Mitosis

The Academic Journal of The RGSHW Biology Department (Summer 2021)

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Introduction

Welcome to the Summer edition of the Biology Academic Journal, *Mitosis*.

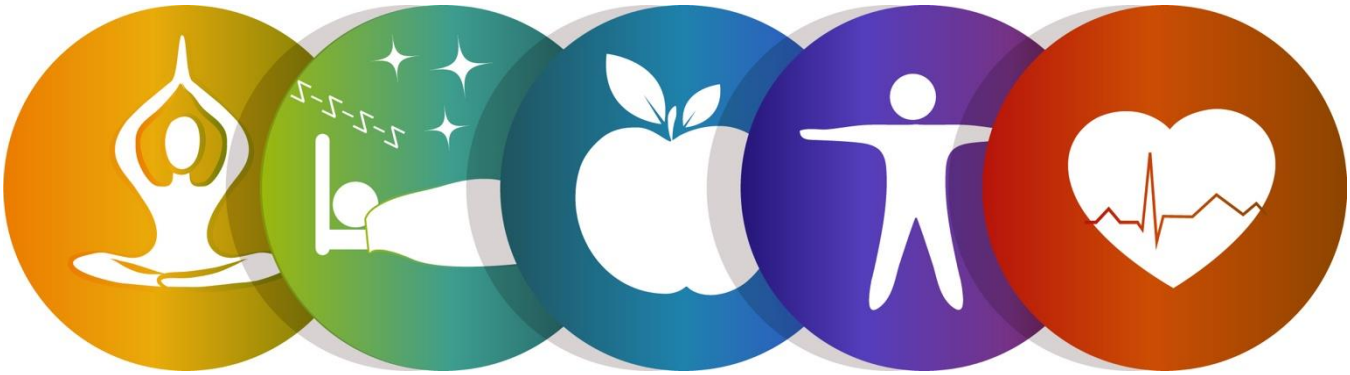
This journal continues to serve as a means of congregating and displaying the research from enthused biologists from The Royal Grammar School. It is fantastic to see the increased interest, from students, in this journal and we hope that this trend continues.

Whether you are a newcomer to *Mitosis* or thinking of writing an article for the journal's next edition, we sincerely hope that you enjoy reading these research projects and share our passion for Biology.

Josh and Krishnan (Biology Subject Ambassadors 2021)

RGS ESTD 1562
HIGH WYCOMBE

Health



Are personalised drugs the future of medicine?

Eric Logothetis

A spine-chilling statistic from the NHS states that one in two people will develop cancer in their lifetime (*Cancer - NHS*, n.d.). It must be understood, though, that many cases are not fatal and may have little to no effect on individuals. However, with 166,533 deaths due to cancer in the UK between 2016-2018 (*Cancer Statistics for the UK*, n.d.), this is not a statistic to disregard. Recent breakthroughs in the field of genome sequencing have yielded the ability to optimise the personalisation of drugs, prominently in oncology. The innovative technology reads the sequences of bases in DNA cheaper, quicker and more precisely than ever before, allowing for a new era of medicine to arise; an era where the "one size fits all" hypothesis of drugs is discarded. The benefits of personalised drugs seem to be endless. Increased effectiveness, earlier diagnosis and reduced antimicrobial resistance will ultimately save lives. But is this all good news for you and me, and can we expect this in our lifetimes?

Research in personalised tumour DNA sequencing has disclosed invaluable data on the development and possible treatment of cancer. The sequencing identifies targets for current pharmacological treatment, as well as targets for new and possible revolutionary drugs. For example, whole exome sequencing (WES) has uncovered a loss of function in TSC1 for approximately 5% of advanced bladder cancers(Esplin et al., 2014). This specific mutation correlates to tumour sensitivity towards everolimus therapy. Around 30% of colon cancer patients will exhibit some toxicity risk and no treatment benefit using EGFR antibodies, due to the lack of identification of KRAS alterations(Esplin et al., 2014). Furthermore, a study of chronic myeloid leukaemia patients found a deletion of BCL2 for cancers resistance to tyrosine kinase inhibitor therapeutics. The distinct benefit with genome sequencing resulted in the FDA recommending genotyping prior to treatment with certain drugs. The targeting of drugs will increase effectiveness, reduce side effects and in turn increase survival chances.

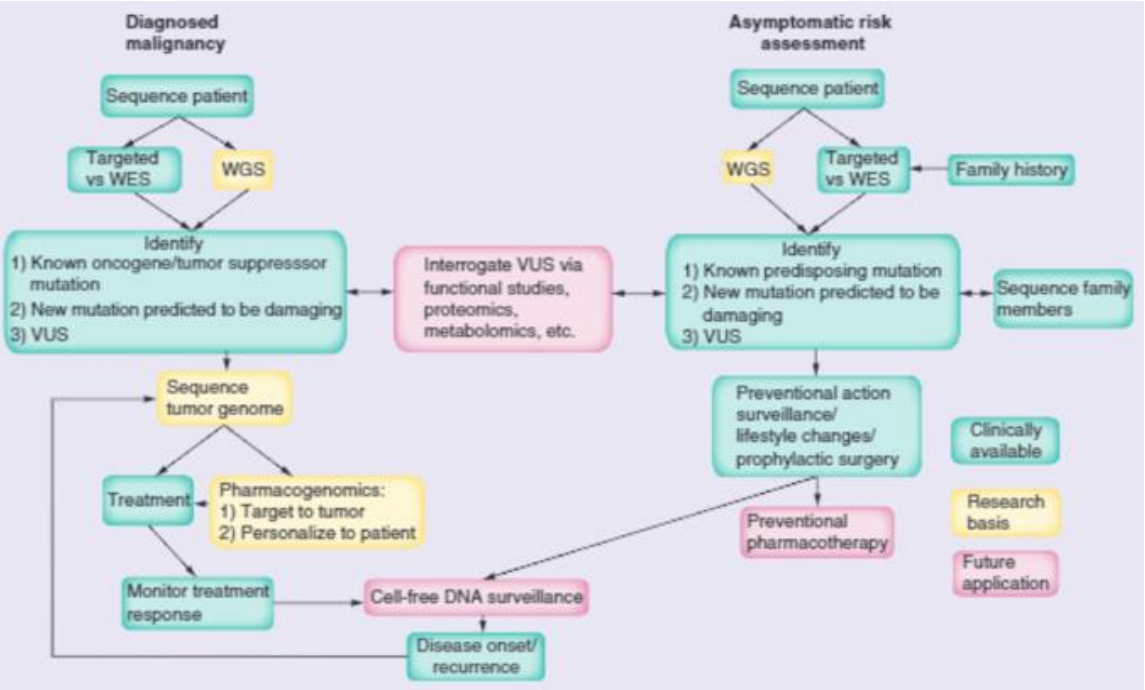


Figure 1: Showing treatment and diagnosis strategies used currently, as well as predicted for the future

Exploiting the 30-70 mutations in cancer proteins has created highly tumour-specific antibodies to steer the treatment of cancer(Esplin et al., 2014). Despite the obvious treatment benefits, there is another advantage. One that is becoming more vital in our time. The evolutionary arms race against antimicrobial resistance often renders lifesaving treatment futile for millions across the world. In the context of cancer drug resistance, this is a substantial problem generating unnecessary deaths, as resistant tumours are selected for in a Darwinian fashion. The future may hold the use of simultaneous personalised drug treatments to combat the resistance, and may be closer in time than thought with genome sequencing becoming cheaper, and so increasing the economic benefit.

Despite genome sequencing already leading advances in cancer therapy, new targets are constantly arising. Pathways in tumor suppressor genes are difficult to target therapeutically, but thanks to genome sequencing it is understood that BRCA1 and BRCA2 gene defects impact DNA repair. This means drugs, like PARP, that inhibit DNA repair can be utilised, with phase II clinical trials underway(*PARP Inhibitors as Initial Treatment for Ovarian Cancer - National Cancer Institute*, n.d.). With only 40 known cancer genes with FDA approved drugs, and a further 30 genes with experimental drugs under development(Esplin et al., 2014), genome sequencing has played and will continue to play an invaluable role in the development of personalised drugs for oncology. A promising area of research includes cell-free DNA (cfDNA) sequencing, where cancer mutations are possible to detect in the bodily fluids of patients. This has enabled revolutionary advances in non-invasive whole genome sequencing (WGS) of a fetus at 18.5 weeks, as well as observing the progression of cancer. The recent understanding of significant levels of tumour DNA in the blood of cancer patients allows for the monitoring and marker of remission.

