Leicester Grammar School's

YOUNG SCIENTISTS journal

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ISSUE 5 ADVENT TERM 2018

A Message from the Team:

“With this being our fifth issue, it marks a change in the editorial team for our school’s Young Scientist Journal (YSJ) as the previous year 12 team have taken over from the departing year 13s as they have embarked on the next stage of their education. We would like to take this opportunity to thank both Maria and Prab for not only introducing our school to the YSJ initiative and instilling its philosophy, but for also guiding us through this transition. Despite this change in leadership, there is still great continuity in our aims; we strive to incorporate participation from pupils of all ages and we definitely encourage scientific passion and curiosity to shine through in our issues. We truly believe that our pupils’ scientific minds are something special and should be celebrated in abundance through the YSJ. Looking forward to the future, in addition to the termly issues, we would also like to expand the YSJ community in our school possibly by the introduction of an inaugural competition involving pupils being given the opportunity to present their ideas or topics of interest to a panel of judges with interactive voting by the audience. However, we are in the early stages and so are open to any suggestions; after all this is a magazine by the pupils, for the pupils!

This issue sees the topics of asthma, AI and possible cancer treatments being discusses, as well as the winning photo (from the school’s biology trip to Costa Rica) of our front cover competition being exhibited.

A reminder to all budding scientists throughout the school of all ages that any input, whether that be writing an article or helping designing the layout of the magazine, is much appreciated and valued. If you would like to get involved then please don’t hesitate to contact lgsyoungscientists@gmail.com or alternatively come to one of our meetings on Thursday break-times (specific details are read out in daily notices).

We would like to acknowledge the following for their contribution:

The LGS Editorial Team:

Marcus Teo / Zain Girach — *Chief Editors*

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Articles in this issue:

Who are We?

We are a collection of Leicester Grammar School students who have come together to produce a variety of pieces of writing about the world of STEM. As a school, we have become a hub for the Young Scientists Journal, an international peer-review written and edited entirely by young people.

Contact Us

Anyone interested in joining the YSJ to help to write, edit and publish is more than welcome to meet us at our meetings during lunchtimes (specific details will be in the daily notices). We welcome submissions from all year groups on any scientifically-related topic; so come along to a meeting or email us at:

lgsyoungscientists@gmail.com

See more of the Young Scientists Journal at:

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Au revoir to 'Le grand K'

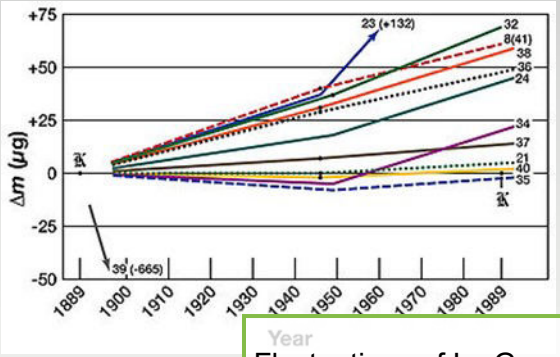
Nazir Sirajudeen discusses the definition of the kilogram

The old definition

For 130 years, we have defined the SI unit of mass, the kilogram, as the mass of an cylindrical object formulated from a platinum alloy named the 'International Prototype Kilogram', more commonly known as 'Le Grand K'. Kept in environmentally controlled conditions under a bell-jar in a vault located in Saint-Cloud, France (a suburb in Paris) along with 6 replicas, it was first used as the definition of the kilogram in 1889. The object was painstakingly replicated 40 times in 1884 and handed to countries all across the globe in an effort to adopt the kilogram as the standard unit of mass over the plethora of different units of mass present at the time, and so far it has served us well. Numerous scientific breakthroughs could not have occurred without the standardisation of the unit and even the unit of a pound (lb) is now legally defined as exactly 0.45359237 kilograms. But there is always an element of risk involved in using an object as a definition of a base unit, and the IPK was no exception to this rule.

Le Grand K

The IPK would seldom be taken out of its case (40 years) along with the other replicas and reweighed carefully, so as to not accumulate any hydrocarbons on the fingertips which would change the mass of the object. The last time this occurred was in 1991, and it was found that the mass of the replicas had been diverging and the original was roughly 50μg lighter than the replicas, ringing alarm bells to scientists all over the globe. In a world where accuracy is becoming increasingly critical in fields such as nanotechnology and drug development, using an object as the definition of a base unit would be unreliable.



Fluctuations of Le Grand K

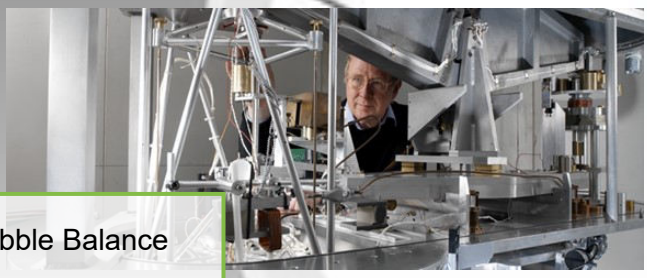
The new definition

After careful deliberation, the International Bureau of Weights and Measures had unanimously decided on the new definition of the kilogram on the 16th November 2018, affecting not only the unit of the kilogram but also three other base units:

- Candela (measuring light intensity)
- Amperes (measuring electrical current)
- Moles (measuring amount of substance)

The new system instead uses fundamental constants of nature, most notably Planck's constant, h, with recent advancements in technology allowing scientists to accurately

measure the constant. The most notable of these was the Kibble (or Watt) Balance, invented in 1975 by Dr Bryan Kibble, and it was instrumental in the redefinition of the kilogram. The Kibble balance contains a coil of wire inside a magnetic field and is suspended



A Kibble Balance

from one end of the balance. A kilogram mass would then be added to the other end and an electric current is then passed and adjusted to balance the force from the coil of wire. Afterwards, the mass would then be removed from the balance and the coil is then moved into a magnetic field, inducing a voltage into the coil. These measurements of voltage and velocity of the coil could then further be used to relate Planck's constant to the unit of mass.

The official definition of the kilogram, which will come into effect in May 2019 will be:

"The kilogram, symbol kg, is the SI unit of mass. It is defined by taking the fixed numerical value of the Planck constant h to be 6.626 070 15 × 10-34 when expressed in the unit J s, which is equal to kg m2 s -1 , where the metre and the second are defined in terms of c and ΔvCs." .

So what does it mean for everyday life?

