is that every basic unit, called a "qubit" (short for quantum bit) can be in a *superposition of states*, or multiple states at once.

To represent the state of a qubit as a superposition of the quantum states "0" and "1", we often use the notations "$|0\rangle$" and "$|1\rangle$." We write the general superposition state of a qubit as $\alpha|0\rangle+ \beta|1\rangle$, where $|\alpha|^2$ is the probability of the qubit being measured in state "0" and $|\beta|^2$ is the probability of the qubit being measured in state "1." When these probabilities are equal, what we call an equal superposition of states, one possible superposition state of the qubit can be $\frac{1}{\sqrt{2}}|0\rangle + \frac{1}{\sqrt{2}}||1\rangle$ (where $|\alpha|^2 = |\beta|^2 = \frac{1}{2}$).

Now, let's see what happens in a larger system. If we look at a classical system with two bits, each being in one of the states "0" or "1", we can represent a total of $2^2 = 4$ numbers, which are: 00, 10, 01, or 11. The general state of an equivalent 2-qubit system would be $\alpha|00\rangle + \beta|01\rangle + \gamma\ |10\rangle + \delta|11\rangle$, where the probability of measuring the states $|00\rangle$, $|01\rangle$, $|10\rangle$ and $|11\rangle$ are $|\alpha|^2$, $|\beta|^2$,$|\ \gamma|\ ^2$, and $|\delta|^2$, respectively. One example of a superposition of the four states the state would be the state $\frac{1}{2}|00\rangle + \frac{1}{2}|01\rangle + \frac{1}{2}\ |10\rangle + \frac{1}{2}|11\rangle$ with a measurement probability of $\left(\frac{1}{2}\right)^2 = \frac{1}{4}$ for each state). As you can see, a superposition of a 2-qubit system contains, or stores four (2^2) two-bit numbers simultaneously. In contrast, a classical two-bit system can only store one two-bit number (one of either 00, 10, 01, or 11).

Scaling this to even larger systems, we can see that a classical n-bit system can store one n-bit binary number comprised of "0"s and "1"s. However, a superposition of n qubits can store 2^n n-bit numbers at once (that is 2^n times more numbers compared to a classical system of the same size). This then indicates that when we perform an operation on one of the qubits in our n-qubit superposition, we operate on all 2^n n-qubit states simultaneously. This suggests that a quantum computer can store and process a much greater amount of information than a classical computer with the same size, and is an example of "exponential scaling." A dramatic example is that if we have 300 qubits we can store 2^{300} 300-bit numbers simultaneously. A classical memory of this size would require more particles than exist in the universe! It is relatively easy to make such a state with trapped ions, but to make useful logic gates for a system this size is much harder [Implementation of quantum logic gates is beyond the scope of this paper, but some of the basic ideas can be found in [8]].

Therefore, for certain problems, in principle, quantum computers could be much more efficient and faster than classical computers and could solve problems that current conventional computers

are incapable of solving. Beyond efficient number factoring (as proposed by Peter Shor), one anticipated application of quantum computers, then, is the ability to simulate the dynamics or behaviors of complex quantum systems, such as the action of molecules in a chemical that might be used in drug therapy, and study them using computer simulations without having to synthesize them in the lab. Similar simulations could also potentially teach us new things about physics, or they could solve difficult physics problems that classical computers cannot.

Many people are wondering when we will have the first quantum computer. The answer is that we already have quantum computers; but so far, the problems they solve can be solved by classical computers (maybe not as efficiently) or they solve problems that are not of practical interest. Building and improving quantum computers will likely be a gradual process—the first quantum computers will only be able to solve simple useful problems and, but as the field progresses, they will be able to do more complicated things. Perhaps in the next 10 years, we will be able to do something useful with quantum computers, like discovering something we did not know before, or simulating an interesting system for practical applications. That is something exciting for us to look forward to.

ADDITIONAL MATERIALS

The transcript of the interview between Prof. David Wineland and Noa Segev can be found here.

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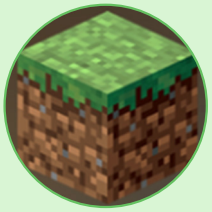
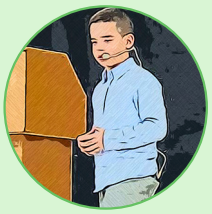
YOUNG REVIEWERS



RYAN, AGE: 15
I really enjoy coding and I love Rubik's cubes. I also really love playing Minecraft.



YARDEN, AGE: 13

I was born and raised in Israel. My main hobbies are KAMI (Israeli martial art) and rhetorics. I have a brown belt in KAMI and I won second place in the Israeli "young speaker" competition. I am also in the scouts and I like to sing.

AUTHORS

NOA SEGEV

Noa Segev is a scientific writer and project coordinator at Frontiers for Young Minds. She earned her B.Sc. in physics at The Hebrew University of Jerusalem and her M.E. in renewable energy engineering at the Technion—Israel Institute of Technology. Since 2019, she has been interviewing Nobel Prize winners and co-authoring articles for the Nobel Collection at Frontiers for Young Minds. Noa aims to make the science behind Nobel Prize-winning discoveries accessible to all, and to share valuable insights from the vast professional and personal experience of Nobel Laureates. *noasegev@gmail.com

DAVID WINELAND

David Wineland received a B.A. degree from the University of California, Berkeley in 1965 and a Ph.D. from Harvard University in 1970. Following a postdoctoral position at the University of Washington in Seattle, he joined the Time and Frequency Division of NIST (National Institute of Standards and Technology) in Boulder, Colorado, from 1975 to 2017, where he was a group leader and NIST Fellow. He is now a Philip H. Knight Distinguished Research Chair and Research Professor in the Department of Physics at the University of Oregon in Eugene, Oregon. Starting with graduate school, a long-term goal of his work has been to increase the precision of atomic spectroscopy, the measurement of the frequencies of atoms' characteristic vibrations. This research has applications to making better atomic clocks and has led to experiments that enable precise control of atomic energy levels and atomic motion. Such control can be applied to metrology whose precision is limited only by the constraints of quantum mechanics and to demonstrations of the basic building blocks of a quantum computer. For this work, he shared the 2012 Nobel Prize in Physics with Serge Haroche, Collège de France, Paris. David is married to Sedna Quimby Wineland and they have two sons. *djw34@uoregon.edu