Table 1. US FDA-approved oncology drugs with package inserts containing pharmacogenetics and pharmacogenomics information.

Drug	Pharmacogenomic biomarker(s)
Ado-trastuzumab emtansine	ERBB2
Afatinib	EGFR
Anastrozole	ESR1, PGR
Arsenic trioxide	PML/RARA
Bosutinib	BCR/ABL1
Brentuximab vedotin	TNFRSF8
Busulfan	Ph chromosome
Capecitabine	DPYD
Cetuximab	EGFR, KRAS
Cisplatin	TPMT
Crizotinib	ALK
Dabrafenib	BRAF, G6PD
Dasatinib	BCR/ABL1
Denileukin diftitox	IL2RA
Erlotinib	EGFR
Everolimus	ERBB2, ESR1
Exemestane	ESR1
Fluorouracil	DPYD
Fulvestrant	ESR1
Ibritumomab tiuxetan	MS4A1
Imatinib	KIT, BCR/ABL1, PDGFRB, FIP1L1/PDGFRA
Irinotecan	UGT1A1
Lapatinib	ERBB2
Letrozole	ESR1, PGR
Mercaptopurine	TPMT
Nilotinib	BCR/ABL1, UGT1A1
Obinutuzumab	MS4A1
Ofatumumab	MS4A1
Omacetaxine	BCR/ABL1
Panitumumab	EGFR, KRAS
Pazopanib	UGT1A1
Pertuzumab	ERBB2
Ponatinib	BCR-ABL T315I
Rasburicase	G6PD
Rituximab	MS4A1
Tamoxifen	ESR1, PGR, F5, F2
Thioguanine	TPMT
Tositumomab	MS4A1
Trametinib	BRAF

F2: Prothrombin; F5: Factor V Leiden; Ph: Philadelphia.
Data taken from (52).

Figure 2: Showing currently FDA approved drugs against cancer

Currently, there are limitations to the technology of genome sequencing, and so the development of personalised drugs. Most prominently this includes cost and time, where despite the resource availability, it is unrealistic to walk into a hospital and leave with a personally created drug. Looking back into the past, it is clear to see a rapid rise of genome sequencing technology, making it possible to sequence the human genome in a fraction of the time and cost. It is plausible to predict this technological advancement to proceed into the future, and with sufficient funding, make drug production more available. The accuracy of genome sequencing is another limitation, but by combining multiple sequencing platforms, in what is known as cross validation, it is possible to reach 99.3% sensitivity(Esplin et al., 2014). It is unclear as to what the future of medicine will look like, but genome sequencing has countless benefits to aid in the more prominent usage of personalised medicine.

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What is the current usage, and future uses for PARP inhibitor drugs in cancer treatment?

Andrew Hayes

PARP (poly-adenosine diphosphate ribose polymerase) are types of enzymes found in the nucleus of cells. They carry out a range of activities, included programmed cell death and genomic instability[1] (bibliography **[2]**). The function that is most interesting, however, is their ability to repair sections of DNA.

Image by Arek Socha from Pixabay

DNA is made up of organic molecules called nucleotides. Nucleotides are comprised of a five-carbon sugar, a phosphate group, and a nitrogenous base.[2] The individual nucleotides are joined together by phosphodiester bonds, to form a strand of DNA. Complimentary nitrogenous groups[3] are bonded with hydrogen bonds, which attach the two strands of DNA together, forming a double helix. **[3]**

When a piece of DNA undergoes single strand damage (one of the strands is damaged in some way)[4], the other side can be used as if it is a template to correct the damaged strand. This works because if the other strand has a nucleotide with adenine as its base, then the complimentary base must be thymine. There are multiple, different ways that cells use to correct damage, but for the purpose of the article the damaged piece is removed and an undamaged piece is inserted.[5] PARP is responsible for binding to the DNA and signaling the enzymes to start this process of DNA repair **[5]**. (For more information on this process, see the end of the article. **[EXTRA]**).

So, what does this all have to do with cancer? Since PARP helps to repair damage in DNA, using PARP inhibitors stops PARP from being able to repair DNA. In cancer cells, this leads to cell death **[6]**. Non-cancerous cells have two methods of repairing damage, yet cancerous cells only have one. PARP inhibits one of the pathways of DNA repair, but not the other. This means that while healthy and cancerous cells are both affected, the normal cells can be repaired by the other pathway. Due to DNA damage, the cancer cell will eventually die, while the normal cell remains healthy **[6]**.

PARP inhibitors (such as *olaparib*, *niraparib*, *rucaparib* and *talazoparib*) **[7,8]** are taken as tablets, or through an intravenous line. Currently, in the US, they have been approved for use by the FDA for cancers such as breast, fallopian tube and ovarian, and are mostly used after chemotherapy fails. A study (2019 **[9]**) tested the effects of Niraparib in patients with a new diagnosis of advanced ovarian cancer. In the double-blind[6] phase 3 trial, patients with a new diagnosis of advanced ovarian cancer were given either niraparib or a placebo once a

[1] (How likely mutations are to occur during cell division) (bibliography **[1]**)
[2] In DNA, these nitrogenous bases are Adenine, Thymine, Cytosine or Guanine.
[3] Adenine pairs with Thymine, Cytosine pairs with guanine
[4] This is just one of the types of DNA damage, others include damage sustained from ionizing radiation, UV damage and Double-strand breaks (where the entire DNA molecule are severed.) (Bibliography **[4]**)
[5] If a single nucleotide is damaged, the DNA will go through Base excision repair, where a glycosylase enzyme removes the damaged **base**, and inserts a new one. There are other mechanisms for more complex damage (bibliography **[5]**).
[6] Neither patients nor medical staff or experimenters know which patients are receiving the drug or not.

day, in a two to one ratio respectively. Out of the 733 patients, just below 51% had tumours that were unable to repair double strand breaks[7]. Out of these patients, the length of time after the treatment of the disease before it got worse[8] was 21.9 months for the group receiving niraparib, while only 10.4 months for the placebo group **[9]**. The PARP inhibitor niraparib was approved on 29th April 2020 by the FDA **[11]**.
So, what does this mean for other cancers? A 2019 study **[12]** suggests there is evidence that these PARP inhibitors could be used across a spectrum of different tumour types. Furthermore, there is "biological and early clinical evidence" **[12]** to use them in other subsets of cancer such as small cell lung cancer. This equates to using them outside of their current uses, which are on the BRCA[9] gene, causing breast cancer, as well as in other cancers such as ovarian and prostate. Being able to use these drugs on other tumours could be a massive breakthrough in cancer treatment **[13]**.

[EXTRA – information below from bibliography **5].** In more detail, before repair, chromatin remodeling must occur. The protein "c-Jun N-terminal Kinase" (JNK) **[15]** phosphorylates SIRT 6 **[16]**, in response to any double strand severing. SIRT6 then "recruits" the PARP1 (or Nicotinamide Adenine Dinucleotide Adenosine Diphosphate-ribosyl transferase 1) **[17]** to the site of DNA damage, which then synthesizes poly ADP-ribose chains. After this, the chromosome remodeler ALC1 (Chromodomain-helicase-DNA-binding protein 1) **[18]** attaches to the produce of PARP1, the poly ADP ribose chains. The ALC1 is at the site of damage within 10 seconds of damage occurring. This allows the DNA repair enzyme MRE11 (Double-strand break repair protein) – coded by the MRE11 gene to start DNA repair. **[19]**

[7] (Homologous-recombination deficiency is the inability to repair double DNA strand breaks)
[8] (The progression-free survival) - (bibliography **[10]**).
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COVID-19: Should you get a vaccine?