For most uses of the kilogram, nothing has changed. We will not need to change the scales we currently used and there will be no dramatic shift in the way in which we measure the unit of mass. Instead the point of the change is to keep the value of 1kg as a constant and unchanging. This allows scientists all over the globe to measure mass to a very high degree of a precision, instead of being refrained by fluctuations of the mass of 'Le grand K'. We can open possibilities of cutting edge research which requires the use of highly precisions of masses. We are in a hugely important stage in the field of all sciences and the future remains exciting and prosperous as we venture forward into an era of new innovations brought about by the definition of the new kilogram.

Nazir Sirajudeen

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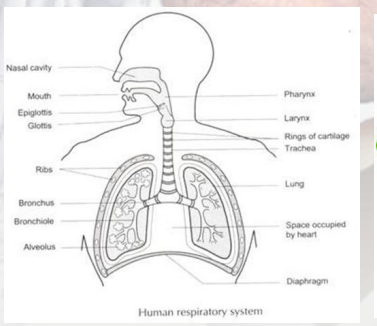
https://www.bbc.co.uk/news/science-environment-46143399 Figure 1-

Asthma

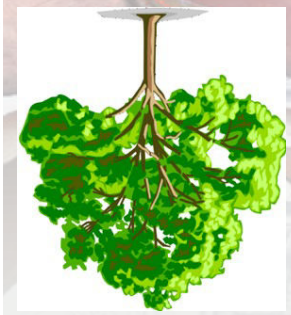
Tejas Easwar investigates causes, effects and treatment of asthma

Asthma

One in twelve people on earth have asthma. The likelihood is that either you or someone you know suffers from asthma. It causes difficulty in breathing and in severe cases even death. In order to understand the condition, we must understand the structure of the normal human lungs.



Human respiratory system



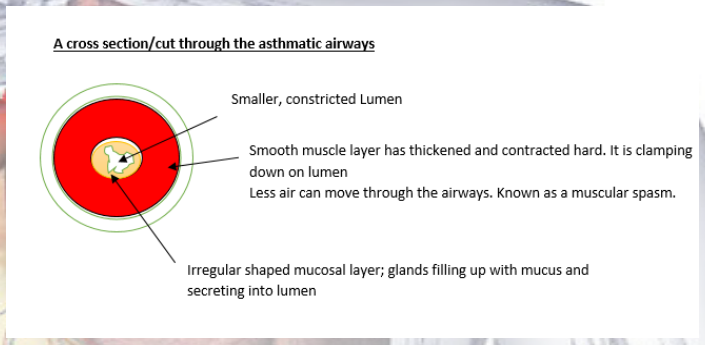
The human lungs are best visualized as an upside-down tree:

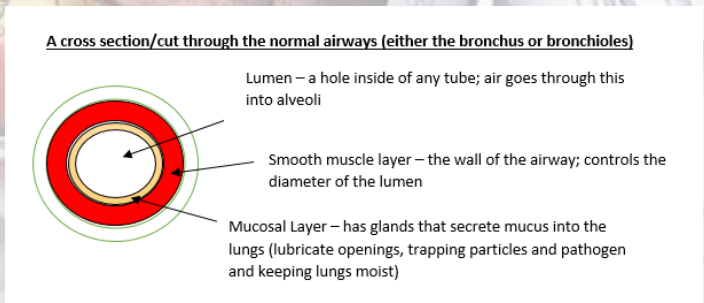
- One main trunk (the trachea)
- Thick branches (the left or right bronchi
- Thinner branches (the bronchioles)
- Finally going into leaves (microscopic alveoli)

When we breathe in, it is similar to a vacuum cleaner sucking in air. Oxygen is sucked into our lungs. Oxygen goes through our nose or mouth, down the trachea, into either the left or right bronchi, into bronchioles, into alveoli and finally diffuses into the blood.

In the reverse, we breathe out carbon dioxide. Asthma affects breathing out carbon dioxide. Carbon Dioxide is toxic and so too much carbon dioxide will kill us.

Air can still be sucked into the lungs. But it has to passively leave through the smaller lumen – it is harder to exhale and remove carbon dioxide





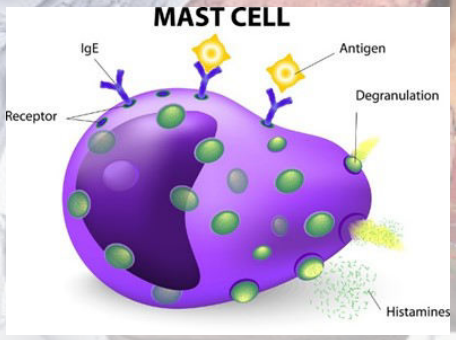
What triggers this constriction/spasm?

- Smoking (first- or second-hand smoke)
- Exhaust fumes, dust and pollution
- Physical activity
- Allergic reactions to food
- Stress – increases inflammation
- Aspirin (the drug to help with headaches)
- For babies, Gastroesophageal reflux (leakage of stomach acid into the esophagus – causes heartburn/ acid indigestion). Sometimes this acid can get into the trachea and trigger asthma

Several different substances can trigger asthma apart from these alone.

These chemicals (allergens) cause an 'over-reaction' of the immune system when they are in the body. They cause antibodies (chemicals that recognize substances that do not belong in the body) to be released. In particular, an antibody known as 'Immunoglobin E' or 'IGE' (an antibody for

allergies) is released. IGEs picks up these foreign allergens and takes it to the 'mast cell'. The mast cell contains a chemical known as histamines. These are the key players in what cause an allergic reaction. When the IGE attaches to the mast cell, little pockets in the cell open up causing histamines to flow out of the cell into the bloodstream. When the histamines are released, it causes allergic reactions. In the lungs, the histamines cause bronchospasms and asthma.



Ways to identify and diagnose asthma

Wheezing on expiration

Why? – There is fluid and mucous secreted into constricted airways (to deal with inflammation). The air and fluid form air bubbles. When these bubbles pop and reform, a high-pitched noise is produced

Methacholine Test

Methacholine is a drug that causes narrowing of airways. For those with asthma, there may be a severe reaction, helping to identify that they are asthmatic

Pulmonary function Test

A machine (PFT machine) is used to record the volume of air, speed of air etc. This can help identify if you have asthma. Some mathematics is then involved in order to work out if you are asthmatic

If

$$\frac{Forced\ Expiratory\ volume\ in\ the\ first\ second}{Forced\ vital\ capacity} \times 100 < 75\%,$$

Then the likelihood is you are asthmatic, or have an obstructive disease that prevents expiration.