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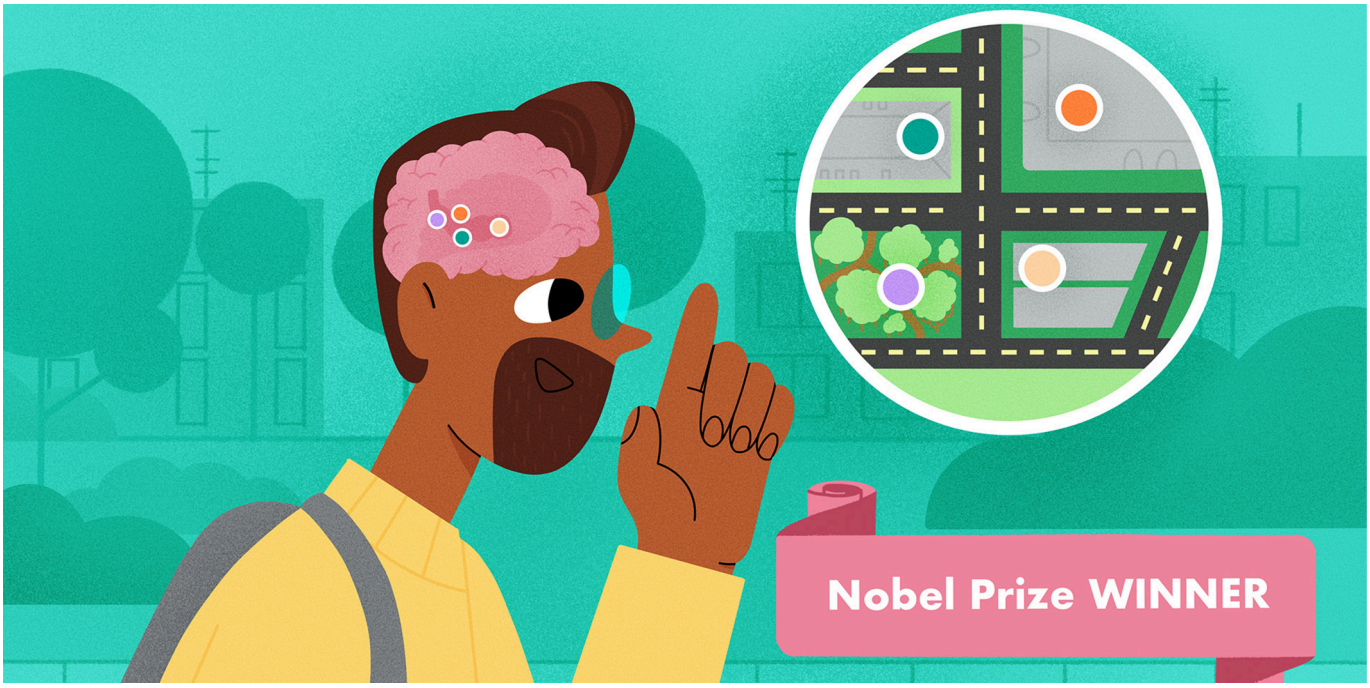

PLACE CELLS: THE BRAIN CELLS THAT HELP US NAVIGATE THE WORLD

John O'Keefe *

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YOUNG REVIEWERS:

GEORG
AGE: 12

SUYANG
AGE: 15

Navigation through the space around us is one of the most fundamental and crucial abilities that humans and other animals have. This ability is so natural that we usually do it easily, without even thinking about it. Though finding our way through our environments seems effortless, it actually requires a complex, fascinating mechanism—the navigation system in the brain. In this article, we will explore a major group of cells that are part of this navigation system, called place cells. As you read, you will discover how the trait of curiosity helps the brain's navigation system, and you will learn some important lessons from taxi drivers in London!

Professor John O'Keefe won the Nobel Prize in Physiology or Medicine 2014, jointly with Prof. May-Britt Moser and Prof. Edvard Moser, for the discovery of cells that constitute a positioning system in the brain.

When you think about navigating from one point to another, what is the first thing that comes to mind? Is it the GPS system in your

smartphone? Or maybe the field map that you got during your last trip with the scouts? Well, if you think about it, navigation is something that you do all the time—even when you take your dog out for a walk or stroll down the street to buy your favorite treat from the local grocery. Your brain uses its navigation system even if you are not moving your own body, but rather driving in a bus, a train, or a car. Have you ever wondered how this internal navigation system works? How do people recognize specific places, and how do we get from one place to another?

ROUTES VERSUS MAPS

The first principle we should be aware of before talking about the brain's navigation system is the difference between routes and maps. A specific *route* usually refers to one pathway that connects a person's current location with some other relevant location. You can think about a route as a set of instructions that leads a person to a desired place, using landmarks. For example, you might know that if you walk down your street, turn left at the first corner, and then turn right near the local Starbucks coffee, you will arrive at the grocery store. If you want to buy a treat in the grocery store, you can simply follow these instructions and landmarks, without needing to know the distance between your home and the grocery, or what other streets and shops are around.

But what would happen if the end of your street was blocked by construction work? Or what if the Starbucks was replaced by a clothing shop? Would you still be able to get from your house to the grocery, if you only knew how to follow the set of instructions described above? The answer is no, you would need a map to get to the grocery under the new conditions. This is key to understanding the brain's navigation system. As you now understand from the grocery example, to successfully navigate through the world, your brain must have an *internal representation* of the relevant locations, as well as of the relationships between those places. This representation, which forms a **mental map** of your environment, allows you to navigate in the world in a flexible way—in which you can use many routes to reach the same location. This flexibility is so important that animals frequently choose to navigate through different routes over simply using the less demanding method of following one known route. In other words, mental maps are the preferred strategy used by the brains of animals to enable them to navigate through the space around them.

MENTAL MAP

A representation of places in the world and their relationships to each other, which is constructed in the brain as an animal explores its environment.

PLACE CELLS

Nerve cells in the brain that help construct a mental map. They are located in the hippocampus and become active when an animal is in a specific location in its environment.

PLACE CELLS

This mental map of locations in the environment is formed in the brain using special cells called **place cells** [1]. Place cells are found

HIPPOCAMPUS

A seahorse-shaped area deep in the middle part of the brain, between the ears. It contains an important part of the brain's navigation system, in the form of place cells.

in a brain area called the **hippocampus** (Figure 1A). It turns out that each place cell responds to a specific location in the world. This means that, when an animal roams around, a specific place cell becomes active when the animal is located in a specific location in space (Figure 1B).