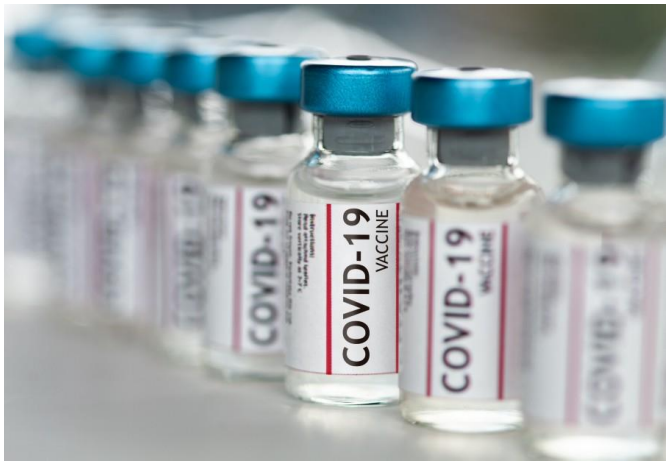
Eeshaan Ghanekar

Almost 50% of people in the UK have been fully vaccinated[1] (as of 28.06.21), and it is only a matter of time until teens are offered the chance to take the jab. Many will be frightened of the effects a vaccine produced so quickly may have on their bodies in the long term, especially after a basic understanding of GCSE biology, where textbooks mention the strenuous 10-year process of vaccine production[2]. So here the question lies: should we allow this unknown substance, that is over 8 years ahead of its time, to be injected in our bodies, or should we remain unvaccinated?

How does the Coronavirus vaccine work?

Although there are different Coronavirus vaccines, they all have several things in common which are necessary for making someone immune to the virus. The aim of a vaccine is to allow the body to come into contact with the virus or viral antigens, which are proteins or glycoproteins on the coating of the virus. Due to this, a primary immune response is triggered, where the body produces chemicals and antibodies to fight and destroy the virus. This is primarily done by the lymphocytes, which are the white blood cells. However, after the primary immune response, some white cells known as memory lymphocytes may remain in the body for a prolonged period of time. Hence, if the Coronavirus spike protein is identified in the body, these memory lymphocytes can rapidly trigger the production of antibodies specific to the virus, resulting in a very fast and effective immune response, greatly reducing chances of illness.

More specifically, the Oxford AstraZeneca vaccine is a very special type of vaccine known as a viral vector. This works by the genetically altered ChAdOx1 chimpanzee adenovirus viral vector used to carry the gene coding for the SARS-CoV-2 (Coronavirus) spike protein to our cells.[3] Once this virus is injected into the body, it enters a cell and the gene coding for the spike protein is transcribed into mRNA and the protein is synthesised in the cytoplasm of the host cell. The spike proteins are presented on the surface of the cell, and this causes T cells to produce antibodies and stimulate an immune response, causing the body to become immune to the virus if the body is infected again due to the memory lymphocytes produced as a result of immunisation.



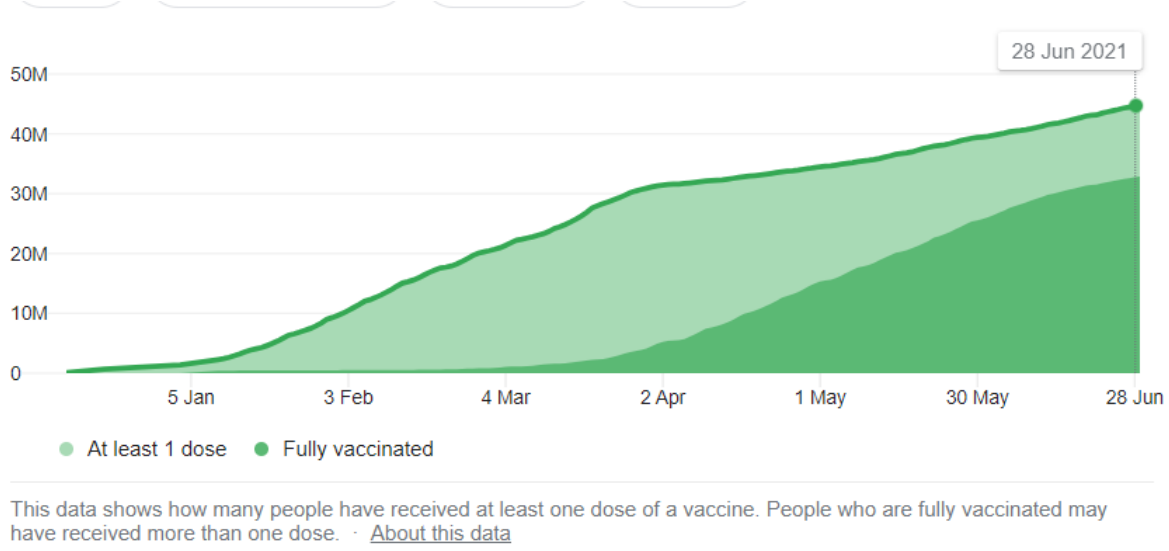
Is the AstraZeneca vaccine safe?

The AstraZeneca vaccine involves the use of the ChAdOx1 viral vector. This virus originates from the flu, causing adenovirus in chimpanzees. Obviously, it seems very strange that a disease-causing microorganism is being injected into thousands of people, claiming to benefit them. However, the reason the vaccine is safe is because this adenovirus is genetically modified to prevent it from replicating, meaning an adenovirus infection simply cannot be caused. Furthermore, the virus only contains sufficient genetic material for producing the SARS-CoV-2 spike protein, meaning that the vaccine cannot cause COVID- 19. The virus does not cause any changes in our genes and it is not incorporated into our DNA

either, meaning that overall the vaccine is perfectly safe to take from the standpoint of infection and the biochemistry of the vaccine itself.[3]

Benefits of getting a vaccine

The main reason vaccines are given is to prevent further infection of individuals and leads to the infection rate being greatly lowered. This was seen in a study on the infection rate observed after the first and second dose of the AstraZeneca vaccine, with only 0.3% of people with a new positive infection after the first dose of the vaccine, and only 0.1% newly infected after both doses.[4] Clearly, the vaccine prevents and slows the spread of COVID-19, and gives a very strong reason for why many people should get it. Furthermore, vaccination has decreased the death rate in the UK as well. According to Public Health England, COVID-19 vaccines prevented more than 10,000 deaths in people aged over 60[5], showing the strong efficacy of the vaccines and the huge successes of the vaccination programme. Finally, another strong reason for people to get the COVID-19 vaccine is the concept of herd immunity. Herd immunity is where a sufficient number of the population is vaccinated to a point where the unvaccinated individuals are also protected from disease, as the number of individuals infected is extremely low and the rate of spread is greatly slowed. However, this will only be possible if many people choose to take the vaccine, including young people under the age of 18.



Potential issues of getting vaccinated

Despite the great benefits of vaccines, there are still issues that need to be addressed that may mean that taking a vaccine is not a good idea. Recently, there was a lot of talk in the media about incidences of rare blood clotting caused by the AstraZeneca vaccine. EMA found a link between these rare cases of unusual blood clots with low blood platelets and concluded that this should be listed as very rare side effects of the vaccine.[6] Clearly, this is very daunting for someone being offered the vaccine, however it is necessary to emphasise that this side effect is extremely rare and most cases of this were not prolonged once medication was given. However, there may be other concerns that may put someone off from taking the vaccine. For example, the vaccination may cause muscle pains in the arm as well as tiredness[7]. However, these small sacrifices can easily be made for the increased

chance to get out of lockdowns as well as saving the lives of so many people. Some people may also have allergies to the components of the vaccine, so they would have to avoid getting the vaccine. Others may be advised against getting the vaccine if they are pregnant or suffer from other conditions such as autoimmune diseases.[8] However, those who may suffer from illnesses such as lung conditions would be advised to take the vaccine, as the risk of dying from being infected by COVID-19 are far greater than the risks of the vaccine.

Conclusion

In conclusion, the positives of getting a vaccine greatly outweigh the negatives, meaning it is beneficial for all people to take the vaccine once it is offered. Although the deaths due to COVID-19 are very low in young people, it is still extremely beneficial to get a vaccine to prevent the spread and lower infections in those who may be at risk of death from the disease.

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What is “Long Covid”, what treatment methods are currently available and what has been done to combat the disease?