Short-term treatments

Treatment for asthma is all about opening up the airways. A trial and error basis of using different combination of drugs

At home

- **Inhalers with beta-2 agonist (a bronchodilator)**

Beta-2 agonist relaxes the smooth muscle, opening up the lumen by combining with a specific receptor

- **Nebulizer**

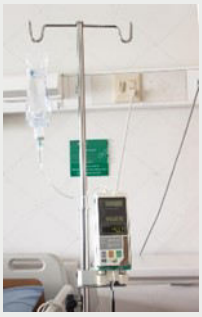
Plenty of oxygen

At hospital

- **An IV may be used**

Allows a drug to be directly infused into the bloodstream.

Beta-2 may be given in a higher dose or an IV steroid.

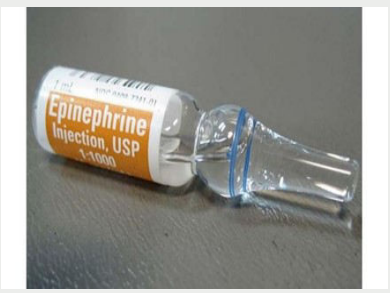


- **Magnesium sulfate**

Forces the smooth muscle cells to open up and help the patient breathe better

- **Epinephrine (often shortened to EPI)**

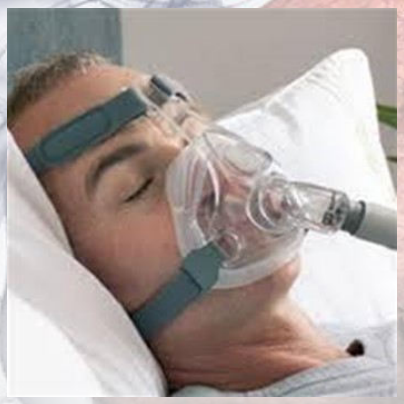
Normally, epinephrine is produced in the adrenal glands and starts the 'fight or flight' emergency response. In the



lungs, it can help open up the airways. It often has other side-effects such as heart palpitations, so is usually used as a last resort.

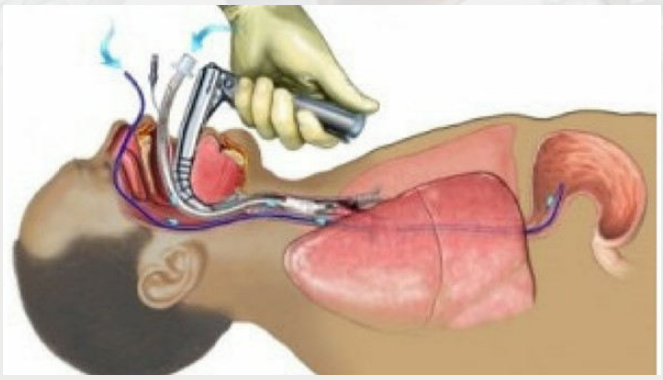
- **CPAP/BiPAP masks**

They push oxygen into the lungs, with a greater force than a nasal cannula or tube



Last Resort

- Intubation



Involves putting a breathing tube down a person's throat and connecting it to a machine that mechanically breathes for the patient. The patient must be under general anesthetic as it can negatively impact the lungs. However, in extreme cases, when the patient is not responding to treatment, it can save lives and prevent oxygen deprivation causing permanent damage

Tejas Easwar

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Is Gene-silencing Therapy Such As IONIS-HTTRx Our Greatest Hope in Finding a Cure for Huntington's disease (HD)?

Riccardo Kyriacou discusses the poitential for curing HD

Huntington's disease (HD) is one of the most devastating neurodegenerative disorders and is currently incurable and fatal. This hereditary disease, which displays autosomal dominance, is caused by the expansion of a CAG trinucleotide repeat in the *Huntingtin* gene (*HTT gene*), which is located on the fourth chromosome. This gene encodes for the protein called *Huntingtin,* and CAG expansion in the gene results in a mutated version of *Huntingtin protein (mHTT)*. Whilst the role of the normal *Huntingtin* protein is still not fully understood, the presence of the mutated version is the main cause of HD onset. Scientific studies point towards HD onset being caused by the protein misfolding, as a result of the CAG expansion, and then aggregating with other proteins, conferring toxicity to cells in the striatum (the movement centre of the brain). The most severe symptom of the disease is a locomotive chorea, resulting in involuntary, jerky movements affecting, in particular, the shoulders, hips and face. Cognitive degeneration, typical of a neurodegenerative disease, is also experienced. HD patients have a median lifespan of 17-20 years after diagnosis of the disease, with death being a result of the chorea like symptoms rather than the disease itself. The media's outburst over the news of UCL's success in a phase 1b/2a clinical trial[1] in December 2017 was a surprise to many who were familiar with the disease. This trial was testing a new therapy by Ionis Pharmaceuticals called IONIS-HTTRx and was carried out at University College London under the lead of Dr Sarah Tabrizi. Indeed, unlike any of the previous trials discussed in this essay, it is this trial that I believe will push us towards a breakthrough cure.

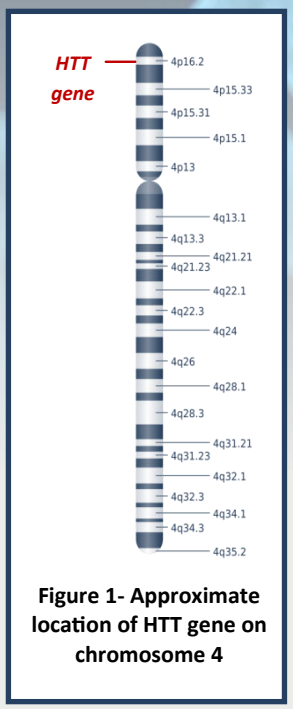

Figure 1- Approximate location of HTT gene on chromosome 4

Firstly, I want to discuss the mechanism by which IONIS-HTTRx inhibits the progression of HD, as it is, in my opinion, the aspect of the therapy which makes it so promising, perhaps even more so than the successful results of the trial itself. In general, there are two ways that we have tried to cure HD. The earliest and most common method, which includes the two FDA approved drugs currently is to use pharmaceutical drugs to target one specific symptom (often the most severe, that being the chorea associated with HD). As discussed, I regard drugs like these to be more akin to management tools because, although useful in alleviating chorea for a period of time, they do not focus on the root of the problem in HD, namely the mutant form of the *huntingtin protein*. This renders them, negligible candidates, from which a complete cure may be modelled off. The second method, however, of which IONIS-HTTRx is the first clinical example, is silencing the *HTT gene* in order to lower the levels of all *huntingtin*, including the mutant form, in the body. Primarily, gene silencing is nothing too new to the scientific community and there are multiple ways that researchers have been able to perform this. In the case of HD, IONIS-HTTRx is the only clinical method used so far and is an example of a gene silencing (also known as RNA targeting) therapy achieved using antisense oligonucleotides (ASOs). To summarise, an ASO consists of chemically modified single-stranded nucleotides known as oligonucleotides, which are inserted directly into human cells. The oligonucleotides will be complementary to a specific