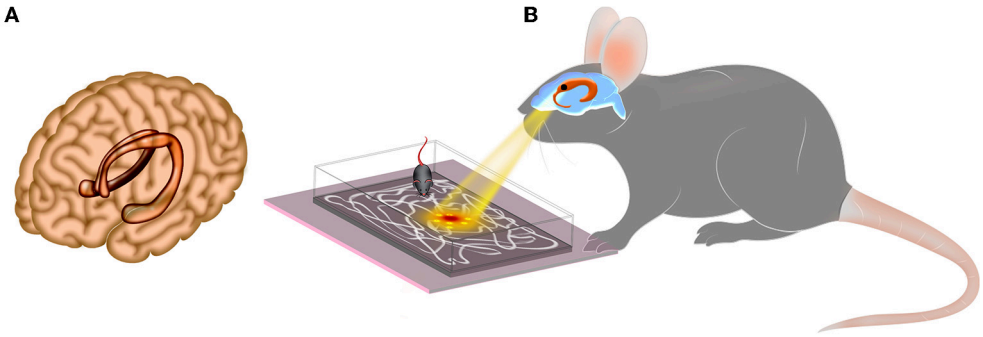

Figure 1

Figure 1

Place cells in the hippocampus. **(A)** The hippocampus is a seahorse-shaped region located deep in the middle of the brain (orange). It contains (among other cell types) nerve cells called place cells, which are fundamental for navigation. **(B)** When an animal moves in the space around it (gray lines in the box), a specific place cell in its hippocampus (black dot in the mouse's hippocampus) becomes electrically active when the animal is in a specific location in the environment (orange spot in the box). This cellular activity helps the animal to build a mental map of the environment, allowing it to flexibly navigate in the world (Image credit: https://medicalxpress.com/news/2015-10-role-hippocampus-memory.html and https://www.nobelprize.org/uploads/2018/06/advanced-medicineprize2014.pdf).

Here is a real-life example to demonstrate how the activity of place cells creates a map in the brain. When you walk around a specific place in your neighborhood, for example in the park near your home, a certain group of place cells becomes active, with the activity of each cell based on your specific location in the park. When you walk around in other place in your neighborhood, say your school yard, another group of place cells becomes active, each cell at a different location in the yard (Figure 2A). This activity of place cells in your hippocampus enables you to create a mental map of your neighborhood (Figure 2B) [2].

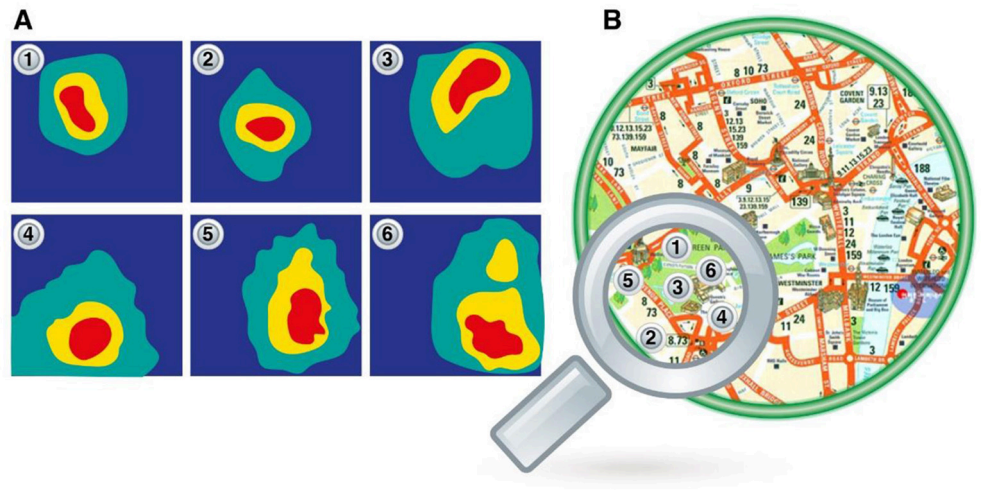

Figure 2

Figure 2

Place cells form internal maps in the brain. **(A)** An example of the activity of six individual place cells **(1–6)**. The location in the environment where each cell is most active is represented by the red area. Yellow and

green areas represent minor activity, and blue represents no activity. Each cell is most active in a specific location in the square, which corresponds to a specific location in the environment. When taken together, the fields of all active cells cover the entire surface of the environment. **(B)** The collective activity of the place cells in a given environment creates a mental map of this environment in the brain (Image adapted from https://www.nobelprize.org/uploads/2018/06/okeefe-lecture.pdf).

WHAT CAN TAXI DRIVERS TEACH US ABOUT THE HIPPOCAMPUS?

Twenty years ago, before the age of smartphones equipped with GPS, people navigated using their own memories. One population that used navigation skills more often than others was taxi drivers! Back then, taxi drivers drove their passengers from one place to another in the most efficient way, based on their mental maps of the city and their experience with traffic conditions at certain times of the day. A study performed in 2000, showed that a specific part of the hippocampus in taxi drivers in London was larger than that of people who did *not* navigate as extensively through the city [3]. This was important evidence showing that the hippocampus is part of the brain's navigation system. It was further shown that the hippocampi of taxi drivers remained larger only as long as the drivers kept navigating from memory. This brain area shrunk back to normal size if drivers stopped this activity.

CURIOSITY HELPS ANIMALS TO FORM MENTAL MAPS

Now that we know that the brain forms an internal map of the environment around us using place cells, let us think about the construction of this internal map from a different angle. To construct a map of the environment, an animal must move around and explore various regions of its environment. However, what would motivate the animal to do so? You might think that the animal would be motivated by hunger or thirst, but it turns out that animals explore their environments *even more* when they are not hungry or thirsty (Figure 3) [4]!

So, what else, besides hunger or thirst, could motivate an animal to move around in its environment? Here is a hint: what do you feel when you arrive in a new place? You probably guessed it—you experience *curiosity*! Curiosity is a very strong motivator, and it prompts animals to move around in their environments. In other words, curiosity is part of our nature as animals, and it is part of the system of building mental maps. Scientists believe that curiosity was formed by evolution, to drive us to explore our environments so that we could build mental maps of them—which helps us to successfully navigate in the world. If you think about it, it is curiosity that motivates us to acquire *any* new information, so it is interesting to wonder whether this ancient evolutionary impulse to navigate our environments also eventually led us to be interested in (and curious about) our favorite hobbies, skills, or crafts!

Figure 3

Animals form internal maps by exploring nature. When animals arrive in a new environment, they explore that environment out of curiosity. So, curiosity allows an animal to form a mental map of its environment.

Figure 3

MENTAL SPACE OR PHYSICAL SPACE?

Let us consider an interesting and complex philosophical puzzle: do we build our mental representations of space based our environments *as they actually are* in the outside world, or do we *create* the characteristics of physical space based on a mental model of space that we are born with?

Personally, I support the second option, which lines up with the ideas of the famous philosopher Immanuel Kant and the psychologist Edward Tolman. According to this approach, we are born with a set of brain structures that organize the world for us in a very specific and elementary way, so that we can make sense of the information we perceive about the world through our senses. In other words, the brain is organized and built to experience the world in a certain way; it uses a specific "lens" or "window" through which we perceive the world as we do. This approach means that we perceive space in a particular way because our brains are built in a particular way—not because the outside world, by itself, is inherently structured the way we perceive it. I admit that this is a hard concept to grasp, so take your time, think about it, and see where it leads you.