Louis Bonnefoy

"Long COVID", otherwise known as post-acute chronic or long haul COVID is a term to describe the effects of Covid-19 that continue for weeks or months beyond the initial illness. It is now believed that 60,000 people have "Long Covid" in the UK 3 months after contracting the virus.

At the start of the pandemic, the focus for treatment was understandably on the acutely ill; saving lives of people admitted to hospital and minimising the risks to the elderly and vulnerable. Now a new and troubling phenomenon is coming to light. While most people recover quickly and completely from COVID-19, growing numbers are finding that they haven't simply snapped back into their pre-COVID lives.

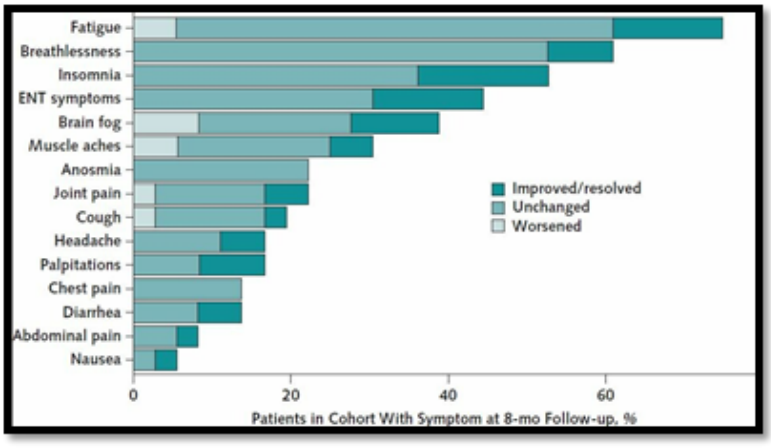
Instead, after what may have been only a mild initial illness, they are experiencing a range of troubling and sometimes disabling symptoms. These include:

- Breathlessness
- Coughing
- Palpitations
- Exercise intolerance
- Mental and physical exhaustion
- Anxiety
- Depression
- Fatigue
- Brain fog

<u>What are the treatment methods available for "Long COVID"?</u>

Since "Long COVID" was first identified a couple of months ago, different treatment methods have been suggested.

The only potential treatment method which has been studied so far is vaccination.
A paper, published on May 25th on the annals of internal medicine, titled "Symptoms after COVID-19 vaccination in patients with persistent symptoms after acute infection: A case series" outlined the results from a study to determine the impacts of vaccination on "Long COVID". In this study, 78 patients, who were hospitalised due to COVID symptoms, were followed after discharge from the hospital every 12 weeks for 8 months. Of these patients, only 44 received a vaccine at random points during this 8-month period. Their symptoms throughout this period were monitored using questionnaires and showed the following results:



Of the 78 patients which were hospitalised in this study, 55 stayed the same, 20 got better and 4 got worse. Although no control study was made for comparison, these results provide compelling proof that vaccination is not an effective treatment method (If a treatment method at all) for "Long COVID".

Since this study was completed, no further possible treatment methods have been identified; research still needs to continue.

What is the probability of contracting “Long COVID”?

Recent data from the COVID Symptom study app now shows that approximately 1 in 20 patients which are symptomatic with COVID will still have symptoms after 2 months and that 1 in 45 patients which are symptomatic with COVID will have symptoms for longer than 3 months. Data also shows that having 5 or more symptoms in the first week after contracting COVID is a strong risk factor for developing “Long COVID”.

Studies also show that females are slightly more likely to contract “Long COVID” than males. This is believed to be due to a difference in the immune response to viruses in men and women.

What has been the response to this growing issue?

Now that more evidence of “Long COVID” is coming to light, that have been calls for more support to be made available. the UK government responded by announcing a £10 million investment to fund “Long COVID” clinics across England similar to that setup in Genoa, Italy. Whether £10 million is going to be enough to deal with this we've yet to see.

The NHS England has also recently told the BBC specialist “Long COVID” services are currently being set up as part of a £100 million expansion of care for those with the condition.

Conclusion

Overall, recent research across the country has demonstrated the severity of “Long COVID” and the importance of finding a suitable treatment method. Moreover, pressure from the public has caused the government and the NHS to invest in “Long COVID” clinics and specialist “Long COVID” services to combat this rising issue. However, research still needs to continue in order to understand why it occurs, what are its long-term effect and how it can be treated.

Real Life Zombies- Prions:

Josh Jankiewicz

Introduction:

In 1997, American biologist Stanley B. Prusiner received the Nobel Prize in medicine for his discovery of "an entirely new genre of disease-causing agents" - prions. Despite Prusiner's work starting in 1972, in 2021 our understanding is still limited. In this article, I hope to shed light on this often unrecognized and vastly interesting topic.

What are Prions?

The term "prions" refers to abnormal, transmissible pathogenic agents which are able to induce abnormal folding of specific normal cellular proteins called prion proteins. These proteins are found most abundantly in the brain and can cause extensive neuron damage. Prion proteins are synthesized using the PRPN gene, and mutations on this can lead to the formation of the toxic and transmissible proteins.

The functions of these prion proteins are still not completely understood. The abnormal folding of the prion proteins leads to brain damage and the characteristic signs and symptoms of prion disease. Prion diseases are usually rapidly progressive and always fatal.

What makes Prions different?

What makes a Prion significantly different, and more dangerous, when compared to other pathogenic agents? Well, Prions lack a nucleic genome, unlike viruses and bacteria, which enables their reproduction. Some scientists hypothesize that the distorted protein could bind to other proteins of the same type and induce them to change their shape as well, producing a chain reaction that propagates the disease and generates new infectious material. Prions are resistant to UV light, extremely high temperatures and can also resist digestion by protease enzymes, ultimately making them immortal.

Prion diseases?

Prion diseases or transmissible spongiform encephalopathies (TSEs) are a family of rare progressive neurodegenerative disorders that affect both humans and animals. They are distinguished by long incubation periods, characteristic spongiform changes associated with neuronal loss, and a failure to induce inflammatory response. More simply, your brain takes on the structure of a house-hold sponge. Although extremely rare, with a few cases diagnosed per million per year, the most common prion diseases that affect humans include Creutzfeldt-Jakob disease, Kuru and Gerstmann- Sträussler-Scheinker disease.

Diseases:

Creutzfeld-Jakob disease has a similar range of symptoms to Alzheimer's and dementia, but kills infected individuals much quicker, usually within a year of infection. This involves a protein randomly becoming misfolded and turning into a destructive prion, which leads to the chain of events described beforehand. Gerstmann-Strauslerr-Scheinker disease is generally very similar to Creutzfeld's.

Kuru has some interesting origins. It originated in New Guinea, when cannibal tribes ate the brains of unknowingly infected individuals as part of their funeral rituals, thus ingesting the prions, and passing on the disease. Because the incubation period is so long, even though the cannibals stopped their practices around the 1960s, there are still cases being diagnosed today. It has a similar range of symptoms to Creutzfeld-Jakob disease, and also causes death within the year.

Finally there is fatal familial insomnia, which seems like one of the most agonizing diseases to encounter. The infected individual loses the ability to sleep due to a build of prions in the thalamus, and this eventually leads to slow and painful mental deterioration.

Risk Factors:

There are a couple of main risk factors associated with prion diseases. These include whether an individual has a family history of prion disease, as many forms can be inherited, or, whether an individual has consumed meat infected with Bovine spongiform encephalopathy, or more commonly known as "mad cow disease".

Mad cow disease is a prion disease which affects cattle and sheep and involves a progressive degeneration of the nervous system and uncharacteristic aggressive or nervous behaviour. This would have been a major concern for people a few years ago, when mad cow disease raged across farms in the UK. It is highly contagious and has a 100% mortality rate in young infant calves. Farmers were forced to burn entire herds of animals just to stop the spread of the disease from farm to farm, and some are still experiencing the financial effects of that today. However, it's also important to note that sporadic forms of some prion diseases require no past risk factors in order to develop, as healthy proteins can incorrectly fold for no apparent reason, to form contagious prion proteins.

Diagnosis and Treatment:

A key symptom on prion disease is rapidly progressive dementia and in the medical world prion disease should always be considered upon the onset of this symptom. A diagnosis can be confirmed with a brain biopsy. Other symptoms also include difficulty speaking, muscle stiffness, confusion, and difficulty walking.

