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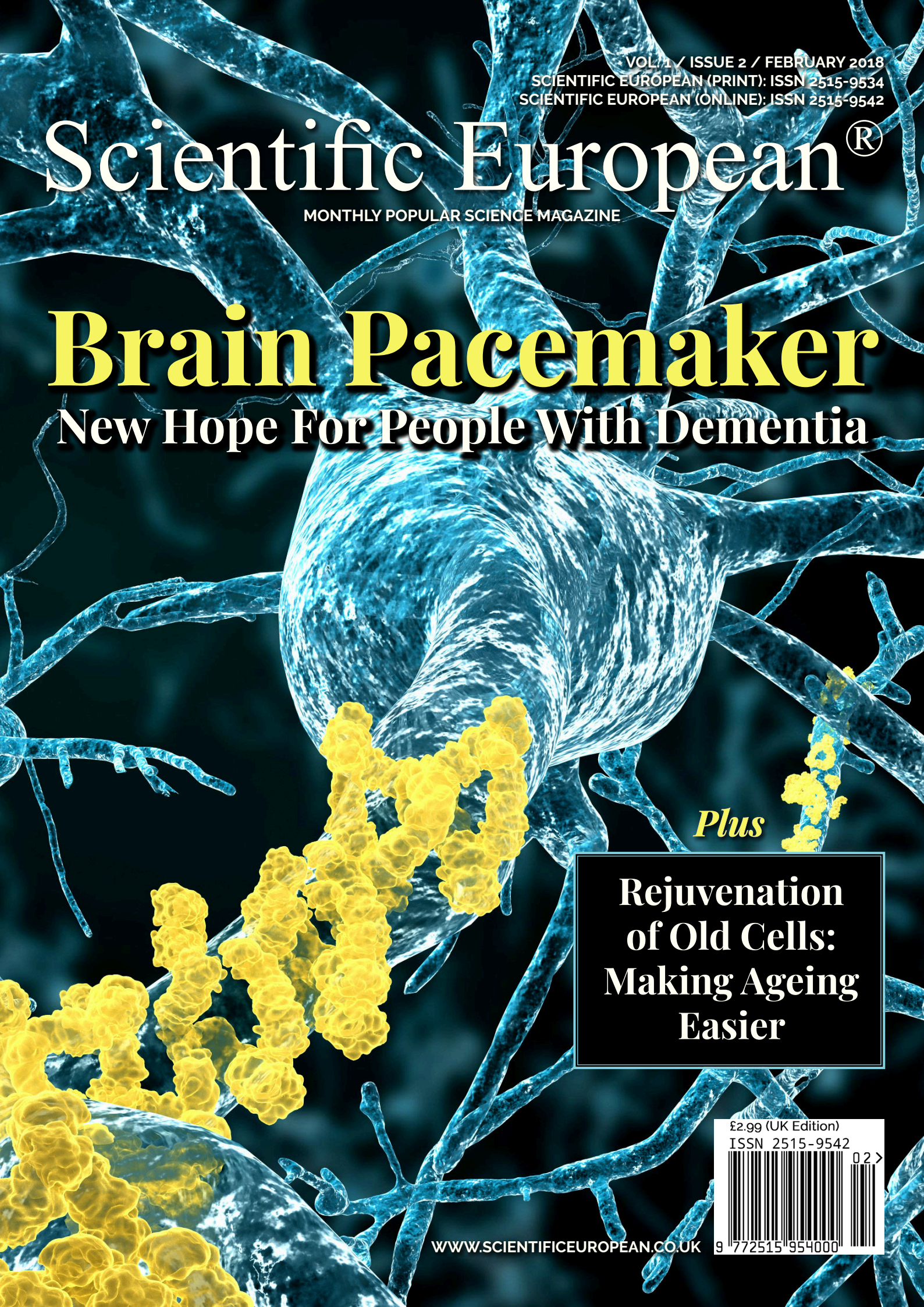

Brain Pacemaker

New Hope For People With Dementia

Plus

Rejuvenation of Old Cells: Making Ageing Easier

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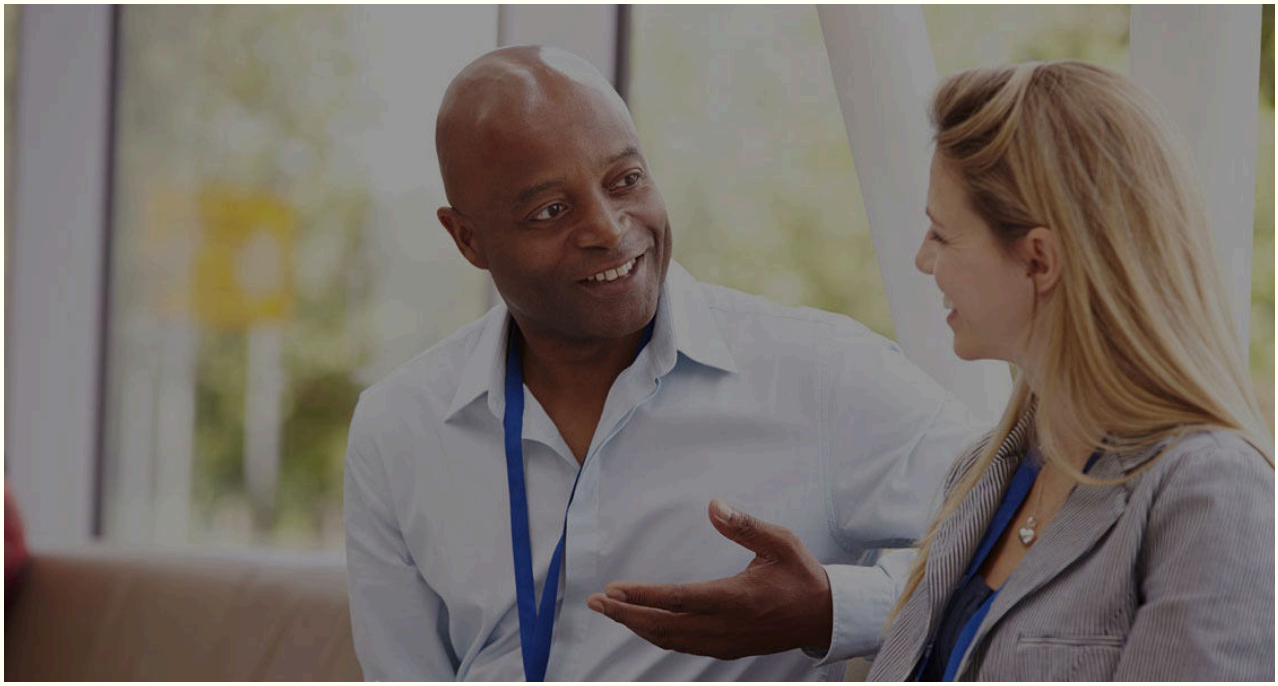

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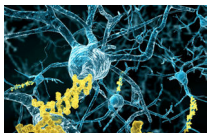

NOTE FROM THE FOUNDER & EDITOR-IN-CHIEF

We are delighted to bring eight articles on latest scientific breakthrough that promise to improve millions of lives – brain pacemaker for Alzheimer's, bionic eye for retinal and optic nerve pathology, way forward for antibiotic resistance, new approach to drug deaddiction and many more.

Hope you find these intellectually stimulating!

Umesh Prasad

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Rejuvenation of Old Cells: Making Ageing Easier

A groundbreaking study has discovered a novel way to rejuvenate inactive human senescent cells providing enormous potential for research on ageing and immense scope for improving lifespans

A team led by Professor Lorna Harries at University of Exeter, UK[1] has shown that chemicals can be successfully used to making senescent (old) human cells to rejuvenate and thus appear and behave younger, by regaining features of youth.

Ageing and "Splicing factors"

Ageing is a very natural yet a highly complex process. As the ageing progresses in a human body, our tissues accumulate old cells which are though alive, they do not either grow or function as they should (like the young cells). These old cells also lose the ability to correctly regulate the output of their genes which basically affects their function. This is the primary reason why our tissues and organs become more susceptible to diseases as we age.