RECOMMENDATIONS FOR YOUNG MINDS

Brain-Inspired Recommendations for Life Decisions

I want to tell you a personal story and share some insights generated from our current understanding of the brain. I did very poorly in high school, so, when I was 18 years old, I had to think about my future and decide whether to accept that I was a failure. I decided that I had to take responsibility for constructing my own personality and my own life, and that I could not blame my failure on the world. I advise you to do this as well—and to understand that the brain is a very active organ. We spend a lot of time deciding what to do, what information to take in, how to handle that information, and how to interpret it. That means that we can take responsibility for, and control over, many of our actions—and their results.

Additionally, inspired by the navigation system in the brain, I believe that you should look at yourself and your situation and try to plan where you want to be—which might not necessarily match where you are now. You can use the brain's navigation system as a metaphor for finding your way through life. When you are at a particular location in your life trajectory, try to decide which direction you want to go. You may not get there—you may find that there are all kinds of roadblocks—but this is still a good way of organizing your life and making decisions. Remember that many routes can lead to the same destination! So be flexible, especially when you come across obstacles that divert you from your original route.

How to Enjoy Science

To be a good scientist, you must have a certain objective view of the world, and you must be prepared to change your mind according to the evidence. Science is not for everybody, because some people do not enjoy the uncertainty of dealing with unexpected truths. But for those who enjoy this type of journey, being a scientist is one of the most rewarding, exciting, and fulfilling careers that I know of (Figure 4). It is like living in a never-ending detective story, one in which every time you solve one mystery, a whole bunch of other interesting problems appear!

The trick is to pick an important area of science and a problem within that area that is solvable with the available tools—or a problem for which you can invent *new* tools that might make it solvable. Then, occasionally, you will be rewarded by the thrill of realizing that you discovered something important about how the world works—something that could influence a lot of people's ideas and perhaps even their lives. This sort of influence certainly is one of the ingredients of a successful and happy life.

Figure 4

Enjoying science. To be a good scientist, you must enjoy journeying in uncertainty, encountering unexpected truths, and changing your mind according to the evidence. Not everyone enjoys this type of journey, but those who do can truly enjoy a career in science. It is one of the most rewarding, exciting, and fulfilling careers available!

Figure 4

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YOUNG REVIEWERS

GEORG, AGE: 12

I am Georg, I like hanging out with my friends, riding my bike and playing sports, especially basketball. I also like natural and technical sciences. I am interested in understanding how things are built and repairing what has been accidentally broken. This is convenient when you consider that as a child, I was much busier breaking what was in my surroundings. So, now I can keep myself busy! I hope you will enjoy this manuscript as much as I did!

SUYANG, AGE: 15

Hello, I am a current 10th grader. I have been involved in several science and speech competitions, and I have been swimming for 10 years and I love it! I also love reading books (mostly science books and biographies), and my favorite historical character is the Chinese poet Sushi (Su Dongpo). I am interested in pursuing a career in either Engineering, or Medicine, or AI. I am excited to be a reviewer for Frontiers for Young Minds.

AUTHORS

JOHN O'KEEFE

Prof. John O'Keefe is a British-American neuroscientist. Prof. O'Keefe earned his bachelor's degree at the City College of New York (USA), where he studied psychology and philosophy. During this period, he also studied filmmaking, advanced English literature, physics, psychology, and philosophy—and this is when he met his wife Eileen. During this time, he got a firsthand taste for experimental brain research, and he was hooked. He supported himself by working in the library, showing classic European films for various courses, and driving a taxicab in the evening. Prof. O'Keefe then went on to earn his master's and doctorate degrees in psychology at McGill University in Montreal (Canada), which was considered

the Mecca for the study of physiological psychology. In 1967, Prof. O'Keefe joined University College London (London, UK) as a postdoctoral research fellow and he is still there, currently serving as a professor of cognitive neuroscience. During his years at University College London, Prof. O'Keefe studied the hippocampus using advanced brain recording techniques that monitored the electrical activity of individual neurons in the brains of rats. This research lead Prof. O'Keefe to the discovery of place cells, which are an important part of the navigation system in the brain. For this discovery, Prof. O'Keefe was awarded the Nobel Prize in Physiology or Medicine in 2014. Prof. O'Keefe won many other prestigious awards, including the Louisa Gross Horwitz Prize (2013), and the Kavli Prize in Neuroscience (2014). He is a fellow of the Royal Society. In 2016, he was elected to the National Academy of Sciences and, in 2019, he was admitted to the Royal Irish Academy as an honorary member. *j.okeefe@ucl.ac.uk

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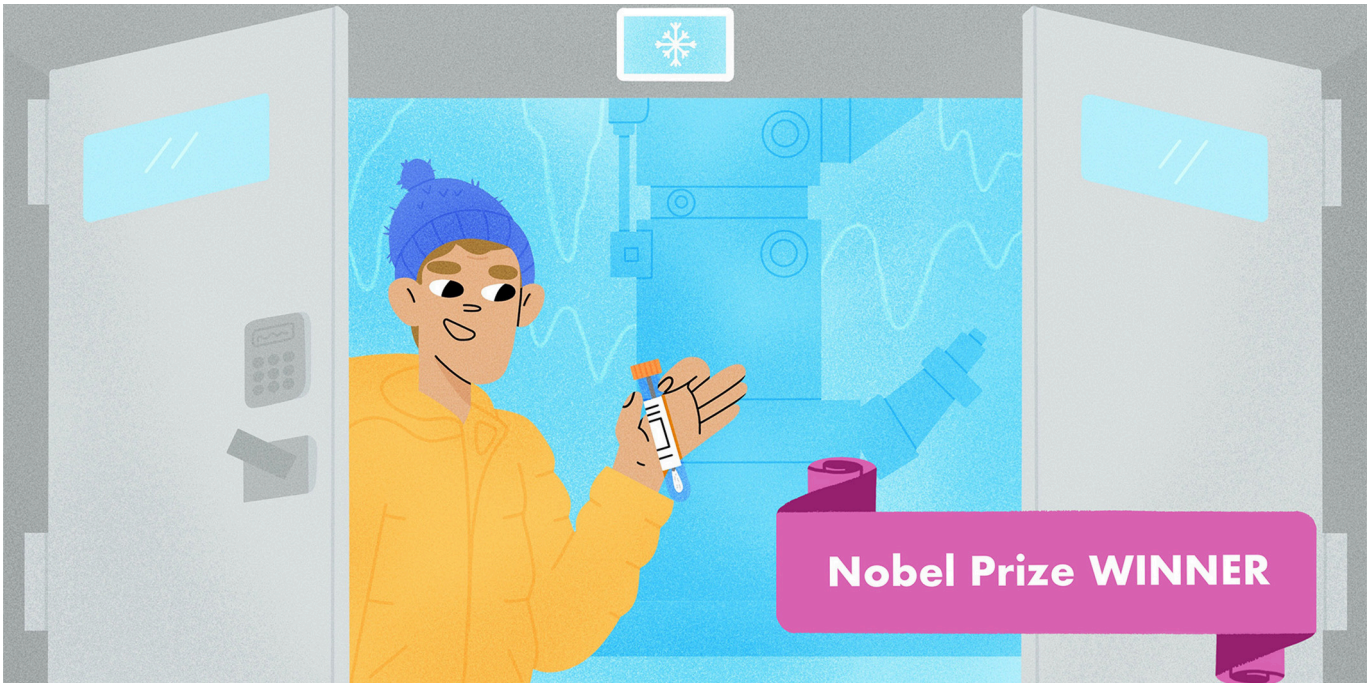

RESOLUTION REVOLUTION—SEEING THE MOLECULES OF LIFE WITH ELECTRON CRYOMICROSCOPY

Noa Segev[1*] *and Richard Henderson*[2*]

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YOUNG REVIEWERS:

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AGES: 11–12

This article is based on an interview between the two authors.