Unfortunately prion diseases are always fatal and cannot be cured, but certain medicines may help slow their progress. Medical management and palliative care focuses on keeping people with these diseases as safe and comfortable as possible, despite progressive and debilitating symptoms.

New Research:

Research today is still focused on figuring out exactly how normal proteins fold into prions, and what causes them to do so. Among them, common neurodegenerative disorders such as Alzheimer's and Parkinson's have recently been linked to prions. Scientists have suggested that these brain diseases are caused by similar protein folding and it has been suggested that they should be called "prionoid" diseases. This would signify how they are similar to prion diseases but differ in not being transmissible- or so we currently know!

In summary, prion diseases are very rare, symptoms can progress rapidly, diseases are always fatal, and our knowledge of prions is still limited. So those were prions, in essence quite a haunting topic to talk about, considering all that it can cause, and the lack of treatments for it.

Thanks for reading.

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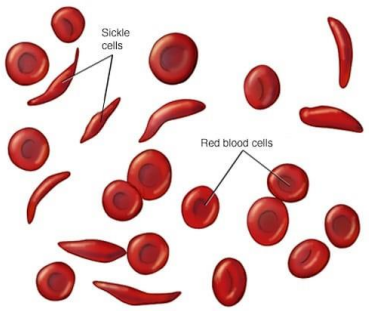
Foetal Haemoglobin; A Simple Solution to Lifelong Conditions

Shiv Mistry

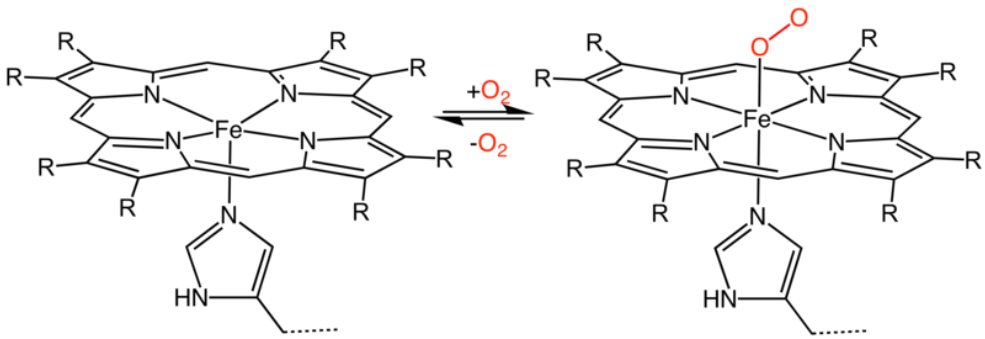
Sickle cell disease and thalassemia are two of the most vexing blood related disorders, with both costing the NHS a significant amount as a consequence of blood transfusions, clotting factor and other medication. With very few permanent cures available, both have been deemed lifelong conditions with a plethora of severe side effects and complications. Despite this, recently, a simple yet novel idea has led to the development of a potential new treatment for the two different genetic disorders, the focus of this article. However, for one to understand this new cure, one must first understand sickle cell disease and thalassaemia.

Normally, haemoglobin should consist of two beta-globin chains and two alpha-globin chains, that interact together to form a quaternary globular protein. It has 4 heme prosthetic groups attached, each containing a central iron atom, allowing for the protein to carry oxygen. Each erythrocyte (red blood cell) contains 250-300 million molecules of haemoglobin, making it one of the most abundant proteins in the body, along with collagen. However those with sickle cell disease have crescent shaped erythrocytes instead of smooth round ones, due to problems with that person's haemoglobin. A point mutation on the haemoglobin beta gene, located on chromosome 11, results in the replacement of a negatively charged glutamate by a neutral, hydrophobic valine in the beta-globin chain that produces sticky patches on the protein surface. This causes the haemoglobin molecules to stick together, and form sickle shaped red blood cells. This leads to pile ups and blood clots inside smaller vessels, which can result in painful episodes known as sickle cell crises. These blood cells also have a shorter life expectancy than normal ones, meaning a sufferer always has less blood cells than required, and this causes anaemia. The condition is recessive, meaning a faulty allele must be received from both parents, and is more common in African and Caribbean families.



A diagram, representing the difference between healthy red blood cells and sickle shaped erythrocytes, which can stick together and form clots inside small blood vessels, leading to sickle cell crises.

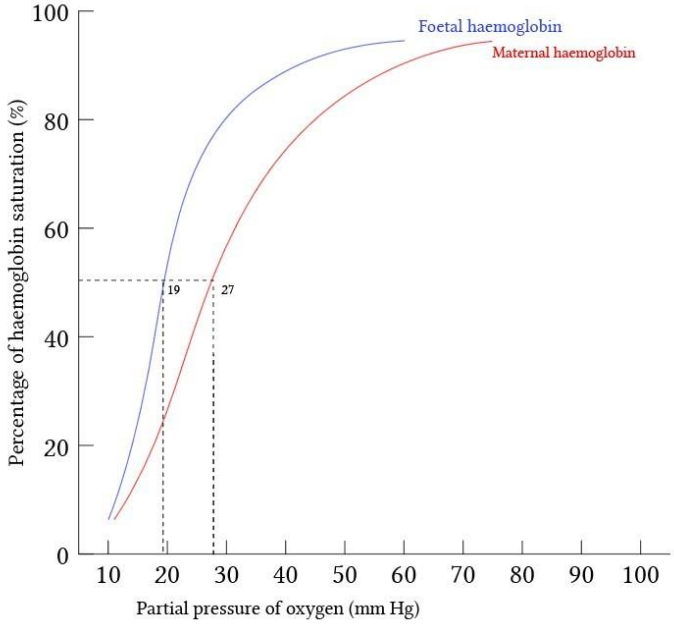
A diagram, showing the bonding of oxygen to heme group. Four oxygen molecules can bind to one haemoglobin molecule, the first one changing the structure of the molecule, facilitating the rest.



On the other hand, thalassaemia is an inherited blood disorder that reduces the production of functional haemoglobin. This causes a shortage of red blood cells and low levels of oxygen in the bloodstream, leading to a variety of health problems. There are two main types of thalassemia, alpha thalassemia and beta thalassemia, both related to the production of the different chains of globin (alpha and beta). Like sickle cell disease, the condition is recessive. Due to a lack of red blood cells, those with thalassaemia are often anaemic and have growth problems.

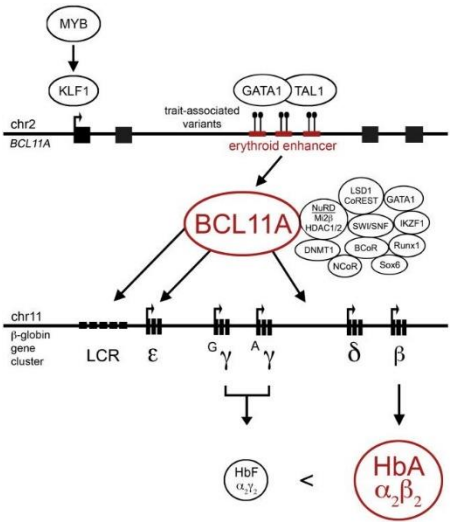
Regarding treatments for both the conditions, blood transfusions are both widely used to replace the damaged blood with healthy samples containing the right amount of healthy haemoglobin. However, this also leads to excess amounts of iron in the bloodstream, so iron chelation therapy is often used to remove this. There are permanent cures to both of these conditions, involving bone marrow transplants since the bone marrow is where erythrocytes are produced and matured. However, these are often complicated and painful, and finding a suitable donor can be even more difficult, so unfortunately transplants are often not a viable treatment option. In terms of sickle cell treatment, when one is experiencing a sickle cell crisis, which is usually at least once a year, there are a few things that person can do to alleviate some of the symptoms, but a lot of treatment focuses on reducing the occurrences of crises. This includes drinking plenty of fluids, dressing up warm and taking Hydroxycarbomide, which makes the blood less saturated.