"Splicing factors" are very crucial in ensuring that genes can perform their full range of functions and the cell will essentially know "what they have to do". This has also been shown by the same researchers in a previous study[2]. One gene can send out several messages to the body to perform a function and these splicing factors make the decision about which message needs to go out. As people age, these splicing factors tend to work less efficiently or not at all. Senescent or old cells, which can be found in most organs of older people, also have fewer splicing factors. This scenario thus restricts the ability of cells to respond to any challenges in their environment and impacts an individual.

The "magic" so to speak

This study, published in *BMC Cell Biology*, shows that the splicing factors that start to "switch off" in old age can actually be switched back "on" by applying chemical compounds called reversatrol analogues. These analogues originate from a substance which is common to red wine, red grapes, blueberries and dark chocolate. During the experiment, these chemical compounds were directly applied to a culture containing cells. It was seen that just a few hours after the application, the splicing factors started to rejuvenate, and the cell started dividing themselves the way young cells do. They also now had longer telomeres (caps" on chromosomes which grow shorter and shorter as we age). This led to natural restored function in the cells. The researchers were pleasantly surprised by the degree and also rapidity of the changes in the old cells during their experiments, as this was not an entirely expected outcome. This was really happening! This has been labelled as "magic" by the team. They repeated the experiments several times and they achieved success.

Easing the ageing

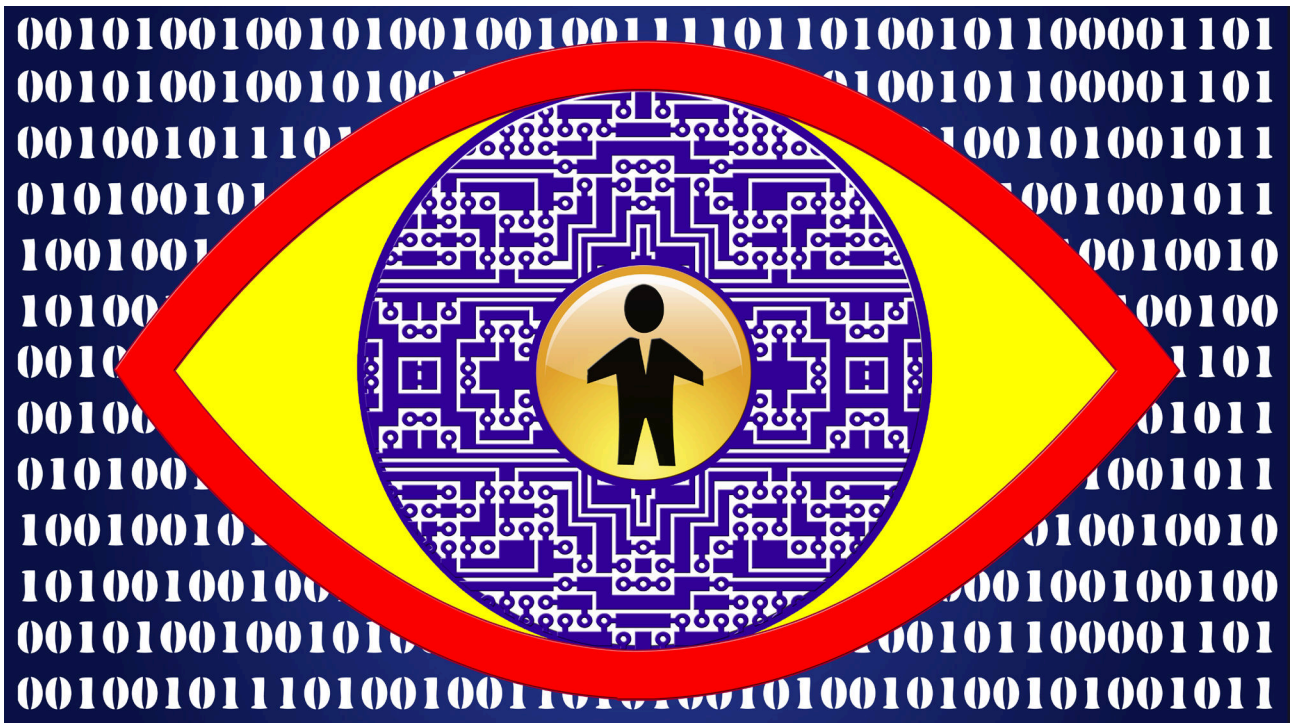
Ageing is a reality and is inescapable. Even people who are lucky enough to age with minimal limitations still suffer some degree of loss both physically and mentally. As people get older they are more prone to stroke, heart disease and cancer and most people by the age of 85 have experienced some kind of chronic illness. Also, it's a common assumption that since ageing is also a physical process, science should be able to address it and be able to ease it or treat it like any other physical illness. This discovery has the potential to discover therapies which could help people age better, without experiencing some of the degenerative effects of getting old, especially deterioration in their bodies. This is the first step in trying to make people live normal lifespans, but with health for their entire life.

Direction for the future

This research, however, only addresses one part of aging. It does not discuss or take into account the oxidative stress and glycation which are also crucial to the ageing process. It is clear that more research is obviously needed at the moment to establish the true potential of similar approaches to address the degenerative effects of ageing. Though many scientists argue that changing ageing would be like a denial of the natural limitations of our human existence. This study, however doesn't claim to have discovered the eternal fountain of youth but does generate immense hope to embrace ageing and to relish and appreciate every period of this gift called life. Just as antibiotics and vaccinations have led to an extension of lifespan in the past century, this is a crucial step towards its improvement. The researchers further insist that more research into the degenerative effects of ageing then would lead to the ethical debate on whether science should be used to only improve or also extend people's lifespans. This is highly controversial but there is no doubt that we need a practical action to not only restore older people's health but also provide every human with a healthier "normal life span".

Source:
1. Latorre, E. et al. 2017, 'Small molecule modulation of splicing factor expression is associated with rescue from cellular senescence'. *BMC Cell Biology,* vol. 8, no.1 DOI: 10.1186/s12860-017-0147-7
2. Harries, LW. et al. 2011, 'Human aging is characterized by focused changes in gene expression and deregulation of alternative splicing'. *Aging Cell*, vol. 10, no. 5, pp. 868–78. DOI: 10.1111/j.1474-9726.2011.00726.x

Bionic Eye: Promise of Vision for Patients with Retinal and Optic Nerve Damage



Studies has shown that the "bionic eye" promises to help restore vision to many patients suffering from partial or complete blindness

The structure of the human eye is quite complex and how we are able to see is quite an intricate sequential process which takes place in less than a millisecond. Any light first passes through a protective sheet of the eye called cornea and then it moves into the lens. This adjustable lens in our eye then bends the light, focusing it into the retina - the tissue membrane that coats the back of the eye. The millions of receptors in the retina contain pigment molecules which change shape when they are hit by light, thus triggering electrical messages which travel to our brain via the optic nerve. Thus, we perceive what we see. When any of these tissues - cornea and retina - or the optic nerve are unable to function properly, our vision gets affected. Though vision problems can be corrected by eye surgeries and also by wearing glasses with corrective lens, many conditions lead to blindness which is sometimes incurable.

Invention of the "bionic eye": a miracle indeed

According to World Health Organization, an estimated 1.5 million people worldwide, have an incurable disease called retinitis pigmentosa (RP). It affects about 1 in 4,000 people worldwide and causes gradual vision loss when light-sensing cells called photoreceptors break down in the retina eventually leading to blindness. The implantable visual prosthetics called the "bionic

eye" [officially named Argus® II Retinal Prosthesis System ("Argus II")] invented by Professor Mark Humayun of the University of Southern California, restores functional vision in people suffering from complete or partial blindness[1,2] due to inherited retinal degenerative disease. The Argus II captures images on an eyeglass-mounted small video camera, converts these images to electrical pulses, and then transmits those pulses wirelessly to electrodes implanted on the retinal surface. Thus, it bypasses defunct retinal cells and stimulates the viable retinal cells in blind patients, resulting in the perception of patterns of light in the brain. The patient then learns to interpret these visual patterns, thereby regaining some useful vision. The system is controlled by a software which can be upgraded for better performance as the researchers continue to develop new algorithms.