Structural biology is a field that seeks to find the structures of all the components that make up living things—from molecules that exist in humans and other animals, through molecules present in tiny microorganisms, to the molecules that make up plants. To determine these structures, structural biologists use sophisticated imaging techniques that are becoming more and more accurate at "seeing", or determining the structure of smaller and more diverse molecules. Electron cryomicroscopy is one very advanced and powerful imaging technique. In this technique, electrons are sent through frozen specimens to determine the structures of single molecules, at magnifications that are enough to see atoms. These images are taking us one step further toward understanding the structure and function of the basic building blocks of life. In this article, we will tell you about the developments that led to what is

called "the resolution revolution" in electron cryomicroscopy, which Dr. Henderson was part of and that eventually allowed him to share the Nobel Prize in Chemistry in 2017.

Dr. Richard Henderson won the Nobel Prize in Chemistry in 2017, jointly with Prof. Jacques Dubochet and Prof. Joachim Frank, for developing cryo-electron microscopy for the high-resolution structure determination of biomolecules in solution.

WHEN LOOKS MATTER: DISCOVERING THE STRUCTURES OF BIOLOGICAL MOLECULES

Living things contain many important structures and processes. In the human body, for example, we know there are organs, which are made from cells, and within these cells are many organelles and molecules that perform all the functions necessary to maintain life—such as producing energy, getting rid of waste, moving, and defending against harmful factors (Figure 1). To understand how living things work and to possibly improve their lives, we need to know which structures are present in a biological system and which activities those structures perform. **Structural biology** is the field that seeks to observe the structures of biological components. In the past, scientists would first look for specific activities that we knew were happening in a biological system, such as the conversion of one source of energy to another, storable type of energy. After we found the activity, we would identify the molecules that took part in it—usually **proteins** and **enzymes**, and only then determine the structures of those molecules.

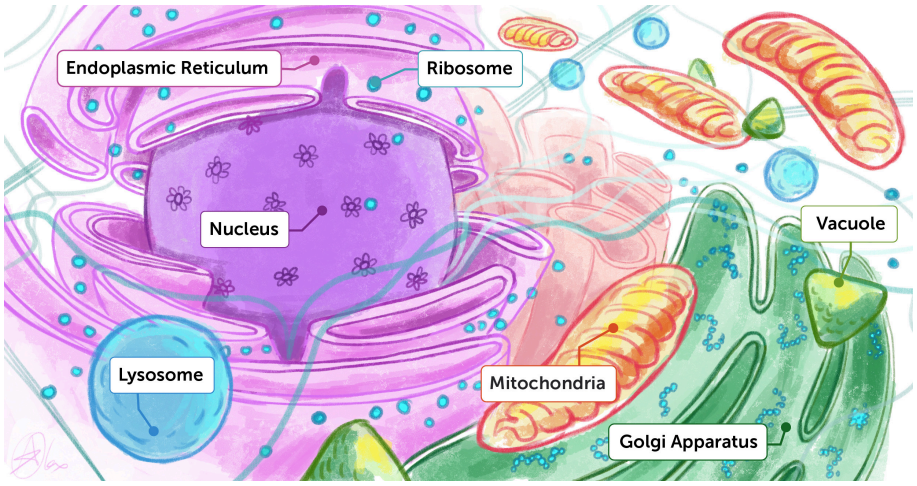

Figure 1

In 2000, the world experienced a revolution in the understanding of **genetic information (DNA)** the information stored in our cells, which we inherit from our parents. Scientists put together the first complete

STRUCTURAL BIOLOGY

A field of biology characterizes the structures of the components that make up living things.

PROTEIN

A tiny biological machine that performs many essential roles in the body.

ENZYME

A biological molecule that speeds up chemical reactions in the body.

Figure 1

Artist's interpretation of the inside of a cell. You can think of the inside of a cell like a dense playground containing many different molecules and organelles, each performing their unique functions. To understand how life works, we want to know both the structures and the functions of each of these biological building blocks.

GENETIC INFORMATION (DNA)

Information passed on from parents to their offspring, that determines the characteristics and behavior of an organism.

"set of instructions" (called the sequence of DNA bases) of the whole package of human genetic information. Since then, rather than looking for an activity, then finding a molecule, and then determining the structure of that molecule, structural biologists can use the genetic information, which tells them about all the enzymes and proteins in the body. In 2000, when the human genome was determined, about 80% of the molecules coded for in human DNA had not even been discovered! This opened up a whole new pathway in structural biology—we could now find the structures of molecules without having to know their functions first. How do we find the structures of these molecules? Using tiny particles called electrons!

ELECTRONS AND ELECTRON MICROSCOPY

Electrons are tiny electrically charged particles present in every atom. The movement of electrons is what creates electricity, and electrons are also the source of light and other forms of electromagnetic radiation such as X-rays. Can you believe that, until 1895, no one even knew electrons existed? In that year, electrons were first identified and named by JJ Thompson, a scientist in the physics department at the University of Cambridge in the United Kingdom. Thirty years later, in 1935, GP Thompson (the son of JJ Thompson), showed that electrons behave as both particles and waves—they have a **frequency** and a **wavelength**, just like other waves do. JJ and GP Thompson were both awarded Nobel Prizes: for the discovery of the electron as a particle and for the discovery of the electron as a wave.

FREQUENCY

The number of times a wave repeats itself in one second.

WAVELENGTH

The distance over which the shape of a wave repeats itself.

Shortly after that, scientists realized that if electrons behave like waves, in some sense they must behave like light—because light can also behave like a wave. So, scientists thought that maybe they could use electrons to illuminate tiny specimens they wanted to look at, the same way we can look at an object with our eyes, with a camera, or with a regular microscope—but using electrons instead of visible light. This was the start of **electron microscopy**. Electron microscopy is a very powerful imaging technique. Electrons have a very short wavelength, about 100,000 times shorter than the wavelength of light. You can think of the wavelength as a "zooming" parameter—the smaller the wavelength, the more we can "zoom in" on our specimen. This means that pictures taken with electrons have a very high level of detail, which is called a high resolution. Due to its high resolution, electron microscopy can be used to discover the structures of tiny molecules in a way that was not possible previously.