Though the genes responsible for haemoglobin production are faulty in those with thalassaemia and sickle cell disease, there are multiple types of haemoglobin, including myoglobin and foetal haemoglobin. The latter is used when one is an embryo, because it has a higher affinity for oxygen than adult haemoglobin, since oxygen needs to be transferred from a mother to her foetus and this cannot happen effectively if they have the same affinity for oxygen. To achieve this, foetal haemoglobin consists of an alpha-globin chain and a gamma-globin chain. For those with sickle cell disease and beta-thalassaemia, the point mutations are on the beta-haemoglobin gene, so foetal haemoglobin was produced effectively in these individuals as embryos. If there were faults with this type, surviving the gestation period would've been significantly harder and most wouldn't have been born. However, the body stops producing foetal haemoglobin 2-4 months after birth, and this is when those with sickle cell and thalassaemia start to exhibit symptoms.



This graph shows the dissociation curves of both foetal and maternal (normal) haemoglobin. The latter releases its oxygen more readily at higher partial pressure of oxygen than the former, meaning it allows for an efficient exchange of oxygen between a mother and her child.

By using CRISPR technology, scientists were able to delete the BCL11A gene that supresses the production of foetal haemoglobin, and allow for the production of this type, which goes on to replace all the faulty haemoglobin. Another technique for deleting the BCL11A gene involved shuttling in a specific length of RNA that alters the expression of the haemoglobin gene. Although BCL11A was not completely knocked down when this technique was used, the suppression was sufficient to reduce production of the mutant adult haemoglobin. This advancement won the team of scientists behind the breakthrough the Nobel prize for chemistry last year. Both the treatments involve taking stem cells from the bone marrow of an individual, modifying them, and then reinfusing them into the patients via a drip, so there's no need to worry about finding a donor or graft vs host disease. However, the treatment poses a lot of complications and side effects, because of the bone marrow extraction. Making this process safer might increase the frequency of this treatment in the future.



This diagram shows the effects of the BCL11A gene. Using a mechanism composed of a number of complicated steps, the gene in question is able to prevent the synthesis of the gamma-globin chain and activate the synthesis of the beta-globin gene, leading to the production of normal haemoglobin, which is detrimental to those with beta-thalassaemia and sickle cell disease.

The treatments were trialled on numerous people with thalassaemia and sickle cell disease, and it was shown to be effective at treating both conditions. Those with beta-thalassaemia didn't need blood transfusions after having the treatment, and those with sickle cell disease didn't have any reported pain crises, indicating the sickle cell erythrocytes were eliminated and the treatment worked. Any side effects the patients had were in relation to the bone marrow extraction. However, we are yet to trial the treatments on a larger demographic and see the long-term effects, so there's still a lot that needs to be worked before the treatment becomes a viable option.

While the mechanisms used to apply this treatment are complex, the idea is simple yet ingenious, and it's an example of how basic concepts can be turned into functional treatments for some of the most serious disorders. Sickle cell disease and thalassaemia have plagued individuals for millennia, and only now are we finding cures to these genetic diseases. Though there is still a long way to go until the treatment can be properly implemented into modern medicine, the large amounts of the hard work have been done and we can look forward to a permanent cure in the near future.

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HIV – An Irrepressible Nightmare

Muneeb Javed

Introduction:

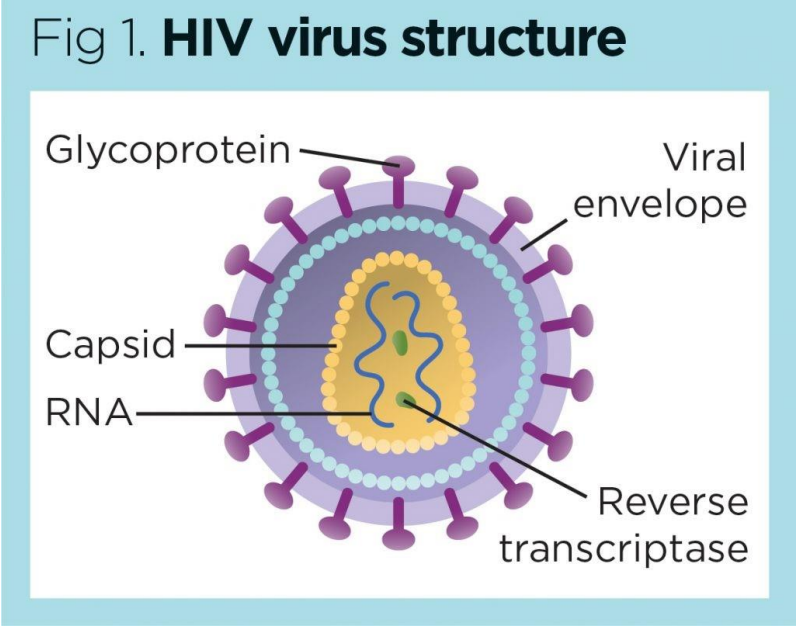
HIV, or Human Immunodeficiency Virus, is an infamous scourge upon modern medicine. It can commonly be seen in news headlines alongside any mention of how dangerous or difficult it is to cure it. There are many reasons for why HIV is so feared and underlying those reasons is the unique biology that has engineered HIV and enabled it to become such a potent pathogen. By the end of this article, you should be well informed at how this virus attacks the immune system and starts a series of events leading to AIDS and other symptoms in addition to how HIV infection is managed.

How do I contract HIV?

HIV can only be obtained if the bodily fluids of another person who is infected gets into your body which can include substances such as blood or semen but not saliva.

How does the structure of HIV relate to infection?

The structure of HIV is directly related to how infection occurs and what makes it so effective.

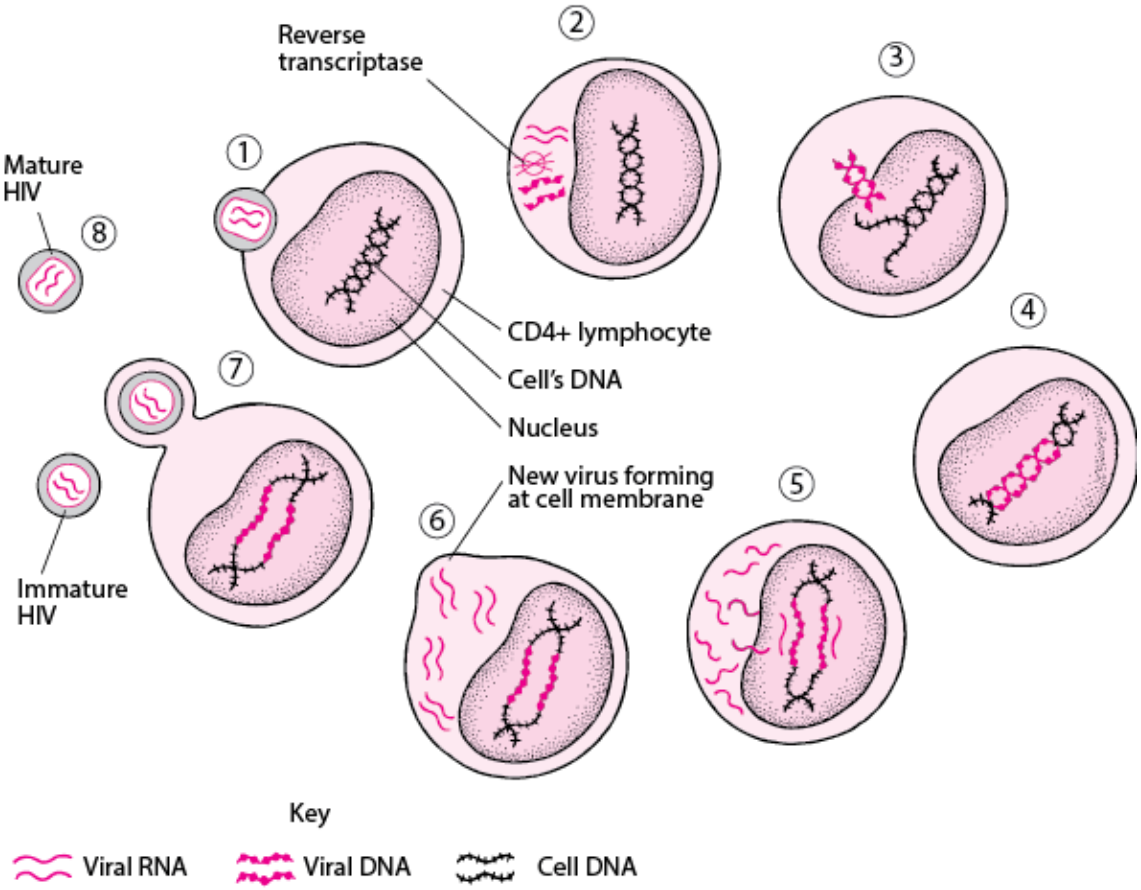


Firstly, the HIV virus has glycoproteins on its surface which allow the virus to be extremely specific as to which cells it attacks. This can be seen when the glycoproteins are used to bind to receptors on the surface of CD4 cells (white blood cells which are integral to the body's immune system). The reason why HIV only attacks the immune system is due to these glycoproteins and if it had a dysfunctional set of these, it would be rendered inert.