Success with human participants

In continuation to their findings, the manufacturer and marketer of "bionic eye" Second Sight Medical Products, Inc. ("Second Sight") [3] has shown that five-year clinical trial results3 of the retinal implant have proven the long-term efficacy, safety and reliability of this device in improving visual function and quality of life for people blinded by retinitis pigmentosa. Their study led by Professor Lyndon da Cruz at Moorfields Eye Hospital NHS Foundation Trust, assessed 30 subjects in the clinical trial who were implanted with the Argus II in 10 centres across United States and Europe. All patients were blind (i.e., with bare light perception or worse) from RP or similar disorders. The results demonstrated the overall safety of Argus II by improved visual function in patients and these improvements were sustained over the course of five years. Patients reported that after using Argus II, they had a renewed connection with the outside world and their family and friends and felt an overall life-altering positive change in their wellbeing. This is an extremely remarkable study and provides promising news for patients blinded by retinitis pigmentosa.

Social aspects of the miracle eye

The Argus II is the first and only retinal implant to have demonstrated safety, long-term reliability and benefit through appropriate studies thus gaining approvals in US and Europe. Since the end of 2016, over 200 patients have been treated of their blindness with the Argus II. The costs evaluated for Argus II (about USD 16,000 for a duration of 25 years when the patient is first diagnosed with RP). In a publicly funded healthcare system (in many developed countries) it could be easily accessible for the patients. The costs could also be justified under a health insurance coverage especially when the onset of the condition happens gradually. The high costs may not act as a deterrent when compared with long term "usual care" needs for such patients. However, if we think of access to this technology in developing countries' or even middle-income countries, the possibilities appear very low because of the high costs involved in an out-of-pocket payments scenario.

Future of bionic eye: the brain link

After successful testing on human, Second Sight is now including a feasibility study of the Argus II and hardware and software upgrades for existing and future Argus II patients. Also, a very interesting new area which they are focusing on is the development of an advanced visual prosthesis, the Orion™ I Visual Cortical Prosthesis[4], aimed at patients with nearly all
other forms of blindness in one or both eyes. This is a just a slightly modified version of Argus II bionic eye, which involves a pair of glasses outfitted with a camera and an external processor, however using 99 percent of Argus II's technology. In comparison to the Argus II, Orion I is a neuro stimulation system that bypasses the eye and instead, an array of electrodes are placed on the surface of the visual cortex (part of the brain that processes visual information). Thus, delivering electrical pulses in this area will possibly tell the brain to perceive patterns of light. This wireless device was recently implanted to a 30-year-old woman patient's visual cortex and several tests showed that this patient was able to perceive spots of light and without any major side effects.

Orion I is currently (end of 2017) approved for clinical trial and has been granted a conditional approval by FDA for testing on only five human subjects at two locations4. Second Sight is currently conducting further testing of the device and answering certain questions before starting the actual trial. A major downside of Orion I is that it requires a more invasive surgery than the Argus II as a small section of the human skull needs will needs to be removed to expose the area of the brain where the array of electrodes will be placed. Such electrical brain implants definitely carry risks of infection or brain seizures and the company only plans to test on human subjects who are completely blind.

By bypassing the eye, the Orion I could be a miracle for other types of blindness which is caused by damaged optic nerve due to any of the multiple reasons including glaucoma, cancer, diabetes, injury or trauma. The technology which the Orion I proposes to use will essentially replace the eye and the optic nerve completely and cure blindness. This device which is now on fast track for trials and approvals is seen as a game changer for people with no cure or treatment available for their blindness i.e. worldwide, nearly six million people who are blind but are not a suitable candidate for an Argus II.
Second Sight estimates that about 400,000 retinitis pigmentosa patients globally are eligible for its current device Argus II. Though about 6 million people who are blind due to other causes, like cancer, diabetes, glaucoma, or trauma could hypothetically use the Orion I instead. Also, Orion I may provide better sight compared to Argus II. However, the researchers are aware they are still in the early days of understanding such a brain implant because it will be medically more difficult and challenging to get right than a retinal implant because the brain's visual cortex is far more complicated than the eye. Also, this device will require more invasive surgery through the brain thus making the patients more prone to infection or seizures. Orion I will also possibly require more approvals from regulators because of all these aspects.

Source:
1. Allen, C., Ho, M.D. et al. 2015, 'Long-Term Results from an Epiretinal Prosthesis to Restore Sight to the Blind'. *Opthamology*, vol. 122, no. 8, pp. 1547-54. DOI: 10.1016/j.ophtha.2015.04.032
2. da Cruz L et. al. 2016, 'Argus II Study Group. Five-Year Safety and Performance Results from the Argus II Retinal Prosthesis System Clinical Trial'. *Ophthalmology*, vol. 123, no. 10, pp. 2248-54, DOI: 10.1016/j.ophtha.2016.06.049.
3. Second Sight Medical Products, Inc.: www.secondsight.com
4. U.S. National Library of Medicine. 2017, 'Early Feasibility Study of the Orion Visual Cortical Prosthesis System', Accessed February 9, 2018, https://clinicaltrials.gov/ct2/show/NCT03344848

Immortality: Uploading Human Mind to Computers?!

The ambitious mission of replicating the human brain onto a computer and achieving immortality.

Multiple research shows that we could well imagine a future where infinite number of humans can upload their minds to the computer thus having an actual life after death and achieving immortality.

Do we have the ability to make the human race immortal?

Every human being completes a life span by undergoing a steady process of ageing - starting from birth and eventually leading to death. Ageing is a natural and inevitable process in which the living cells in our body start to degenerate as we age. Thus, the human species has a 'limited' life span and every human being will go on to live for an average of 80 years. Still, it is not unusual that humans 'want to be' or rather 'wish' to 'live forever' and be immortal. Immortality has been tagged as a matter of fiction and a trait which in many cultures is possessed by spirits and Gods. People have always envisioned about possibilities that lie beyond the limitations of their biological bodies, an afterlife and no fear of death.

Currently, a lot of research is happening to understand if this science fiction can be turned into reality. It is being believed that the unthinkable might be achievable and science can provide a futuristic way for humans to evolve beyond their physical form and existence. A recent immortality research has shown that implementing certain ideas can extend the human life to around a thousand years[1]. In this study published in *Plos One* scientists have detailed how they were able to produce a pattern very similar the fluctuations in the brain. Basically, suggesting that considerable portions of the post-mortem human brain might retain certain capabilities through which it can still respond.

Through his 2045 initiative[2], Russian billionaire Dmitry Itskov claims that humans will achieve digital immortality by uploading their minds to computers and thus staying alive forever by transcending the need for a biological body. He is working along with a network of scientists including neuroscientists and computer experts to develop what is termed as "cybernetic immortality", within the next few decades (or by 2045). He and his team have proposed to create an 'avatar' in the next five years in which the entire human brain can be transplanted after death. The avatar will be essentially robots who shall be controlled by the mind and they will keep sending feedback to the brain through an efficient brain-computer interface. This avatar could store a human personality till about 2035 and by the year 2045 a hologram avatar would be available. Itskov, labelled as a "transhumanist" claims that once this perfect mapping of the human brain and transfer of the consciousness into the computer becomes a success, any human can live longer as a humanoid robot body or as a hologram. Ray Kurzwell, director of engineering at Google Inc., has also boldly pointed out that the "human race is going to transcend to a non-biological entity for which the biological part is not important any more".

The human mind can be immortal?