ELECTRON MICROSCOPY

A technique that uses electrons to image small structures, including biological molecules.

HOW DOES ELECTRON MICROSCOPY WORK?

In electron microscopy, an energetic beam of electrons emerges from an electron source and passes through the specimen being studied (Figure 2A). When electrons pass through the specimen, they interact

DIFFRACTION

The scattering of a wave by an object; for example the scattering of electrons by a specimen.

with its atoms and get **diffracted**, or thrown off course, in a way that is specific to the arrangement of atoms they encounter. In this way, the electrons "pick up" the structure of the material as they pass through it. After the electrons are diffracted, they are collected and focused using lenses (much like the lenses inside a camera), and then they are recorded by an electron detector. At this stage, scientists have an image of the electrons that were diffracted from the specimen, and they must convert it to an image of the specimen itself. This conversion is based on simple physics that describes the relationship between a measured object and the resulting image. The conversion depends on many factors, including the wavelength of the electrons and the lenses that are used; but that is all taken care of by microscopy experts.

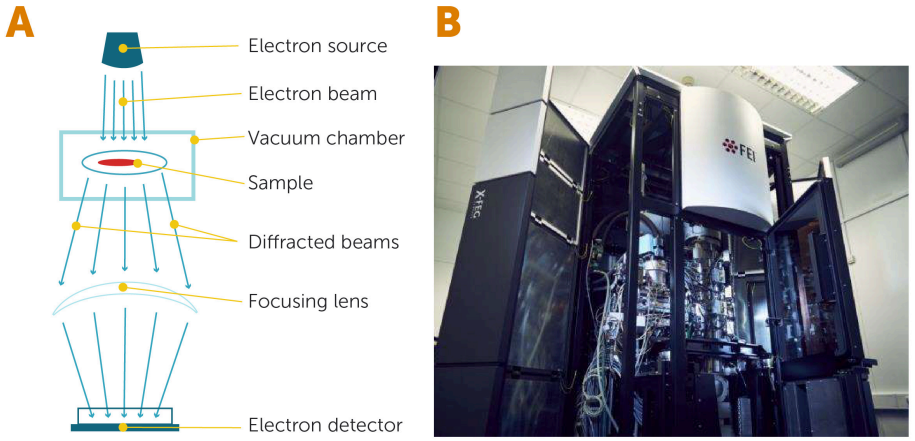

Figure 2

Figure 2

Electron microscopy. **(A)** In an electron microscope, a source of electrons releases a beam of hot, energetic electrons that passes through a specimen, which is located inside a vacuum chamber. When the electrons interact with the specimen, they get diffracted (scattered) and are then collected and focused by special lenses before being detected by an electron detector. **(B)** An electron microscope from the University of Cambridge (United Kingdom), which allows scientists to image frozen biological specimens (Image credit: University of Cambridge).

CHALLENGES IN ELECTRON MICROSCOPY

Even though electrons can help us get remarkable images of molecules, there are major challenges to be overcome when using them to image biological molecules. First, as quantum physics tells us, individual electrons are not "logical"—when you ask them a question (for example, what happens when they meet a specific molecule), they do not return a definite answer like a human would. Instead, they have a certain *probability* (likelihood) of participating in each possible outcome. In the electron world, everything that could happen *did happen*, with a certain probability for each option. This means that scientists must collect many answers from many electrons, and combine the information intelligently to get the overall answer. To accomplish this, we illuminate the specimen with millions of electrons and use the overall *average* of their properties to obtain a sensible answer.

Second, the electrons can damage the specimen, because they are very energetic and must pass all the way through the specimen to arrive at the detector. Their temperatures can get to about two thousand million°C—for comparison, water boils at 100°C!

These super-energetic electrons, and any other type of energetic radiation, can pull electrons out of the specimen's molecules. This changes the shapes and properties of the specimen's molecules, because biological molecules are relatively delicate. Therefore, it is difficult for scientists get enough information about the structure of a single biological molecule before it is destroyed. One way to address this challenge is to take images of many *separate, identical* molecules—at least 500, in the case of electron microscopy of biological molecules—and average the images to get the structure of a typical molecule. Another way we can deal with this challenge is to cool the specimen in a special way that makes it more resilient to electron damage—this will be described in the next section.

Yet another challenge comes from the fact that electrons are diffracted as soon as they are near any atoms. This means that there must be a completely clear pathway between the electron source and the specimen, so that the electrons will arrive at the desired molecules and not be scattered due to other molecules, even oxygen and nitrogen in the air, that are in the way. In other words, scientists must create a vacuum around the specimen in the electron microscope. Since biological molecules are always in a water-containing solutions (think, for example, about the molecules in your blood), the problem is that water evaporates in a vacuum, and the specimen dries up. This drying often damages biological molecules in the specimen. Overcoming this challenge required structural biologists to use their creativity to take advantage of the unique properties of water.

CAN WATER STAY LIQUID WHEN IT IS VERY COLD?

Here is a really nice experiment you can try at home to understand one of the unique properties of water (Figure 3). Take an empty jar with a lid and fill it full of water. Try to make sure there are no air bubbles in the jar by screwing the lid on tightly under water and put it in the freezer. Leave the jar in the freezer for a day—by then the temperature of the water will go down to −10°C or −20°C (Water normally becomes ice at 0°C). The next day, take the jar out of the freezer and take a look—has the water turned into solid ice, or did it stay liquid?

SUPERCOOLED

Cooled below the freezing temperature while staying liquid (i.e., without crystalizing).

Most often, you will find that the water is still liquid—it has been **supercooled**, meaning that it cooled down to a temperature lower than its freezing temperature (0°C), but without turning into ice. In our experiments, we want to cool water even further, to below −170°C, because at this temperature it becomes very still and stable. We also want to avoid creating ice crystals, because they interfere with our measurements. To accomplish this, we must use a special cooling method developed in the lab of Jacques Dubochet, who shared the Nobel Prize in Chemistry with me, Richard Henderson, and Joachim Frank in 2017. In this method, we use very cold liquid ethane or propane (substances found in natural gas, made from carbon and

Figure 3

Supercooling water at home. **(1)** Take an empty jar, fill it up completely with water, and make sure there are no air bubbles inside. **(2)** Seal the jar tightly and **(3)** put it in the freezer for a day. **(4)** Then, take the jar out. Is the water frozen or still liquid? If it is still liquid, you have created supercooled water!

hydrogen), cooled to −185°C. We then plunge a very thin film of water into the cooled ethane/propane liquid, and it cools down so quickly—in about 1/1,000 of a second—that it has no time to form organized ice crystals and stays in the unorganized, liquid form [1] that we call amorphous ice. In this way, we get supercooled water.