messenger RNA (mRNA) strand made in the nucleus of the cells. In the case of IONIS-HTTRx, these oligonucleotides will be complementary to the mRNA that codes for the *huntingtin* protein. Due to their complementarity with the mRNA, when inserted into the cells, the oligonucleotides will bind to the mRNA and act to inhibit the process of translation which produces the protein. This inhibition can be done by the ASOs either physically blocking the process of translation, or by releasing an enzyme known as *RNase H* to break down the mRNA. In this way, the ASO IONIS-HTTRx will deplete the production of both forms of huntingtin: the normal and the mutant. The simplified diagram shown in ***Figure 2*** helps to visualise this process. Since the accumulation and aggregation of *mHTT* is not only responsible for the chorea, but the entirety of the neurodegeneration that affects HD patients, should IONIS-HTTRx work as well as theorised, it could provide an extremely effective way of actually curing HD. This, to say the least, is extremely promising news as for the first time ever, a therapy has progressed through the clinical trials that target the underlying issue of HD.

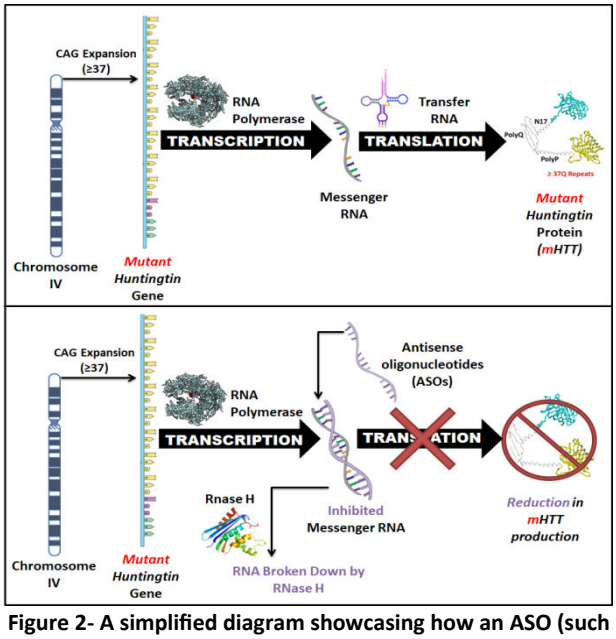

Figure 2- A simplified diagram showcasing how an ASO (such as IONIS-HTTRx) leads to depletion in huntingtin levels

Whilst this is all great in theory, the fact remains that IONIS-HTTRx must show some results in order for it to be even remotely considered promising. Of course, this is exactly what headlined the media on 11th December. This was the first-in-human, multi-centre, double-blind clinical trial for HD and saw 46 patients receive four does of either IONIS-HTTRx or a placebo (in a 3:1 ratio) via injections into the spinal cord. The results found that IONIS-HTTRx was not only well tolerated, with few side effects, at the doses tested, but according to Tabrizi *et al* in a 2018 *Neurology* article, *"the ASO was measurable in CSF and plasma, and concentrations were generally aligned with predictions from a linked PK/PD preclinical model. Significant, dose-dependent reductions in CSF mutant HTT (mHTT) were observed.* This is extremely promising news, as the trial was in its 1b/2a phase. This means that because the ASO was detected and reached its target in the nucleus of the cells (one of the defining features needed for a drug to pass through the first clinical trials phase), as well as showing a decrease in *mHTT*, it is safe to say that the results of these trials were extremely successful. Indeed, Frank Bennett, Ionis' Senior VP of Research, has even been quoted stating that the results "substantially exceeded our expectations".

However, there are still some unanswered concerns that arise from the results of this trial. As mentioned in an earlier section of this essay, the exact role of *huntingtin* in the human body is not fully understood. This means that whilst the therapy causes depletion in *mHTT*, a heterozygous HD patient (one who contains one mutated *HTT gene* and one normal *HTT gene*) will also see a depletion in the normal *huntingtin* protein. This could have unforeseen side effects, which we cannot yet predict. Whilst they are unlikely to be anywhere near as bad as HD itself, the possibility is still there. This is ultimate, one of the hurdles that IONIS-HTTRx faces, and in order for the FDA to approve this therapy, the side effects that arise when depleting *huntingtin* must be understood. Another big question facing IONIS-HTTRx currently is whether the lowered *mHTT* levels in patients are substantial enough to slow or even prevent the onset of the disease. The answer to this is what the future of the therapy holds, as IONIS-HTTRx progresses further into the 2nd and, hopefully, the 3rd phase of the clinical trials. However, even in the scenario that the answer to this question is no, and HD onset, progression and symptoms are found to be unaffected in this trial , the foundation that this therapy has laid will still make a significant positive contribution towards a cure, as lessons learned from it will facilitate the development of any future ASOs therapies.

Therefore, even in the unlikely scenario that this therapy is completely ineffective in curing Huntington's disease, we may still be on the brink of a cure. In this scenario, I believe that the future breakthrough will use the results of this clinical trial as a way to find a future ASO that will ultimately work, due to the undeniable success this therapy has already had in showing that ASOs can work in preventing the translation of the toxic protein. Even if this process takes place after 10 years, I'd still consider us to be on the "brink" of a cure, as the pharmaceutical world is a slow-moving one. However, there is also the possibility that we are potentially already looking at the very drug that cures HD. Of course, the most likely scenario will probably be somewhere in the middle. In my opinion, considering the positive results obtained in the previous clinical trials, I believe that IONIS-HTTRx will definitely have a remarkably positive effect on the ongoing search for a cure for HD. To stress once more, even if the final results were not substantial enough to consider IONIS-HTTRx a complete cure, the preliminary results of this trial are so outstanding, that I believe the future of curing HD lies within the grasp of an ASO. Whether it be IONIS-HTTRx or one that is modelled after it, the success of this trial has seemingly placed us in an advantageous position that we perhaps would have not thought ourselves to be in so soon.