The human mind is a collection of different cognitive capabilities which include consciousness, sub-consciousness, perception, judgement, thoughts, language and memory. From the technology point of view, making one's mind immortal is not as unreasonable as it sounds, because a human mind is simply a software and the brain its hardware. The brain therefore turns inputs (the sensory data) into outputs (our behaviour) through computations just like the computer. This point is the start of the theoretical argument for mind uploading. It has been described as mapping the connectome - the complex connections of all the neurons in a brain – which hold the key to the human mind. If this process could be thoroughly mapped, then the brain could be technically 'copied' onto a computer, along with the individual's 'mind'. Thus, the matter of our mind (the neurons) could be possibly transferred to a machine and erased from the brain while the mind will still have the continuity of experience that typically defines a human's individuality. According to many neuroscientists, connectome could be very possibly implemented into a computer simulation controlling a robotic body outside of our physical bodies.

However, to be fair and realistic, this is a far more bigger challenge than it appears especially in the context of the existing technology and further complicated by the fact that there are trillions of connections between the approximately 86 billion neurons in a human brain and these neurons constantly change their activity. The "mapping" of all these connections, with the current technology can only be done on a dead and sectioned brain if at all. Also, most of the number and kind of molecular-level interactions of the brain are not completely understood yet. Further, simulating one or several aspects of the brain might be achievable but that cannot let us emulate the brain collectively i.e. the "mind" even with the fastest computing power available.

The debate

On an encouraging note, the field of neural engineering is making significant advances toward modelling the brain and developing technologies to be able to restore or replace some of its biological functions. Mind uploading is very ambitious goal and whole lot of debate is happening in the scientific community worldwide over the very central idea of whether the intricacies of

the human brain can even be replicated in a machine at all. Many Physicists disagree with the interpretation of the brain as merely a computer, and they rather define the human consciousness as quantum mechanical phenomena which arise from the universe. Also, the human brain possesses a dynamic complexity giving us various feelings and emotions at different points of time and transferring the conscious as well as the sub-conscious mind is much more complex and challenging.

Interestingly, the scientists who are part of this transcendence research are sure of "what" they have do to achieve this, but are not clear about "how" in the present time and technology available. The fundamental challenge is to be able to precisely travel from a physical substrate of cells that are connected inside this marvellous organ - our brain- to our mental world which comprises of our thoughts, memories, feelings and experiences. 'Human Immortality' remains the biggest thought-provoking debate of the human existence. If we do have the ability to make the human race immortal, does that mean we should do it? This would mean that in 2045, the entire human race consisting of more than eight billion people—would have this incredible power at their fingertips to make themselves immortal. Cryopreservation is being considered as a Plan B to make life spans indefinite and not let people continue dying, until the unloading of human is achievable in the next two decades. This process involves freezing of living cell, tissues, organs or even entire bodies (after death) in low temperatures to prevent and protect them from decaying. The basic premise is that once this preservation is done for an indefinite period of time, we could bring them back to life and be able to treat them for the medical conditions (which had killed them) in a rather future span of time when medicine and science would have progressed much ahead than what it was at the time of the actual preservation.

Keeping in view all the observations and speculations that are being made, scientists worldwide comment that mankind's scientific priorities should lie in making sensible choices about generating technologies to solve our very real current problems. And speculating about brain uploading, as it stands, sounds like a can of worms, very deviant from our future.

Source:
1. Rouleau, N. et al. 2016 'When Is the Brain Dead? Living-Like Electrophysiological Responses and Photon Emissions from Applications of Neurotransmitters in Fixed Post-Mortem Human Brains'. *PLoS One*, vol. 11, no. 12, e0167231, DOI: 10.1371/journal.pone.0167231..
2. The 2045 initiative: www.2045.com

Drug De Addiction: New Approach to Curb Drug Seeking Behaviour

Breakthrough study shows that cocaine craving can be successfully reduced for effective de-addiction

Researchers have neutralized a protein molecule called granulocyte-colony stimulating factor stimulating factor (G-CSF) that is commonly seen among cocaine users (both new and repeat users) in their blood and brain. This protein is responsible for affecting the reward centres of the brain and thus neutralizing this protein or "turning it off" would reduce the craving among cocaine addicts. The study published in *Nature Communications* has been conducted on mice and is being suggested by medical professionals as the first step towards a potential medication to help people beat cocaine addiction.

The highly addictive cocaine

Cocaine is a very lethal drug and can cause serious health effects or even sudden death and it's also the second most trafficked illegal drug in the world. Worldwide, around 15 - 19.3 million people (equivalent to 0.3% to 0.4% of the total population) use cocaine at least once in a year. Cocaine is highly addictive as it's a powerful stimulant, and usually drug tolerance can form in just a few doses, with a rapid eventual drug dependence. Thus, cocaine creates a psychological dependence and affects the brain. Addiction to cocaine leads to long term damages to a person's health including one's physical, mental and emotional wellbeing. The young population (under 25 years of age) is the most vulnerable to cocaine because it causes temporary stimulation and euphoria and this age generally has higher propensity for addiction.

Cocaine drug addiction is a complex disease which involves not only changes in the brain of the user but also enormous changes in a wide range of social, familial, and other environmental factors. Thus, treatment of cocaine addiction is also complex as it must address all these changes alongside other co-occurring mental disorders that then require additional behavioural or medicinal interventions. The traditional approaches to treat cocaine deaddiction or seeking behaviour, generally include psychotherapy and "no medication-assisted therapy". The '12-step programmes' traditionally involve encouraging physiological principles such as courage, honesty and compassion and also psychotherapy done parallelly.

However, most of such psychotherapy and behavioural interventions are subject to high failure rates and also increased occurrences of relapse. This study led by Dr. Drew Kiraly at Icahn School of Medicine at Mount Sinai, USA has been termed as "exciting" and "novel" because this is really the first time an alternative to regular de-addiction programs has been described. It's a big step in a new direction to control and erase cocaine addiction in patients.

A novel approach to cocaine de addiction

The G-CSF protein is seen capable of producing a positive signal at the reward centres of the brain. Thus, the researchers expectedly found that when they directly injected this protein into the mice's brain's reward centres (called the "nucleus acumbens"), there was a significant increase in the cocaine seeking behaviour and also the overall cocaine consumption among the mice and they were seen to be basically craving. It is clear that targeting or neutralizing G-CSF can be a safe, alternative approach to curb this addiction. Interestingly, safe and tested treatments are already available for neutralizing G-CSF. These drugs are being routinely used to stimulate the production of white blood cells (infection fighting cells) after chemotherapy during treatment of cancer since chemotherapy typically suppresses the white blood cells. When these drugs were administered to neutralize the G-CSF, mice then lost all motivation and desire to seek out cocaine! Just like that this was a huge turnaround. Also, no other behaviour of the animal was altered in this process, whereas several clinical trials before have reflected unnecessary abuse potential of any kind of medication which has been tried for de addiction. This was a crucial find for researchers to be able to address cocaine addiction through these already tested and FDA approved drugs.

But is it feasible?

The authors point out that starting to use any kind of new medication is always laden with challenges which include possible side effects, routes of delivery, safety, feasibility and also the abuse potential. The authors insist that once more clarity is available in understanding how this protein can be best targeted to reduce addictive behaviour, higher possibilities of translating the results to trials with human participants will occur. Also, this has generated hope that for similar therapies that's could be applied to other drugs as well like heroin, opium which are cheaper (in comparison to cocaine) and available to a larger population in middle income and low-income countries and are also illegally trafficked. Since most drugs have similar effects and target the overlapping regions of the brain, this therapy could be successful for them as well. Though at the time of publishing this study, the possible timeline for human trials is unclear, nevertheless, there are standard methods to overcome many of these challenges and this certainly is a potential new area of medications for de-addiction and could soon become a "reality". This breakthrough study inches scientists a little closer to the finding the ultimate cure for cocaine (and similarly other drugs) addiction in humans without implicating any other behavioural changes or any side risks of developing other addiction.

Source:
1. Calipari, ES. et al. 2018, 'Granulocyte-colony stimulating factor controls neural and behavioural plasticity in response to cocaine'. '*Nature Communications,* vol. 9, DOI: 10.1038/s41467-017-01881-x

Cloning the Primate: A Step Ahead of Dolly the Sheep

In a breakthrough study, first primates have been successfully cloned using the same technique used to clone the first mammal Dolly the sheep.