THE MAGIC FORMULA OF HOT ELECTRONS AND COLD SPECIMENS

It turns out that supercooled thin films of water are great for suspending the biological molecules we want to image with electron microscopes. When we add this cooling step to the imaging process, this is called **electron cryomicroscopy** ("cryo" is short for "cryogenic," which refers to cooling). Electron cryomicroscopy allows us to deal with two of the challenges mentioned above: it stabilizes the specimen, making it more resilient to damage by high-energy electrons, and it allows biological molecules to be in their natural watery environment, without evaporation of water due to vacuum. There is one more important advantage: unlike most other liquids, water *expands* when it is cooled below 4°C. This feature of water helps biological molecules to remain undamaged when they are in supercooled water. If water contracted when cooled, it would squeeze the molecules and possibly break them.

ELECTRON CRYOMICROSCOPY

A technique that uses electrons to image biological molecules that are in water and are cooled to low temperatures very rapidly.

This rather simple yet highly effective electron cryomicroscopy imaging method allows us to image biological molecules at a resolution that was previously unattainable. This is why it is sometimes referred to as the "resolution revolution".

Figure 4 shows examples of beautiful images obtained using electron cryomicroscopy. We are dealing with extremely tiny scales—10's of nanometers, which is less than 1/1,000 the width of a human hair! Hopefully you are beginning to appreciate the wonder of electron cryomicroscopy.

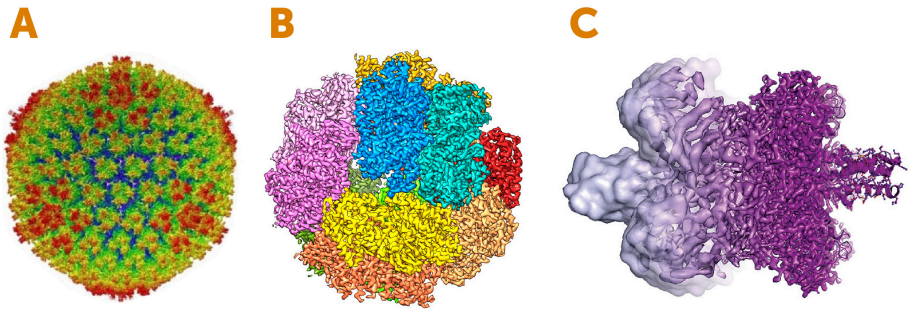

Figure 4

Figure 4

Images created using electron cryomicroscopy. **(A)** Structure of a disease-causing virus called Adenovirus. The image shows the outer surface called the capsid, which is the protein shell that wraps the virus's genetic material. The colors represent the distance from the center of the sphere: red is the furthest from the center and blue is the nearest. **(B)** An enzyme involved in energy generation in microbes. The colors represent the individual subunits (pieces) of the enzyme. **(C)** An example of how the resolution of electron cryomicroscopy has improved between 2013 (left, light purple) and 2017 (right, dark purple). Image Credits: **(A)** adapted from [2]; **(B)** adapted from [3]; **(C)** Martin Högbom, Stockholm University, based on an image by V. Falconieri.

WHAT DOES THE FUTURE HOLD FOR ELECTRON CRYOMICROSCOPY?

Electrons are the best particles to use for imaging tiny biological molecules. To give you a sense of just how good they are, let us compare them to two other commonly used particles: X-ray photons (similar to light particles but with short wavelengths), and neutrons (particles from the nuclei of atoms). When we calculate the amount of information we receive from using a certain particle compared with the damage that particle creates in the specimen, we get a measure of how good the particle is for imaging. Using that calculation, electrons are 1,000 times better than X-rays, and three times better than neutrons! That is why my colleagues and I started using electrons instead of other particles many years ago. Nowadays, electron cryomicroscopy has become so successful that the number of structural biologists using it is high and increasing rapidly.

There are still significant improvements to be made in electron cryomicroscopy. One is improving the electron detectors, which are still not large or efficient enough and require us to use many more electrons than theoretically required. It would also be helpful to minimize the motion of the specimen (both the water molecules and the biological molecules) when it contacts the electron beam [4, 5]. We believe that, in about 5 years' time, there will be significant advances to address these challenges. We will then have an even more powerful tool that will allow us better to understand many biological questions, such as how life works and how it reproduces. The information we acquire might help us to maintain the health of people, animals, and plants. We can expect a very bright future for electron cryomicroscopy!

RECOMMENDATIONS FOR YOUNG MINDS

I, Richard, want to share some practical advice that I have followed throughout my career. It comes from the writing of Peter Medawar, who won a Nobel Prize in Physiology or Medicine in 1960. After

winning the Nobel Prize, Peter Medawar published two books called "The Art of the Soluble," and "Advice to a Young Scientist." In his books, he said that there are many interesting things in science and life, and that we should be interested in everything. But we should also pick something that we are particularly interested in to work on. Moreover, he said that scientists should work on something that will successfully produce new knowledge *soon*—not in 100 years, because that is beyond a scientist's lifetime. His idea was that science is the art of the *soluble*, meaning problems that can be solved. Scientists should do experiments that work *now*, with current techniques.

When I was a young student of physics, I wondered where physics was going, and I remember making a list of all the interesting topics of the future. There was fusion research, which involves producing unlimited power from hydrogen fusion. Then there was high-energy particle physics, which led to the discovery of new particles, including the Higgs boson and more. There was solid-state physics, which advanced the computer industry and the development of the microchips that fuel computers. Biophysics, astrophysics, cosmology, black holes, and neutron stars, to name just a few, were other interesting topics (Figure 5). If I had picked any of those topics to study, they would have been equally interesting and exciting. So, if you decide to go into science, you must pick something that you are interested in, so that you will keep studying and working on it without anybody forcing you to do so. When you are interested and self-motivated, if you run into difficulties. it will not bother you too much—you will just take it as a challenge and move on. Once you have chosen an interesting topic, before you actually head off in that direction it is best to find out as much as you can about the various activities that you could pursue to study the topic. If, after 6 months or a year of your best effort, it turns out that your idea was not so good, do not hesitate to think again and find a new direction.

Figure 5

Choosing a scientific field. When I was a physics student, there were many interesting topics I could choose from. In hindsight, I realize that all of them would have been equally interesting for me. When you chose a field, make sure to choose something that you find interesting and that will keep you motivated over a long period of time.

Today, science is moving very rapidly compared to the past. Only a 100 years ago, we did not even know about the existence of X-rays and electrons, and now we have information about the whole human genome, we have sophisticated methods to work with DNA, and we can figure out the structure of virtually anything we want. The next 100 years will be a very good time to be alive—and to be a scientist. Enjoy your life and invest yourself in whatever is most interesting to you!