Riccardo Kyriacou

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P53 Therapy: an example of apoptosis-targeted gene therapy for cancer

Ellen Rogers investigates a possible cure for cancer

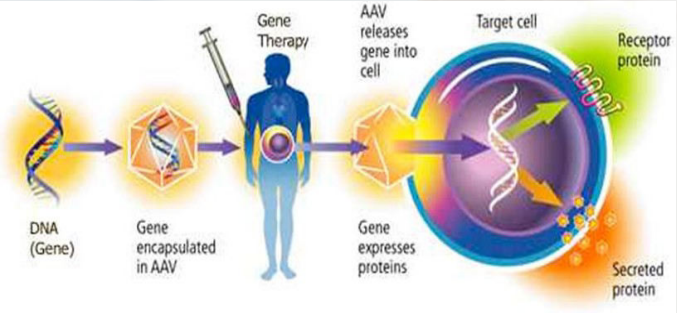
What is apoptosis-targeted gene therapy?

A major problem facing oncologists when treating patients is that many tumours have a high resistance to the chemotherapeutic drugs normally used as treatment, which can kill healthy body cells. This resistance is most commonly a result of the overexpression of certain proteins in the Bcl-2 group, which prevent damaged cells from undergoing apoptosis (programmed cell death, or cell 'suicide' (Miyashita T et al, 1994). Apoptosis-targeted gene therapy involves the alteration of the DNA or biochemistry of cells in the hopes of reregulating apoptosis, which results in the automatic death of damaged (cancerous) cells. Given that cancer is caused by mutations and faulty genes (and many tumours share the same key mutations), the insertion of 'working' versions of these genes may prove successful in inducing apoptosis in cancerous cells, whilst reducing the severity and frequency of side effects experienced by patients.

P53 therapy

One method of gene therapy involves the insertion of a working version of the TP53 gene. The mutation of TP53 is the most common mutation found across all cancers, as any damage or mutation to the gene has severe biological consequences. The P53 protein detects damage to the DNA of cells and prevents any further cell division (mitosis), and instead forces these cells to undergo apoptosis. If a mutation occurs, P53 no longer does its job correctly and damaged cells are able to divide uncontrollably, resulting in the formation of a tumour.

Although a tumour can "rapidly accumulate additional mutations and progress toward a more malignant phenotype", tumour cells are still sensitive to the effect of p53 when the gene is corrected (Almazov VP, Kotchetkov DV, Chumakov PM, 2007). In order to insert this working gene into the cells, a virus is genetically engineered and altered so that it is capable of expressing the working copy of the TP53 gene. When these genetically-altered virions enter the cancerous cells, they begin to produce working P53 proteins, which detect the cells' damaged DNA and initiate apoptosis, resulting in the death of large amounts of cancerous cells.

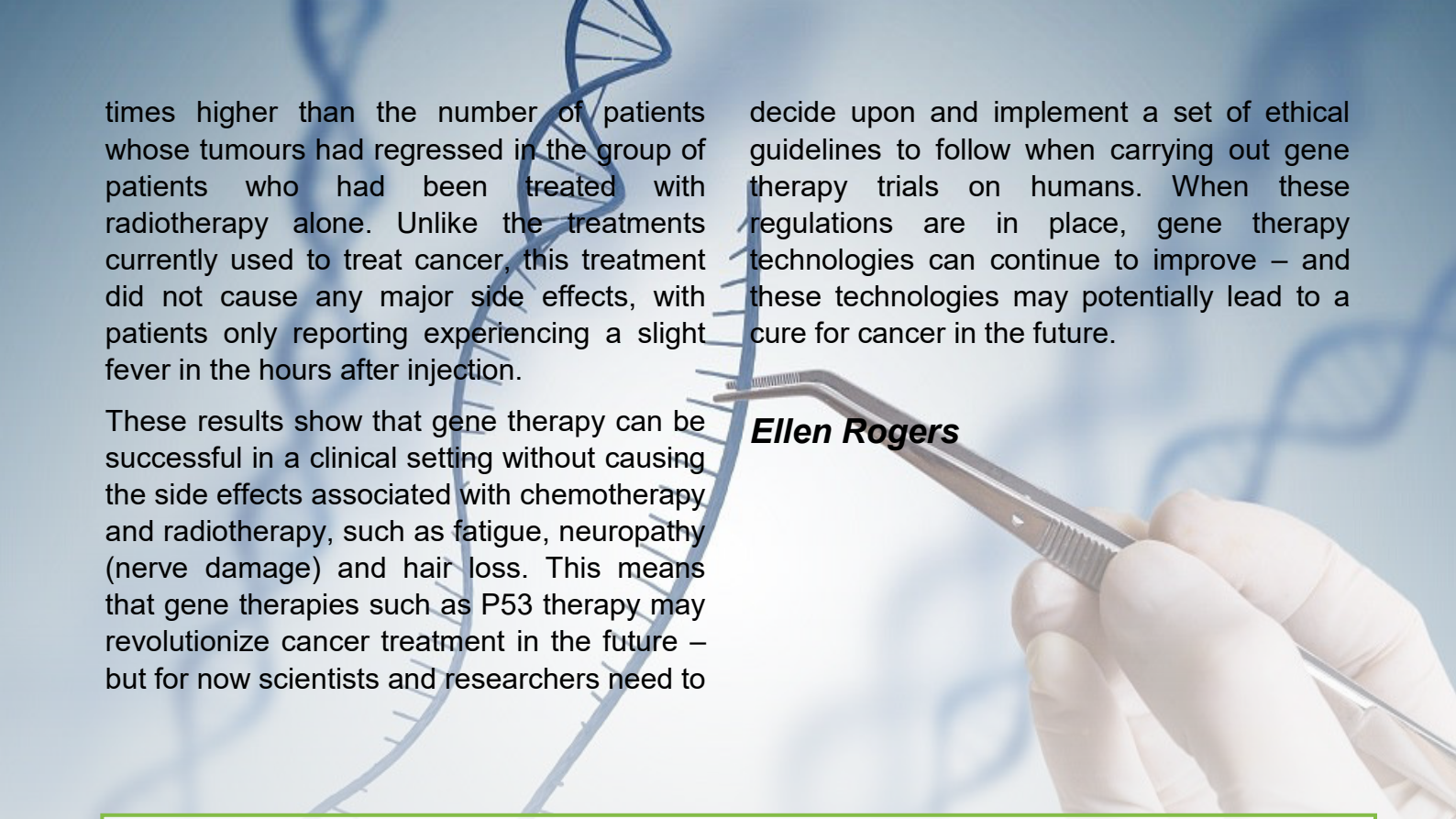


P53 therapy has been shown to be very effective when treating many different types of cancer. In the biggest trial ran by the company SiBiono Genetech (who produced Gendicine, the first approved gene therapy for cancer), 120 patients with nasopharyngeal cancer were either given radiotherapy or a combination of radiotherapy and Gendicine. Throughout the trial Gendicine was injected into tumours once a week for eight weeks- and at the end of the trial, 64% of tumours treated with Gendicine had completely regressed, and 29% of tumours had regressed partially. This figure was three

times higher than the number of patients whose tumours had regressed in the group of patients who had been treated with radiotherapy alone. Unlike the treatments currently used to treat cancer, this treatment did not cause any major side effects, with patients only reporting experiencing a slight fever in the hours after injection.