The first ever primates have been cloned using a method called somatic cell nuclear transfer (SCNT), the technique which had earlier failed to produce live primates up till now and was only successful for the mammal Dolly the sheep in the mid-1990s. This remarkable study[1], published in *Cell* is being termed as a new era for biomedical research and has been carried out by scientists at Chinese Academy of Sciences Institute of Neuroscience, Shanghai.

How did they clone?

Primates (unlike other mammals like cow, horse etc.) have always been very tricky and complicated to clone and many attempts have been made by researchers using standard cloning techniques. In this study, the researchers optimized a technique in which they injected the genetic material (DNA) of a donor cell into another egg (of which the DNA has been removed) thus generating clones (i.e. having identical genetic material). This somatic cell nuclear transfer (SCNT) technique

has been described by researchers as very delicate process and it needs to be done swiftly but efficiently to minimize damage to the egg. They were able to use the foetal cells (grown in the lab) to success, before they mature into adult offspring. Using these foetal cells, they created a total of 109 cloned embryos, and implanted about three-quarters of them into 21 surrogate monkeys resulting in six pregnancies. Two long-tailed macaques survived birth and are currently few weeks old and have been named. Zhong Zhong and Hua Hua. They tried using adult donor cells instead of foetal cells, but those clones did not survive after few hours of being born. The first primate ever cloned named Tetra[2], a rhesus monkey, born in 1999, was cloned using a simpler method called embryo splitting which is the same technique by which twins are naturally conceived. This approach had a major limitation of generating only up to four offspring at a time. However, with the currently demonstrated somatic cell nuclear transfer (SCNT) technique, there is no limit to generating clones!

Now monkey, are humans next to be cloned?

Amidst the breaking of this research story, scientists worldwide are raising the inevitable ethical question- can this technique be allowed to clone humans as well? Since primates are the "closest relative" of humans. Cloning has remained a debatable topic in medical and scientific research since its impact on human life can have enormous implications and it carries multitude of ethical, moral and legal dilemmas. This work will yet again trigger the human cloning debate in society. Many bioethicists and scientists worldwide have commented that it would highly unethical to even attempt to clone a person in the same way as it would be a complete violation of the natural norms and the human existence. Though, the human race is obsessed by the idea of human cloning which is merely termed as "delusion" by scientists because cloning any individual would still make the cloned individual as a completely different entity. And, variety in our species is the pivotal reason which makes this world unique and wonderful.

The authors of this study are clear that though this technique can definitely "technically" facilitate human cloning, they themselves do not have the intention to do so. They elucidate that their main intention is to generate cloned non-human primates (or genetically identical monkeys) which can be used by research groups to further their work. Despite this, there is always fear of a chance that it might be attempted illegally somewhere on humans in the future.

Ethical and legal issues

Even if we don't consider the risks of possibility of human cloning, there are various laws for prohibiting reproductive cloning. This study was conducted in China where there are guidelines to prohibit reproductive cloning, but no strict laws. However, many other countries including the United States do not have any prohibition on reproductive cloning. Thus, to maintain research ethics, regulatory bodies worldwide need to step in and devise various guidelines. Some scientists say that cloning of primates itself brings up the matter of animal cruelty and such cloning experiments is a waste of lives and also money not to mention the animal sufferings. The authors experienced a lot of failure before achieving success and the overall failure rate is being set to at least 90% which is enormous. This technique is also very expensive (currently one clone cost about USD 50,000) besides being highly unsafe and inefficient. The authors of this study insist that the question about cloning non-human primates should be openly discussed by the scientific community so that the future is clearer in terms of strict ethical standards.

The real advantage of such a cloning

The main aim of researchers is to facilitate labs in conducting research with customizable populations of genetically uniform monkeys thus improving the animal models for studying human disorders including brain diseases, cancer, immune system and metabolic disorders. This technique, along with gene editing tool– another remarkable technology- can be used

to generate primate models to study specific human genetic diseases. Further, such a cloned population would offer significant advantages over otherwise non-cloned animals because the actual differences between a test set and a control set within a study will not need to be attributed to genetic variation because all subjects will be clones. This scenario would also lead to lower requirement of the numbers of subjects for every study – for instance – 10 clones would be sufficient for studies where currently over 100 monkeys are being used. Also, efficacy of new drugs can be easily tested on primate subjects during clinical trials.

Cloning has also been discussed as a possibility for growing tissues or organs for organ transplants. However, the human embryonic stem cells can be used to re-grow tissue and organs, and, theoretically speaking, it should be possible to grow any new organs from stem cells and later used for organ transplant – referred to as 'organ cloning'. This process really does not require actual 'cloning' of the individual and the stem cell technology takes care of it in entirety by side stepping the need for human cloning.

This study is already high on possibilities and promises for the future in terms of primate research, thus Shanghai is planning to set up an International Primate Research Centre which will generate clones for scientists around the globe for profit or non-profit research purposes. For achieving this larger purpose, the researchers plan to continue improvise their technique by following strict international guidelines.

Source:
1. Liu, Z. et al. 2018, 'Cloning of macaque monkeys by somatic cell nuclear transfer'. Cell, In Press, DOI: 10.1016/j.cell.2018.01.020
2. Chan, AWS. et al. 2000, 'Clonal propagation of primate offspring by embryo splitting'. Science, vol. 287, no. 5451, pp. 317–319. DOI: 10.1126/science.287.5451.317.

Antibiotic Resistance: An Imperative to Stop Indiscriminate Use and New Hope to Tackle Resistant Bacteria

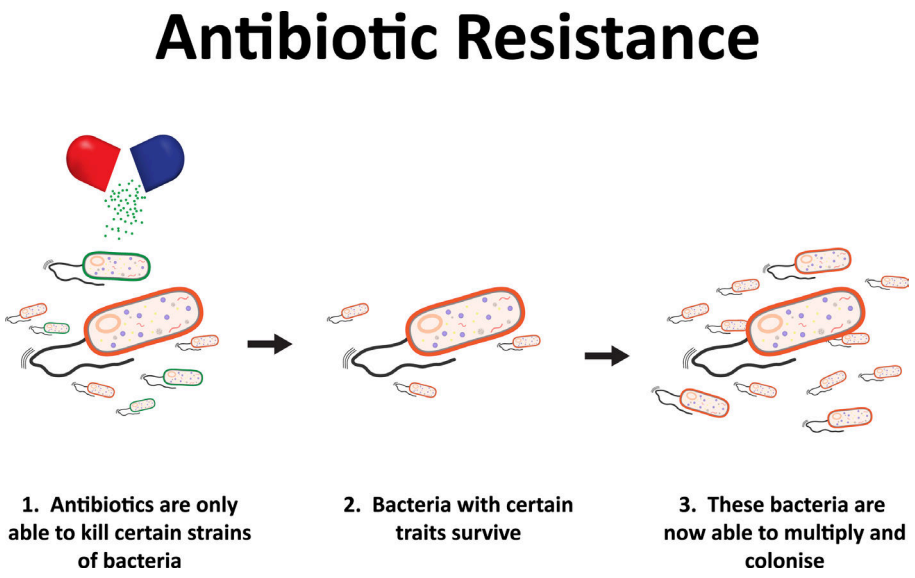
Recent analyses and studies have generated hope towards protecting mankind from antibiotic resistance which is fast becoming a global threat.

The discovery of antibiotics in mid 1900s was a significant milestone in the history of medicine as it was a miracle therapeutic for many bacterial infections and bacteria-causing diseases. Antibiotics were once termed as a "wonder drug" and now antibiotics are indispensable in both basic healthcare and advanced medical care and technology as they have really changed the world by protecting lives and being an essential part of treating various medical conditions as well as assisting in critical surgical procedures.