In addition, a HIV virus has a protein capsid coat which is designed to house the viral genome and to deliver it to an unfortunate host cell. It also has the function of interacting with the host cell, but this is a feature present in all viruses.

You may be wondering what makes HIV different to other viruses and that would mainly be due to its genome and enzymes. HIV's genetic material consists of 2 RNA strands which enter the cell upon the lipid envelope fusing with the host cell whereupon it releases its contents. However, before this RNA can be incorporated into the host cell DNA, the HIV enzyme known as reverse transcriptase converts the viral RNA into proviral DNA and proceeds to incorporate the viral DNA into the host cell's nucleus.

What happens once CD4 cells have become infected?



As soon as the first virus has incorporated its DNA into a CD4 cell nucleus, the virus will have begun its attack. Every single time that cell replicates, it inadvertently replicates the virus within it too. At this stage, the virus is said to be in a latent stage.

Whenever a trigger occurs, usually when a CD4 cell encounters the antigens of an infectious particle, the virus will suddenly activate and enter what is known as the lytic pathway where HIV cells will actively replicate within host cells. This occurs until the host cells undergo lysis and burst. The viruses replicate as the protein chains making up the virus are assembled at the cell wall and the virus proceeds to bud from it by pushing through the cell wall. In a further parasitic act, the virus takes lipids from the host cell to produce its own glycoproteins and resulting in a mature virus, which is now fully infectious and capable of harming more cells. This is where acute infection will begin to set in as CD4 cell numbers drastically fall as the infection of one's lymph nodes progresses. For approximately 2 weeks, symptoms such as a fever, rash and sometimes swollen glands will be present and the number of viruses in your system peaks at over 1 million copies per ml of blood during this period. However, after this the number of viruses lowers and the number of CD4 cells will gradually increase too until 6 months pass and these levels stabilise at the 'set point'. This is known as the asymptomatic phase.

Unfortunately, this leaves your immune system permanently crippled due to the low CD4 cell counts and will eventually progress to AIDS if left untreated. If infected with AIDS, your immune system is so weak that common illnesses known as 'opportunistic infections' can easily take advantage of HIV's effects on your body. This will eventually lead to death as your immune system struggles to protect you from pathogens without the CD4 cells which are so critical in the process.

Can HIV be treated or cured?

Unfortunately, it is currently impossible to completely cure HIV. This is due to the nature in which it is latent as it is impossible to detect which cells have HIV genetic material incorporated into its genome and the only other option would be to kill off all your CD4 cells, which would only result in death anyway.

On the other hand, many treatments have been developed for HIV in the form of antiretroviral drugs. As research and development on these drugs have continued, the side effects have become progressively less severe and more effective at the same time. These drugs work by inhibiting the viral enzymes that are essential for the HIV virus replication process and in turn stops HIV viruses from increasing in numbers so that your immune system begins to recover. Normally, multiple different medications are prescribed as HIV can rapidly adapt and become resistant to these drugs and taking multiple combinations works as the virus cannot adapt to be resistant to all of them at the same time. According to the NHS, antiretrovirals are so effective that the number of viral particles in your blood become undetectable on tests within 6 months of starting treatment.

Conclusion:

HIV may be terrifying, and justifiably so, but with the wonders of modern medicine, it is no longer the 'nightmare' that haunted communities in the past thanks to the development of antiretroviral drugs and further research into the functions of the virus. The risk of contracting it is almost none if practising safe sex and if you avoid sharing needles. Although incidents such as the NHS blood scandal occurred in the past, spreading the virus to unsuspecting patients, reforms have been passed to confirm that further tragedies will never affect humans again. Thus, humanity has begun to push back against this formerly irrepressible illness.

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Sport

How do muscle increasing steroids work?

Alex Darvill

Certain steroids have a lot of advantages for athletes and can aid muscle growth, strength, and resilience, however they also carry a large number of risks to your body.

Anabolic steroids

To begin with, 'Muscle increasing steroids' is a colloquial term for anabolic agents – anabolic steroids. The term 'anabolic' in biology refers to the process of chemical reactions that build larger molecules out of smaller molecules. Therefore, the way that anabolic steroids work is by increasing anabolism, meaning an increase in the process of building muscle.

Anabolic hormones

Hormones are defined as a 'regulatory substance produced in an organism and transported in tissue fluids such as blood plasma or sap to stimulate specific cells or tissues into action'. An anabolic hormone, however, is a growth hormone that stimulates muscle growth. The anabolic hormone specifically targeted by these anabolic steroids is testosterone, which is the primary sex hormone and anabolic steroid in males which serves to develop the males' reproductive tissues and promote secondary sexual characteristics, such as increasing bone and muscle mass and the growth of hair.

Consequently, anabolic steroids increase testosterone levels, thus leading to an increase in muscle mass. In more detail, an increase in testosterone levels leads to more muscle protein synthesis, causing more proteins to be made which increases muscle mass.

Overall, this increase in testosterone is also the way that people who take anabolic steroids get caught, because a simple blood test or urine test can reveal increased levels of testosterone, because the hormone is transported around in the blood.

Mechanism of *how* testosterone gets effected.

This depends on the type of steroid being used.

Firstly, 'androgenic' steroids work by binding to the androgen receptors. Androgens are hormones, much like testosterone, that work by interacting with receptors around the body. By binding with these receptors' steroids, such as 'Dianabol' (an anabolic steroid), they can trigger an increase in testosterone and testosterone-like effects. Androgenic steroids are said to be the most powerful of the various forms.

Another way that steroids work is by providing the building blocks for testosterone and other androgens. These are called 'precursors' and an example would be 'Sustanon', which is converted into testosterone in the body. Sustanon is one of the chemicals used if you receive 'testosterone' injections from your doctor and is one of the closest things to injecting 'pure' testosterone.

Side effects and dangers

Firstly, the use of anabolic steroids is illegal, unless for specific and prescribed medical conditions They are a class C drug meaning can only be sold with a prescription. As we already know, the main reason people take anabolic steroids is to significantly increase muscle mass and is most likely taken by bodybuilders and weightlifters to improve their performance. However, there are many side effects. To begin with, regular taking can cause:

- Infertility
- Baldness
- Reduced sperm count
- Severe acne
- Aggressive behaviour
- Mood swings
- Paranoia
- Restricted growth (in adolescents)

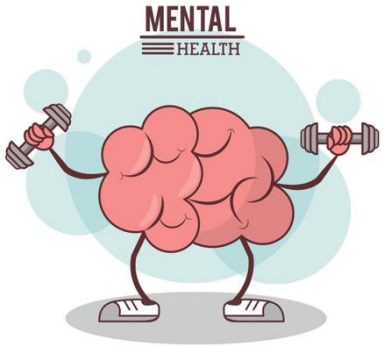
As well as these, anabolic steroids are addictive and therefore can cause depression and headaches and other psychological effects.

Lastly, the number of anabolic steroid users have increased from 1991-2003. This was mostly due to trend and the lack of education about the risks of taking them. The figures saw an increase of steroid users in teenagers, from 2.7%-6.1%. However, from 2003-2005 figures show that this decreased to 4.0% and is ever decreasing due to harsher laws and increased awareness of the dangers. However, figures still show that in the United States a total number of 1-3 million people still use anabolic steroids for non-medicinal purposes.