These results show that gene therapy can be successful in a clinical setting without causing the side effects associated with chemotherapy and radiotherapy, such as fatigue, neuropathy (nerve damage) and hair loss. This means that gene therapies such as P53 therapy may revolutionize cancer treatment in the future – but for now scientists and researchers need to decide upon and implement a set of ethical guidelines to follow when carrying out gene therapy trials on humans. When these regulations are in place, gene therapy technologies can continue to improve – and these technologies may potentially lead to a cure for cancer in the future.

Ellen Rogers



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Molecular Toxicity

Harroop Bola investigates what makes a molecule poisonous

A poison is defined as a substance that expresses adverse effects and possible lethality to an organism. To understand the breadth and nature of poisonous molecules it is important to recognise their mechanisms of action, their interaction with biological systems and models, and most significantly the relevant dosage for a molecule to express toxicity. Although, antibiotics such as streptomycin may be classified as molecular poisons within the prokaryotic domains, the development of antibiotic resistance and the fact that they are not effective poisons means that they will not be considered. Any molecule can be considered poisonous at high dosages and are dependent on their interactions with bodily functions which may differ between species. Although through using case studies, it is important to note toxins which have distinct toxicology at low dosages. Commonly, molecular poisons all have the feature to target specific systems that are essential to an organism's function.

Structure

Organophosphates are anticholinesterases, expressing varying degrees of cholinergic and noncholinergic effects, commonly involved in insecticides and nerve agents (neurotoxins). Acetylcholine (ACh) is synthesised at the presynaptic end of a neurone. ACh carries the signal from nerve cells to effector muscle cells. Acetylcholinesterase (AChE) functions as a regulating agent of nervous transmissions by reducing the concentration of ACh in the junction through AChE catalysed hydrolysis of ACh into the products choline and acetic acid. These products do not stimulate the postsynaptic membrane, effectively stopping the transmission signal, within 80 microseconds. The function and mechanisms of action of AChE is important to understand before discussing the mechanisms of inhibition by anticholinesterases, and the toxicity resulting.

Inactivation of AChE by organophosphorus result in enzyme inhibition, thus discontinuing hydrolysis of ACh. As a result, the concentration of ACh persists to an extent of high concentration, continuing the transmission signal and causing continuous stimulation of muscle and nerve fibres; leading to tetany and exhaustion.

The mechanisms of inhibition occur because of a chemical reaction in which the serine hydroxyl moiety in the enzyme active site is phosphorylated. An acetylated enzyme rapidly degrades the complex to form acetic acid and choline, then regenerating. Whereas, a phosphorylated enzyme, is highly stable, and dependent on the attached R & R' groups, is irreversibly inhibited. Therefore, the hydroxyl group is blocked by the phosphoryl moiety; AChE can no longer participate in hydrolysis of ACh. Identifying this, it suggests a relationship between chemical reactivity and structure to biological molecules with molecular toxicity.

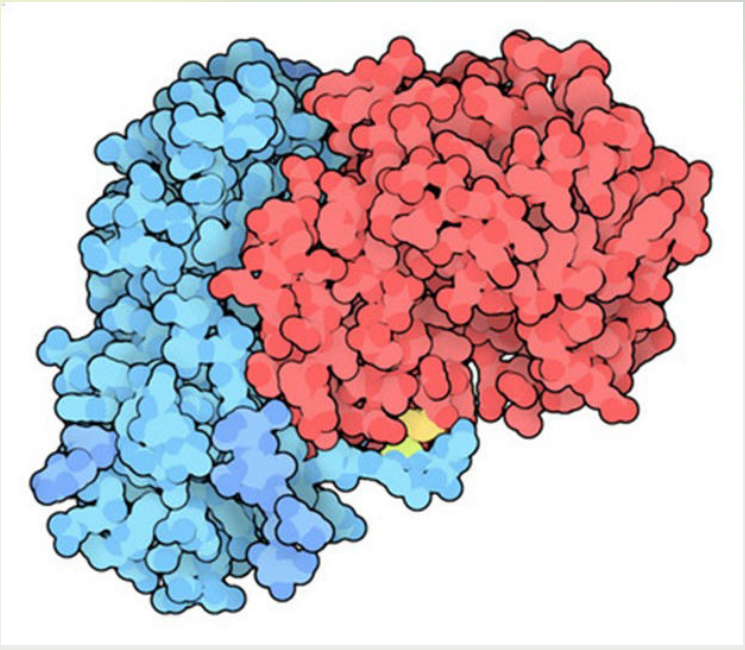
Other neurotoxins include α-bungarotoxin from snakes of the genus *Bungarus*; a cobratoxin from cobras preventing ACh receptor channels from opening, by binding specifically and irreversibly to its α subunits. ACh antagonists that prevent channel opening further explore the concept that an effective toxin specialises in targeting specific molecular structures through a binding process; aiming to hinder the structural function to limit the biological significance and process, in this case preventing ACh from having an effect. Furthermore, a combination of molecular neurotoxins can significantly enhance the effectiveness of a toxin; a collection of pre-synaptic neurotoxins and post-synaptic neurotoxins can effectively block skeletal neuromuscular transmission by preventing ACh neurotransmitter release; whilst blocking receptor ACh receptor sites. A reduction in ACh, enables neurotoxins which have a stronger affinity to receptor sites, to effectively bind without competition, preventing transmission and the effector response.

Reactivity and Binding

A molecular toxin can be rendered more potent through its interaction with bodily functions such as hepatic metabolism, resulting in metabolites which can cause harm, through their antagonistic interference with essential processes, haematopoiesis, being an example. Benzene derived metabolites cause a plethora of toxicity. To understand its toxicological process, it is important to discuss and understand the significant function of haematopoiesis and the mechanisms of action of benzene metabolites.

Reactivity of quinone metabolites provides a relationship with toxicity, a similar trend explored with organophosphates. Benzene metabolites formed by hepatic metabolism are less likley to survive long enough to reach the bone marrow, however reactive metabolites may be bound to carriers, that release them after transport to the target tissue. The toxicity of Benzene is enhanced by the interactions of metabolites with the bone marrow, containing low levels of cytochrome P450 and high levels of peroxidases. Therefore, it seems that toxicity occurs because of the involvement and processes of the target tissue. Reactivity being the significant factor, which enhances a metabolite's toxicity.