Resistance to antibiotics is growing at a fast pace

Antibiotics are medicines which are naturally produced by microorganisms and they stop or kill bacteria from growing. It is of critical importance because bacterial infections have plagued mankind throughout time. However, the "resistant" bacteria develop defences that protect them against the effects of antibiotics when previously they were killed by them. These resistant bacteria then are able to withstand any attacks by antibiotics and consequently if these bacteria are disease-causing, the standard treatments stop working for that disease, persisting the infections which can then easily spread to others. Thus, the "magical" antibiotics have unfortunately started

to fail or started becoming ineffective and this is posing immense threat to the healthcare system worldwide. The number of resistant bacteria already cause more than 500,000 deaths every year and are eroding the efficiency of antibiotics for prevention and cure by being a silent killer by residing in almost 60% of the world's populations in some form. Realistically and factually speaking, antibiotic resistance threatens our ability to cure many diseases like tuberculosis, pneumonia and carry out advances in surgeries, treatment of cancer etc. It is estimated that approximately 50 million people will die from antibiotic resistant infections by 2050 and the day might actually come when antibiotics can no longer be used for treating critical infections the way they are being used now. This issue of antibiotic resistance is now an important health topic which needs to be addressed with a sense of urgency for a better future and the medical and scientific community and the governments worldwide are taking steps toward achieving this goal.



WHO Survey: The 'post-antibiotic era'?

The World Health Organization (WHO) has declared antibiotic resistance a high priority and serious health issue through its Global Antimicrobial Resistance Surveillance System (GLASS) which was launched in Oct 2015. This system collects, analyses and shares data on antibiotic resistance worldwide. As of 2017, 52 countries (25 high-income, 20 middle-income and seven low-income countries) have enrolled in GLASS. It's first report[1] contains information on antibiotic resistance levels provided by 22 countries (one-half million participants enrolled in the survey) showing growth at an alarming rate – overall a huge 62 to 82 percent resistance. This initiative by WHO aims to create awareness and coordinate between different nations to tackle this serious problem at a global level.

We could have prevented antibiotic resistance and still can

How did we reach this phase of humanity where antibiotic resistance has turned into a global threat? The answer to that is quite simple: we have extremely overused and misused antibiotics. The doctors have overly prescribed antibiotics to any or every patient in the past many decades. Also, in many countries, especially the developing countries of Asia and Africa, antibiotics are available over-the-counter at the local pharmacist and can be purchased without even requiring a doctor's prescription. It is estimated that 50 percent of the time, antibiotics are prescribed for virus-causing infection where they basically do no good because the virus will still complete

its life span (generally between 3-10 days), whether antibiotics are taken or not. In fact, it's just wrong and a mystery for many as to how exactly antibiotics (which target bacteria) will have any effect on viruses! All the antibiotics could do is 'maybe' relieve some symptoms associated with the viral infection. Even then this continues to be wrong and medically unethical. The correct advice should be that since no treatment is available for most viruses, the infection should just run its course and in the future, these infections should be alternatively prevented by following strict hygiene and keeping one's environment clean. Furthermore, antibiotics are being routinely used in enhancing agricultural output worldwide and feeding to livestock and food-producing animals (chicken, cow, pig) as growth supplements. Thus, by doing so humans are also put to huge risk of ingesting antibiotic-resistant bacteria which reside in those food or animals causing rigorous transfer of resistant strain bacteria across borders.

This scenario is further complicated by the fact that no new antibiotics have been developed by pharma companies in the past several decades – the last new antibiotic class for gram-negative bacteria was the quinolones developed four decades ago. Thus, as we stand currently, we can't really be thinking of preventing antibiotic resistance by adding more and different antibiotics as this will only further complicate the resistances and transfer. Many drug companies have pointed out that developing any new drug is firstly very expensive as it's a long process requiring huge investments and the potential profit from antibiotics is generally very low that they are unable to 'break even'. This is actually convoluted by the fact that a resistant strain would develop for a new antibiotic somewhere in the world within two years of its launch since no legal framework is in place to curb antibiotic overuse. This doesn't exactly sound hopeful from a commercial as well as a medical point of view and thus developing new antibiotics is not really the solution for prevention of their resistance.

WHO recommends plan of action[2] for preventing antibiotic resistance:
a) Healthcare professionals and workers should be doing a careful detailed assessment before prescribing antibiotics to humans or animals. A Cochrane review of various methods[3] aimed at reducing antibiotic abuse in any clinical set up has concluded that the '3-day prescription' method was fairly successful, in which the patient suffering from an infection (which is not bacterial) is conveyed that his/her condition will improve in 3 days, else antibiotics can be taken if symptoms get worse - which they generally don't since the viral infection has run its course by that time.
b) The general public should be confident to ask questions when they are being prescribed antibiotics and they must take antibiotics only when satisfied that it is absolutely necessary.
They must also complete the prescribed dosage to prevent fast growth of resistant bacterial strains.
c) Agriculturists and livestock breeders should follow a regulated, limited use of antibiotics and do so only where it matters (eg. to treat an infection).
d) Governments should setup and follow national level plans to curb antibiotic use1. Customized frameworks need to be set up for developed countries and middle- and low- income countries relating to their needs.

Now that the damage is done: tackling antibiotic resistance

So that we do not plunge into a new 'post antibiotics' era and return to the pre-penicillin (first antibiotic to be discovered) era, lot of research is happening in this field loaded with failure and occasional successes. Recent multiple studies show ways to tackle and maybe reverse antibiotic resistance. The first study published in *Journal of Antimicrobial Chemotherapy*[4] shows that when bacteria become resistant, one of the ways which they adopt to restrict antibiotics action is by producing an enzyme (a -lactamase) which destroys any antibiotic that is trying to get into the cell (for treatment). Thus, ways to inhibit the action of such enzymes could successfully reverse antibiotic resistance. In a second subsequent study from the same team at University of Bristol, UK but in collaboration with University of Oxford published in *Molecular Microbiology*[5], they analysed the effectiveness of two types of inhibitors of such enzymes. These inhibitors (from the bicyclic

boronate class) were seen to be very effective on a particular type of antibiotic (aztreonam) such that in the presence of this inhibitor, the antibiotic was able to kill many resistant bacteria. Two of such inhibitors avibactam and vaborbactam – are now undergoing clinical trial and have been able to save a life of a person suffering from untreatable infection. The authors though have succeeded with only a particular type of antibiotic, nevertheless, their work has generated hope in turning back the tide of antibiotic resistance.

In another study published in *Scientific Reports*[6], the researchers at Université de Montréal have devised a novel approach to block the transfer of resistance between bacteria which is one of the ways the antibiotic resistance spreads in hospitals and health units. The genes which are responsible for making the bacteria resistant are coded on plasmids (a small DNA fragment which can replicate independently) and these plasmids transfer between the bacteria, thus spreading the resistant bacteria far and wide. The researchers computationally screened a library of small chemical molecules which would bind to the protein (TraE) that is essential for this plasmid transfer. The inhibitor-binding site is known from the protein's 3D molecular structure and it was seen that once the potential inhibitors were bound to the protein, the transfer of antibiotic-resistant, gene-carrying plasmids was significantly reduced thus suggesting a potential strategy for restricting and reversing antibiotic resistance. However, for this kind of study the 3D molecular structure of a protein is required which makes it slightly limiting as many proteins are yet to be structurally characterized. Nevertheless, the idea is encouraging and such inhibitors could likely play an important role in everyday health care.

Antibiotic resistance is threatening and undermining several decades of improvements and gains which we have made in human health care and such positive research needs to be further developed and implemented because this is the need of the hour as it will have a huge direct impact on the capability of people to live healthy, full and fruitful lives.