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ADDITIONAL MATERIALS

Richard Henderson Nobel Lecture 2017.

Electron Cryomicroscopy—Richard Henderson at Serious Science.

Explainer: What is cryo-electron microscopy (Chemistry World).

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YOUNG REVIEWERS

HOLLY, AGE: 15

I am an aspiring biomedical student and love all things related to the human body. I enjoy watching crime shows that use science to solve the mystery. I have been surrounded by medical science and research my entire life. When I am not studying, I am a musician, dancer, and an artist.

Y7 LAURUS INTERNATIONAL SCHOOL OF SCIENCE, AGES: 11–12

We are the Laurus Year 7 class in Tokyo! We are interested in anything Science! Also we like to play Fortnite and chess.

AUTHORS

NOA SEGEV

Noa Segev is a scientific writer and project coordinator at Frontiers for Young Minds. She earned her B.Sc. in physics at The Hebrew University of Jerusalem and her M.E. in renewable energy engineering at the Technion—Israel Institute of Technology. Since 2019, she has been interviewing Nobel Prize winners and co-authoring articles for the Nobel Collection at Frontiers for Young Minds. Noa aims to make the science behind Nobel Prize-winning discoveries accessible to all, and to share valuable insights from the vast professional and personal experience of Nobel Laureates. *noasegev@gmail.com

RICHARD HENDERSON

Dr. Richard Henderson is a Scottish biophysicist and molecular biologist who serves as a research scientist at the MRC Laboratory of Molecular Biology, affiliated to the University of Cambridge (England). Dr. Henderson earned his B.Sc. in physics at the University of Edinburgh (Scotland) and his Ph.D. in molecular biology at the University of Cambridge (England), where he studied the structure of a digestive enzyme.

Dr. Henderson then did postdoctoral research at Yale University (Connecticut, United States). In 1973, Dr. Henderson returned as an independent research scientist to the MRC Laboratory of Molecular Biology in Cambridge, where he currently works. Over the years, Dr. Henderson worked on improving electron microscopy, increasing its resolution, and making it applicable for imaging delicate biological specimens. This was a major technological advancement, which supported the field of molecular biology by allowing scientists to image a much wider variety of biological specimens. For this advancement, Dr. Henderson shared the Nobel Prize in Chemistry in 2017. In addition to the Nobel Prize, Dr. Henderson has won numerous other prestigious awards, including the Rosenstiel Award for Distinguished Work in Basic Medical Research (1991) and the Copley Medal of the Royal Society (2016).
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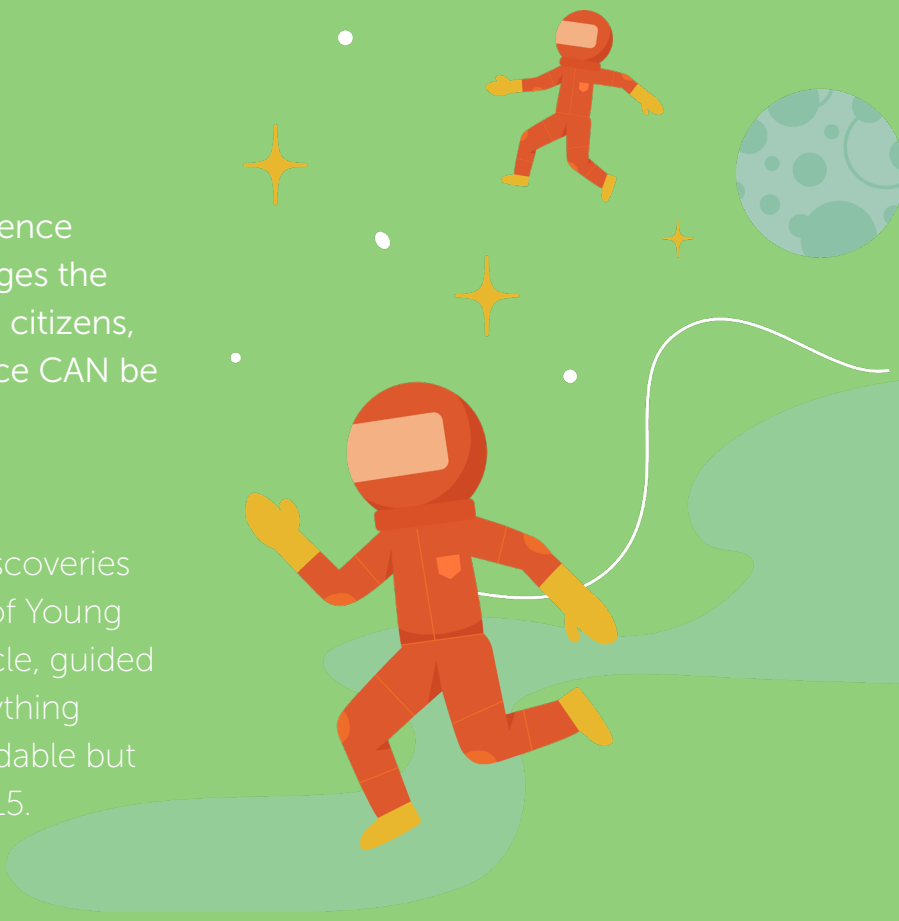

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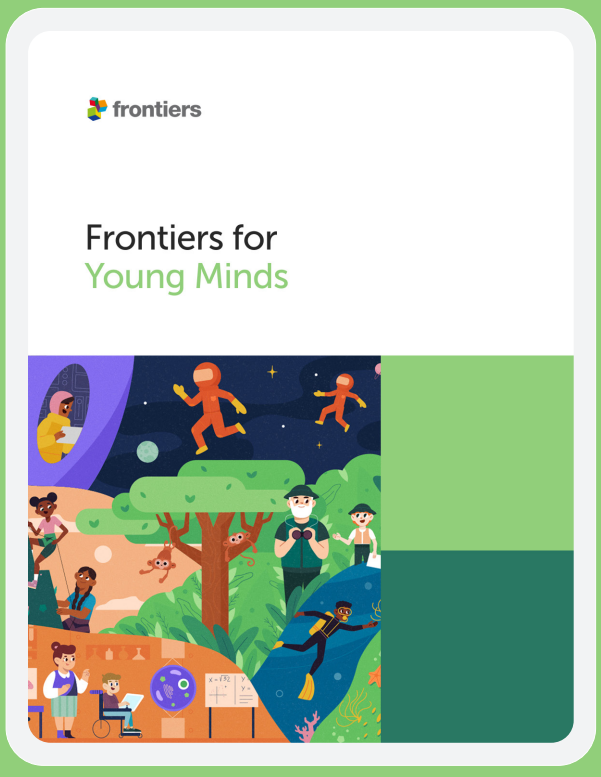

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