To understand how bone marrow depression occurs by covalent binding, it is important to discuss the relevance and function of haematopoiesis. Haematopoiesis is the production of erythrocytes, platelets, megakaryocytes and white blood cells. This process occurs in the bone marrow. Haematopoiesis controls and regulates a correct number of red blood cells in the circulatory system. Pluripotential stem cells differentiate into mixed myeloid progenitor cells and lymphoid precursor cells which proliferate into specialised cells such as granulocytes and monocytes. The mechanism of actions that induce toxicity are dependent on cellular functions and their complimentary reactivity with para-benzoquinone; an important aspect of molecular poisons is that independently they are not poisonous; their interaction with essential biological molecules such as proteins express adverse effects through inhibiting their function. Benzene metabolites are capable of covalently binding to DNA, inhibiting RNA and protein synthesis. Demonstrated by Irons and Neptum, hydroquinone inhibits polymerisation of tubulin. Tubulin possesses nucleophilic sulfhydryl that binds guanosine triphosphate (GTP), responsible for the stabilising of tubulin molecules for further polymerisation to microtubules necessary for spindle formation during mitosis. Tubulin is the main constituent of microtubules, therefore significantly providing the essential formation of mitotic spindles responsible for haematopoiesis. Therefore, a consequence of tubulin polymerisation inhibition causes the replenishment of erythrocytes to decrease, contributing to the acceleration of aplastic anaemia. The consequence of binding leads to bone marrow depression, fibrosis and reduction in immunity. As a result of bone marrow depression, the organisms' survival is put at risk, since the dependency on transporting oxygen across the body and



defence against pathogenic invaders is threatened by benzene metabolites. This means that as a toxic molecule it has reduced the efficiency of an important function, through its mechanism of binding.

Same molecule, different effects?

Molecular toxicity varies in different organisms, this helps to establish the idea that toxicological effects occur because of a molecule debilitating a specific function important to the survival of an organism, since the organism may be

dependent on the affected target tissue. Most toxins work as competitive inhibitors, and so to be considered effective, large concentrations of the molecule are needed. Every molecule is poisonous at high dosages because of their ability to alter the required balance of concentrations across the body, which many processes rely upon for mass transport (osmosis, active transport and diffusion). Dosage and toxicity have a strong relationship, an example evident in theobromine, found in chocolate. Theobromine and caffeine are examples of methylxanthines and alkaloids, and are the major toxic compounds composed in chocolate, with an LD_{50} of 100 to 200mg/kg^3 in cats and dogs, as opposed to the LD_{50} of 1000mg/kg^3 in humans. This illustrates that different organisms have distinct tolerances in their response to a molecule, which potentially possesses toxicological effects, and hence toxicity is dependent on the structure, size and physiological aspects of an organism. Through hepatic metabolism, theobromine undergoes enterohepatic recirculation; the half-life of theobromine is 17.5 hours in dogs, a contrast to 2.5 hours in humans. Consequently, considering the difference in physiology in dogs, toxicity occurs since theobromine concentration in dogs remains at a higher level for a longer period, to express diuretic effects.

Conclusively, the primary reason why molecules are considered poisonous is a result of their physiological interactions, by specifically altering or hindering other biological molecules. The consequence of this prevents a stage of a critical process from working effectively. To emphasise the definition of a molecular toxin, it is important to note that independently no molecule is poisonous. Features of a molecule may contribute to the developing enhancements of molecular toxicology such as structure and reactivity; interactions with bodily processes; working together with other toxins; being undetectable, and most importantly, their relative concentration. All molecules can be considered poisonous at high concentrations and volumes, including water, however what defines a successful toxin that can effectively debilitate an organism at low concentrations, is their specificity to adversely affect one significant process such as neurotransmission. Ultimately, molecular toxicity is defined differently according to the targeted organism, however, the general trend suggests that molecules are poisonous because of their specific ability to interfere and disturb the natural order of bodily processes, that are vital for the survival of an organism.

Harroop Bola

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Artifical Intelligence and Robotics in Medicine

Oscar Shearer-Rivera investigates the possibility for AI and robots in Medicine

The definition of Artificial Intelligence is the theory and development of computer systems able to perform tasks normally requiring human intelligence, such as visual perception, speech recognition, decision-making, and translation between languages.

History in Medicine

The use of Artificial Intelligence in medicine is not necessarily something completely new, or some far off future innovation only just starting to take root. An early use of Artificial Intelligence was in fact as long ago as 1987 in a system developed in the University of Massachusetts known as DXplain. This piece of early technology could come up with a diagnosis, given a set of symptoms. While it is not a revolutionary piece of technology that removes the need for Doctors all together, it did open up a door into using Artificial Intelligence to improve the system. While this was only the first step of many, we are now seeing results in which robotics in medicine is really starting to take off. Nowadays, DXplain is no longer used to help with diagnosis, but other forms of AI, such as one developed in John Radcliffe Hospital in Oxford can now diagnose Heart Disease more accurately than human doctors. It is claimed to be accurate at least 80% of the time. While it is only specific to Heart Disease, it is one of the first instances in which Artificial Intelligence has surpassed Humans in an area of medicine. While the actual machine might not be ground-breaking in its usage, the idea that AI can now overtake Humans in this field is both daunting and exciting.

Looking at surgery specifically, the first documented use of a robot-assisted procedure was in 1985 when the PUMA 560 robotic surgical arm was used in a neurosurgical biopsy. It was a first step along the path that we are currently very far along. It allowed for greater precision and led the way to the first Laparoscopic procedure in 1987. Later on, in 2000, the Da Vinci operating system paved the way for future robotic surgery by becoming the first FDA approved robotic surgical system to be available for general use in Laparoscopic surgery. It actually removes the need to leverage itself on the incision walls. This means there in less contact between the surgical equipment and any exposed tissue, lowering risk of infection. The Da Vinci operating system is important as even though it is not Artificial Intelligence itself, it was the first step along the line of involving robotics in the operating theatre, and to gain FDA approval meant it could be used anywhere in surgery. Da Vinci surgery is a robotic

Da Vinci System

arm that is controlled by a human, used to create smaller incisions than ordinarily possible and to allow the doctor to see a clear image in 3D. It is now an available option in neurological, gynaecological, urological and cardiothoracic procedures. This small step is now seemingly normal, as in the United States in 2017 over 693,000 robot-assisted procedures were carried out.