Source:
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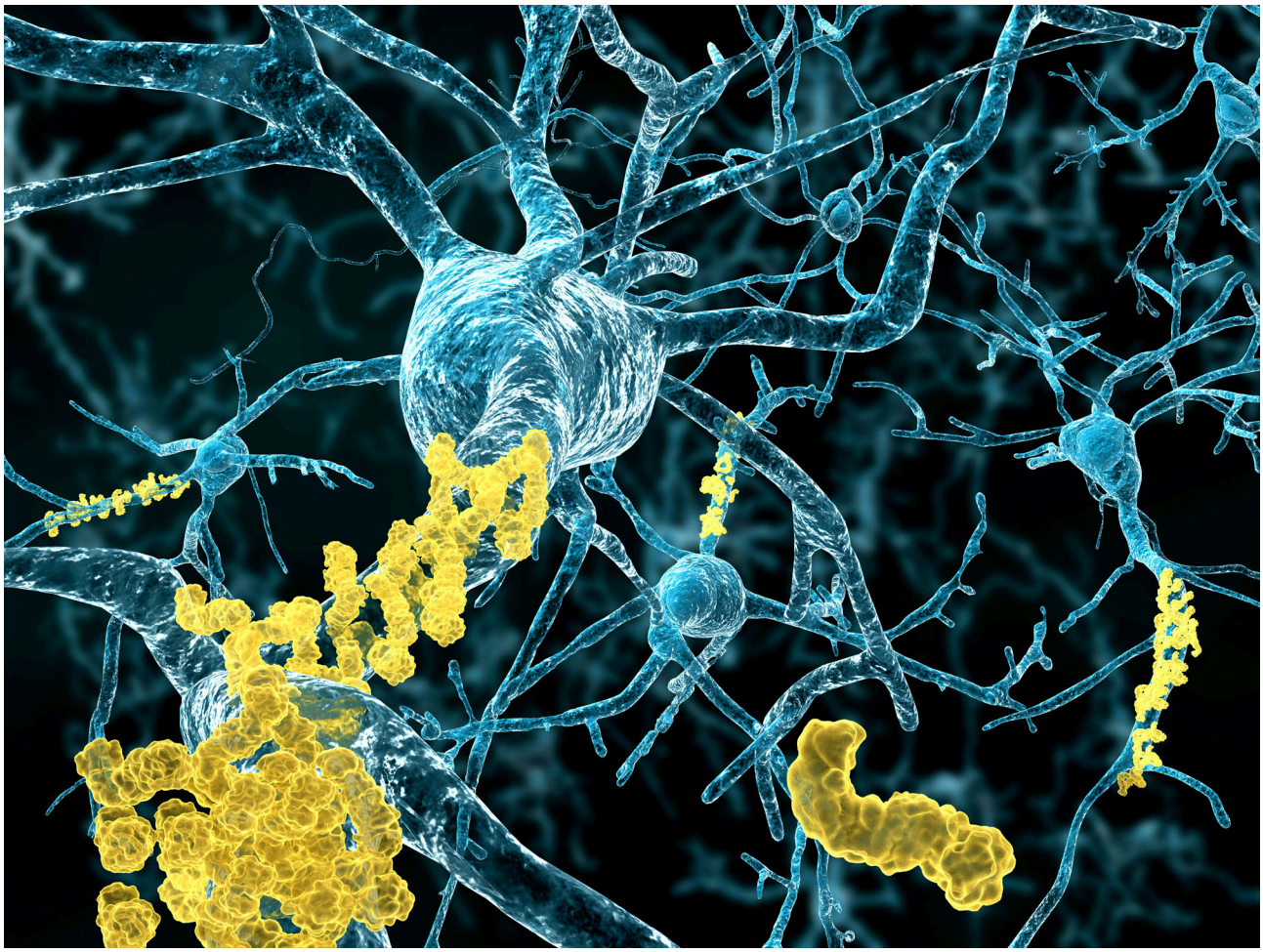
Brain Pacemaker: New Hope for People with Dementia



The brain 'pacemaker' for Alzheimer's disease is helping patients to perform daily tasks and take care of themselves more independently than before.

A novel study has for the first time attempted to use deep-brain simulation to counter brain activity related to performing a function in patients of Alzheimer's disease (AD) the cause of which is still poorly understood. Many previous studies have targeted the parts of brain which are thought to be involved in memory – since memory loss is the key symptom of Alzheimer's disease (also called Dementia). Most medications and treatments are also focused on improving memory, however, huge change in thinking power and skills of the patients which happens in the course of AD, also needs to be similarly addressed. Since no new Alzheimer's disease drug has been produced in the last decade or so, this potential innovative treatment offers hope to Alzheimer's disease patients and to this field.

The study of human memory is still at a very early level but is nevertheless fascinating in whatever we know about it. Human memory is simply data. Memories are stored as microscopic chemical changes at the different connection points between billions of neurons in the human brain. Memory involves all structures and processes that are involved in the storage and subsequent retrieval of information from our brain. A patient suffering from Alzheimer's disease starts showing

signs of loss of short-term memory (e.g. a recent event). This is the most crucial symptom of AD, when information cannot be retrieved from the brain and this is termed as "memory loss". This loss in retrieving information then affects thinking power and skills and daily functioning.

Alzheimer's disease: affecting our elderly

Alzheimer's disease has affected approximately 50 million people at the end of 2017 and this number is expected to cross 130 million by 2050. The elderly population is growing at a faster rate (in both developed and developing countries) because of more population (in developing countries) and overall higher life expectancy worldwide and AD is affecting this ageing population at a fast pace. It's being estimated that someone in the world is affected by dementia every 3 seconds. Unfortunately, there are no treatments available for AD and there seems to be no cure in sight with many failures seen in the trial of potential drugs leading to pharmaceutical companies to abandon the such trials. Thus, it can be safely stated that development of new medications for Alzheimer's disease is completely stalled as of end of 2017.

Simulating the brain: the brain pacemaker

This study, published recently in *Journal of Alzheimer's disease* has conducted a novel experiment to improve the everyday capabilities and function of AD's patients unlike most trials conducted earlier for AD have attempted to treat the memory loss exclusively. This technique called "deep brain simulation" has seen to be beneficial on patients of Parkinson's disease (another neurological condition) and thus urged the researchers to try it for Alzheimer's disease. There is no iota of doubt that Alzheimer's disease is a very devastating condition which affects patients adversely and also their near and dear ones. Researchers feel that this new discovery may not be able to completely cure Alzheimer's disease but can surely provide mental strength to patients to carry out most daily functional tasks on their own, be more independent with reduced help from the caregiver.

The deep brain simulation (device is called the 'brain pacemaker') is thought to affect the interaction of neurons in the brain thus affecting brain activity and involves implantation of small, thin electrical wires into the patient's frontal lobe — a part of the brain associated with "executive functions". These wires are connected to a battery pack which sends electrical impulses into the brain. The device continuously stimulates the frontal lobe in the brain, very similar to a cardiac pacemaker which stimulates the heart. The brain pacemaker basically increases "brain metabolism" in certain areas and increases the connection between neurons thus facilitating what is known as "functional connectivity". This connectivity is thought to decrease steadily over the course of Alzheimer's disease thus leading to decline in decision making and problem-solving skills.

The study led by Dr. Douglas Scharre at the Ohio State University Wexner Medical Centre, USA claims that the "brain pacemaker" can help patients to improve their judgments, be able to make sound decisions, increase their ability to focus on a particular daily task and avoid mental distractions. The researchers highlight the increased ability to do simple daily tasks like making the bed, choosing what to eat and well-meaning social interactions with family and friends. The main goal of the researchers was to slow down the progression of Alzheimer's disease with a safe and stable device.

Impact of brain pacemaker on the future of Alzheimer's disease's treatment

This study still needs to accepted with caution since the study was done on only three patients, though the results were seen after a good duration of 2 years and these three participants were

compared with a set of 100 other participants who had similar age and Alzheimer's disease symptom levels but did not get the brain pacemaker implanted. Two among these three patients showed progress and included 85-year-old LaVonne Moore of Delaware, Ohio who showed great improvement in functional independence in daily tasks like cooking, getting dressed and planning outings. There was considerable improvement in many areas including decision-making, problem-solving, planning and focus and she expressed satisfactory outcome.

Though at a very elementary stage, this study nevertheless has generated encouragement for researchers in the Alzheimer's disease field and also hope for millions of patients worldwide. It is quite clear the tackling Alzheimer's disease will require more such multitude approaches which cover various features of this disease and its extremely important to lay emphasis on the overall quality of life of patients. Since, no new treatments have been discovered for AD in the past 10 years and also clinical trials are also stalled for any new AD drugs, such alternative approaches to treatment must be continued to be further researched upon to draw steady conclusions about how such treatments could work on an ensemble of patients.