Future in Medicine

The main question involving the future of Artificial Intelligence and robots is whether it can replace a human in this area. The answer

at the moment, is unsurprisingly no. In the first direct comparison in diagnosis accuracy, human doctors were able to show why they are in the hospitals and not computers. The results showed that humans diagnosed with 84.3% accuracy compared to a measly 51.2% accuracy.

So it clearly has got a long way to go before it can even be considered a substitute for

Doctors. However, it is gaining ground, and it is managing to do so with extreme pace. The future in other areas such as surgery is very bright for machines also. With the successful operation carried out on the pig's small intestine and the even more impressive replacement of two teeth by a robot in China, surgery is quickly becoming a robotic nursery. It has the potential to do things previously impossible; in the case of the pig's intestine, it was done to a higher standard than the surgeon could manage, and in the case of the robotic dentist in China, it can help solve the massive deficit of dentists. So clearly there is a future for Artificial Intelligence in more than one field. It is on its way to becoming as adept at diagnosing as a human doctor, and actually being better than a doctor when it comes to planning treatment in areas such as cancer, as well as being a brilliant surgeon.

Oscar Shearer-Rivera

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Do we understand how memories are formed and lost?

Marcus Teo discusses the science behind memories

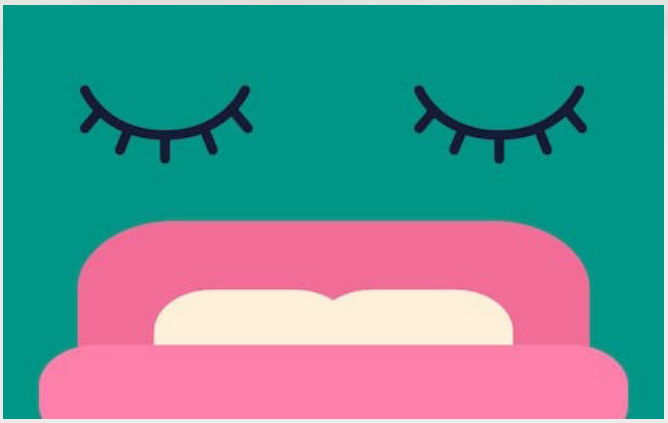
Have you ever walked into a room and completely forgotten why? Have you ever opened your mouth to speak to realise you can't remember what you were about to say? Have you ever sat down in an exam and felt your mind go blank? Memory is such an interesting phenomenon that has been baffling people for centuries from top leading scientists to schoolkids such as me. With hypotheses about it dating back over two thousand years to Aristotle and his dissertation 'On the Soul', the topic has been so widely researched but still it holds mysteries that we may never solve.

The brain is full of neurons, specialized cells that transmit nerve impulses (information) and these are all linked by synapses. Scientists believe that these hold the answer to how memories are formed and stored. The theory devised by Spanish neuro-anatomist Santiago Ramòn y Cajal was that memories are created by strengthening of certain neural connections and experiences can cause this. Subsequently, when one neuron is triggered, the others with strong connections to it will also be activated resulting in memories coming to the forefront of your mind. This is all aided by the hippocampus in the brain.

A fundamental concept that allows the aforementioned theory to be legitimised is neuroplasticity. This was first hypothesised by William James in The Principles of Psychology. Neuroplasticity is the ability for the brain to change and remain changed (demonstrating plastic behaviour) and this is quintessential to how memories are formed. It means that the strengthened connections between neurons in the brain can remain strong and therefore form associations between events for a long period of time. As technology has advanced we have gained the capability of observing the brain at a much more detailed level. This has allowed us to see that the connections are 'strengthened' due to changes in the dendritic spines (protrusions from a neuron). By changing of shape, volume and density of these, the memories 'stored' in your brain can weaken or strengthen. However, what still amazes scientists is how the brain can store these in such intricate detail.

There are also many hypotheses that claim sleep plays an essential part in the formation of memories. Our time asleep is split into two different sections; rapid eye movement (REM) and slow wave sleep (SWS). Research has shown that REM plays a part in strengthening past memories and SWS consolidates newly formed memories by reactivating these neurons.

One major issue linked to memory and a hot topic at the moment in medical research all across the world is dementia. With recorded



cases of this illness rapidly rising and approximately 10 million new people developing dementia every year worldwide it's important that we try and uncover the mysteries of it and bring a halt this devastating disease that is affecting so many people. At the moment, it is thought that dementia is brought about by the death of neurons in the brain, and as they are terminally differentiated and cannot reproduce, they are not replaced. The loss of neurons means the loss of memory and connections between events.

Another interesting topic is false memories, "a mental experience that is mistakenly taken to be a veridical representation of an event". This has been baffling scientists for years however there are many hypotheses on why they form. This

can range from having a vivid memory of yourself locking a door when you leave your house when you didn't to a more interesting example of the famous line in Snow White being regularly misquoted as 'Mirror mirror' instead of 'Magic mirror'. With people previously believing that memories could only form from experiencing something, these examples have proven that memories can be manufactured.

This has been proved by two scientists from Massachusetts Institute of Technology, Steve Ramirez (a doctoral student) and Xu Liu (a neuroscientist) who were able to implant false memories into mice. There have been many legal incidents that have been majorly affected by this phenomenon. Distinguishing between false and true memory can prove to be almost impossible in some cases and this causes many problems.

Although, advancements in knowledge of how memories are formed and lost have been great over the past years, the increase in number of sufferers of mental illnesses such as anxiety (often a result of experiences and therefore memories of it) and our inability to provide a solution to it shows that we still lack a true understanding of the subject. It also shows that our brain is such a complex organ that even we cannot control, and if we can't how can we claim we know everything about it? Over the years so much has been done in medicine to help more 'physical' illnesses. Antibiotics, discovered in 1928, have brought a solution to easily cure people of illnesses that were fatal previously. However, few medications are available for people suffering with mental illnesses (many of the ones that are successful have negative side effects) and therapy is not a sure way to help. More knowledge in this field would certainly have implications on the ability for doctors to help and work done on the subject such as Ramirez and Liu's experiment that prove we can alter memory opens pathways and gives us the opportunity to look at the problem from different perspectives. Being able to modify our memory could lead to solutions for illnesses such as PTSD and depression. In my opinion, this should be the key focus of research over the following years in medicine and science considering one in six people suffer from some sort of mental health problem. Discoveries could change the lives of millions around the world but these solutions are locked away from us and the key is to discovering them is through a greater understanding of how the brain works and how it processes and stores information; memories. One thing is for sure, we have a complex machine living inside our head whose true potential and powers are still unknown to us.

Marcus Teo

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