Also, a larger multi-centre trial would be needed to be able to get more participants to evaluate the extent of this study. The authors maintain that a section of Alzheimer's disease's patients may benefit from the brain pacemaker, some others may not because every patients' neurons will respond differently and some may not respond at all. So, a larger and more comprehensive trial will reveal a clearer picture. Nevertheless, such a device would definitely slow the progress of Alzheimer's disease in most patients translating into an improved everyday functioning.

Source:
Scharre, DW, et al. 2018, 'Deep Brain Stimulation of Frontal Lobe Networks to Treat Alzheimer's Disease', *Journal of Alzheimers Disease.* vol. Preprint, no. Preprint, pp. 1-13, DOI: 10.3233/JAD-170082

Homeopathy: All Dubious Claims Must Be Put To Rest

It now a universal voice that homeopathy is 'scientifically implausible' and 'ethically unacceptable' and should be 'rejected' by the healthcare sector.

Healthcare authorities are now averse on wasting valuable government and public funds and resources towards 'nonsense' homeopathy because this only provides credibility to this absurd practise and puts people's lives at risk by avoiding or denying them proper medication and care. The implausibility of homeopathy is now very much established because homeopathic preparations are highly diluted thus do not really contain any significant amounts of the "so called" active ingredients and therefore cannot have any kind of effect on the patient. There is also no concrete evidence available to support its effectiveness despite numerous studies being carried out.

The European Academies Science Advisory Council (EASAC), an umbrella organisation representing 29 national academies in Europe is calling for tougher regulations to control the spread of homeopathy in their report published recently[1]. The member academies are now reinforcing heavy criticism on the various health and scientific claims made for homeopathic products. The analysis and conclusions in this report are based on excellent, impartial scientific assessments which have already been published by legal authorities. The team has emphasized that while it is good to have alternative approaches to treatments but all these must strictly be driven by evidence and not some hyperbole of wishful thinking which puts patients to additional risks.

Homeopathy: a scientific implausibility

First and foremost, the very core of homeopathy is scientifically implausible. There is an absolute lack of scientific support for all the different mechanisms that are claimed by homeopathy. Most of its remedies are prepared in umpteen serial dilutions of water (based on the theory that a 'substance' will leave its 'imprint' on the water) resulting in an inconsistent or rather useless solution having no trace of the 'original 'substance in it. This mechanism, first of all, fails to be justified2 because it is neither plausible nor demonstrable and also doesn't follow the principles of drug-receptor interaction of pharmacology[3].These principles have been long-established to explain drug-receptor interaction and set central principles for any drug/medicine when delivered to a biological system. These principles have been substantiated from time to time through continuous research[4]. Further, there is not a single scientific evidence for any of the mechanisms claimed by homeopathy including electromagnetic signals (if any) and the so called 'water memory'[2].

Secondly, let us analyse the 'mechanism' of homeopathy in a greater detail. Looking at the chemical structure of water, if any ingredient is dissolved in it followed by several serial dilutions, then the actual impact of this ingredient on water will be of a very short range (in nanometres, 10-9 meters) and so the impact will not extend beyond the hydration layer thus having no consequential long-term effects. This is proposed from various theoretical scientific studies based upon spectroscopy findings and measurements which define long-range molecular order effects and interactions in space and time[5,6]. Therefore, the chemical structure and dynamics of water itself refute the claim made that the ingredient which is dissolved in water through serial dilutions is leaving any 'imprint' on it at all – the central idea on which homeopathy is based upon- and these explanations has been published time and again to prove the scientific implausibility of the proposed 'long-term' memory of water[7,8].

Placebo effect: more of a chance treatment

Scientists say that since homeopathic treatment is not scientifically possible, and the homeopathy 'sugar pills' don't contain any active ingredients, any benefit seen on the patient can be mainly due to the placebo effect - when people believe the pills are going to help them with a condition, this belief can trigger a healing response and most of the time, the nature course of illness and regression will take care of things. These happenings start propagating the false notion that homeopathy is of benefit. A comprehensive literature analysis of 110 homeopathy trials and 110 matched conventional medicine trials have shown[9] a similar assessment confirming that the clinical effects of homeopathy are statistically very similar to placebo effects. Further, a detailed assessment of five large meta-analysies of different homeopathic trials has also concluded same results[9,10]. In this analysis all inadequate trails, bias and random statistical variation were excluded and showed that homeopathy medicine produced results statistically similar effect when compared to placebo and nothing more.

The Cochrane Database of Systematic Reviews (CDSR)[11] is the leading, reliable resource for systematic reviews in health care. These reviews are very comprehensive, encompassing peer-reviewed protocols, standard evaluation processes and most importantly transparent analysis of data. The Cochrane Reviews of homeopathic treatments include those for dementia, asthma, autism, influenza and many more and the systematic assessments carried out in these reviews conclude 'no' or 'insufficient' evidence to assess any possible effect of homeopathy. A debate published in 2015 in *British Medical Journal*[12] showcases a comprehensive review of literature discussing the efficacy of homeopathy and also the contested claims put up by various sources which support or promote claims of homeopathy.

Questions raised on safety and quality

Since a homeopathic medicine or preparation is believed to be diluted to several degrees, it is very well assumed that no questions need to be raised about any types of safety concerns. Many scientists believe that this may not be necessarily true in practice. For example, in a very recent report, a starting ingredient (belladonna) for a homeopathic teething drug for infants was found to be having toxicity and it led to adverse effects in patients[13]. Such evidences - which have been investigated by USA's Food and Drug Administration (FDA) - on lack of clarity and compromise on safety and quality by homeopathic practitioners is a big cause of concern and needs immediate attention. Highly consistent regulatory requirements need to be in place to demonstrate the efficacy and safety of all homeopathic products (used in preparing medicines) and these need to be based upon verifiable and solid scientific evidence which is currently not the case. Since no clear evidences are available, these homeopathic products are recommended by regulatory authorities to be not be granted approved or even registered at all1.

Keeping patient in the dark

Actually, with any type of medical treatment, there is likely to be some degree of placebo effect, hence this can be true for homeopathy. Interestingly, supporters of homeopathy argue that if the patient feels a placebo effect then there is 'still' a benefit to the patient. Scientists counter argue that if this is indeed correct and homeopaths accept that 'placebo' is the only benefit then they are effectively lying to the patients by claiming other non-achievable aspects and not clearly informing the patient about the placebo effect. This approach is against the core principal of ethics in the medical field – transparency with the patient and an informed-consent for treatment.

Also, the homeopathic solutions are never revealed to the patients making them to only guess all along their so-called treatment. For majority of homeopathic drugs, the bottle is not properly labelled with ingredients and it is never highlighted that their efficacy is actually based only on traditional homeopathic theories with no backing of any scientific concepts. On the contrary, homeopaths make bold direct or implied claims that their drugs have the potential to treat various medical conditions. All these aspects are unethical and these are misleading to the general public. To tackle this, the EASAC, for instance has set up regulations within Europe1 to diminish dubious claims and false, misleading advertisements by homeopaths. They have imposed restrictions on media coverages on homeopathic treatments on all public TV channels and public health programs. For now, they have made it mandatory for homeopathic product labels to clearly identify ingredients and their amounts for patients' information.

Action is needed now!

Such measures need to be implemented in countries where homeopathy is already widespread e.g. India and Brazil. It is extremely important to make the public realize that homeopathy does not follow the fundamental ethical principles and going this route only creates unnecessary delays in seeking appropriate medical care. It also becomes the moral duty of every healthcare worker to take a stance against homeopathy and especially the pharmacists who try to sell these homeopathic remedies over pretence that they are more than placebos. Sometimes, homeopathy is confused with natural products such as herbal medicines (some of which may even have a plausibility unlike homeopathy). Therefore, media can play an important role in facilitating accurate dissemination of evidence-based scientific knowledge to the public.

Source:
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