The Benefits of Exercise on Mental Health

Scott Avery

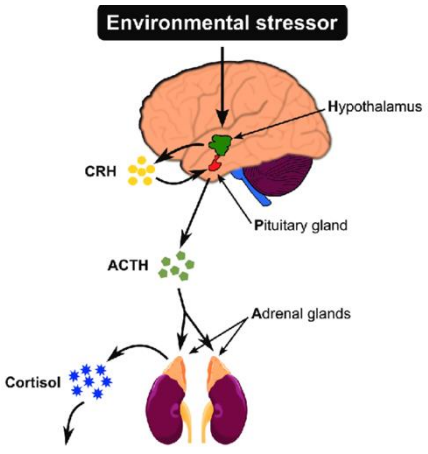
Exercise is considered a fundamental cause of a good mental state.



When we exercise, the body releases chemicals that boost your sense of well-being and suppress hormones that augment stress and anxiety. The chemicals released are endorphins, serotonin, and dopamine neurotransmitters, which are related to pain and depression emotions. Exercise improves mental health by reducing anxiety, depression, and negative mood and by improving self-esteem and cognitive function. Exercise has also been found to alleviate symptoms such as low self-esteem and social withdrawal. Physical fitness, achieved through regular exercise, induces positive psychological and physiological benefits, blunting stress reactivity, protecting against potentially adverse behavioural and metabolic consequences of stressful events and preventing many chronic diseases. Physical fitness prevents stress-related disease due to the effects on hormonal stress responsive systems, such as the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system. This contributes to reduced emotional, physiological and metabolic reactivity as well as increased positive mood and well-being.

Furthermore, regular exercise will minimise excessive inflammation. Chronic psychological stress, physical inactivity and abdominal adiposity have been associated with persistent, systemic, low-grade inflammation and exert adverse effects on mental and physical health. The anti-inflammatory effects of regular exercise can promote behavioural and metabolic resilience and protect against various chronic diseases associated with systemic inflammation. Moreover, exercise may benefit the brain by enhancing growth factor expression and neural plasticity. This will lead to improved mood and cognition.

The most important mechanisms relate to modulation of the body's main stress responsive systems.



Firstly, the HPA axis, the hypothalamic pituitary adrenal axis, is our central stress response system and is activated during stress. Hypothalamic neurons within the HPA axis secrete corticotropin-releasing hormone that causes the release of adrenocorticotrophic hormone (ACTH) from the pituitary. The ACTH causes the adrenal gland to secrete cortisol, which is a stress hormone.
Secondly, the autonomic nervous system, which is a component of the peripheral nervous system that regulates involuntary physiological processes including heart rate, blood pressure, respiration, digestion, and sexual arousal. It contains three anatomically distinct divisions: sympathetic, parasympathetic and enteric.

Lastly the immune system. When we're stressed, the immune system's ability to fight off antigens is reduced. That is why we are more susceptible to infections. The stress hormone corticosteroid can suppress the effectiveness of the immune system, such as lowering the number of lymphocytes.

The Impact of Ice Baths on Exercise Recovery

Charlie Stone

The impact of ice baths on exercise recovery:

With the rise of sports technology, particularly in athletics, athletes are performing better than ever, records in sports are being shattered year on year. In the Valencia half marathon in December 2020, not only did the world record get beaten by 29 seconds, with a time of 57:32, the top 4 male finishers all beat the previous world record held by Geoffrey Kamworor, who had only held the record for less than 15 months. Similarly, the fastest three female performances of all time were all run in 2020.

Partly, this comes from the progress in training over the last few decades. Training sessions are more intense and often more frequent than they used to be, this means that what the athletes do in between these sessions, is just as important as what they do in them. Ensuring they get good enough nutrition, sleep, rest, and water has been known to be key for athlete's recovery for a while. The latter being recently researched more, but this is not the only way athletes can recover. An athletes diet is also controlled, with exact meal portions provided for almost every meal to ensure a fast recovery occurs due to a perfect balanced diet.

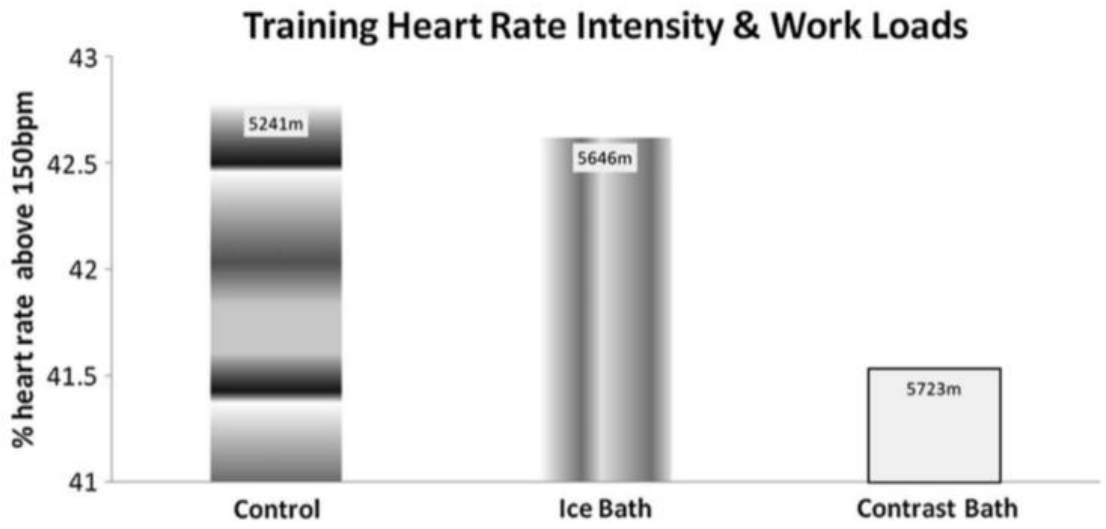
An ice bath usually consists of a 3:1 water to ice ratio. This helps achieve a temperature of around 10-15°C, which is the suggested temperature as the aim is to reduce blood flow temporarily, not prevent it completely. 8-15 minutes is normally recommended for the time spent in an ice bath. The overall idea is that upon leaving the ice bath, vaso-dilation will occur at the muscles promoting blood flow and flushing out waste products like lactic acid, produced in anaerobic, usually intense exercise.

Ice baths have been a treatment used throughout history for many different purposes. Spas in the 17th and 18th centuries used hot and cold baths and treated them as a luxury. Also in the 18th century, at the other end of the spectrum, ice plunges were used at mad-houses to attempt to treat the insane. [1] Moving forward to the 2002 European Championships, Paula Radcliffe, a British 10,000m runner stated she credited her victory to the ice baths that she frequently took before a race, to ensure that she was fully recovered. Radcliffe isn't the only well-known athlete to endorse the use of ice baths, 3-time grand slam winner Andy Murray and the most decorated olympian of all time, swimmer Michael Phelps also endorsed the use of Ice Baths. With athletes at the very top of their discipline being vocal advocates of the use of Ice Baths, it wasn't long before they became popular among intermediate and high-performance athletes, with some beginners backing its use.

Backed by all these high-level athletes, why don't all athletes from beginner to elite, use it constantly? With all the research done in the last 20 years, leading sports scientists still are not fully certain. Conflicting investigations and studies have produced results suggesting for, against and indifference for ice baths on recovery all dependant on the sports and training routine. A study done by Higgins et al [2] (2011) on 26 individual u20 rugby union players tested the effects of ice baths, contrasting baths and passive recovery. The ice baths were 5 minutes of submersion in 10–12°C water below the midline, contrasting baths were 7 cycles of one minute of cold (10–12°C) and one minute of warm (38–40°C). The relevant players took ice baths/contrasting baths after all training sessions (with at least two per week) and after each competitive match (at least one per week).

All players used a phosphate decrement test that depletes the ATP-PC system, the energy system used for rapid and high intensity exercise, as it synthesis ATP (the energy currency in humans) the fastest. It involved 7 all-out 7 second sprints with 21 second recovery. After this, a 300m test was done and results were recorded. This was completed in the week before the first game and after the 4th and final game and was the dependent variable to measure how well athletes recovered.

Overall, the results suggested no significant difference in timings of the 300m run between the 3 groups. Between pre and post-tests, the ice bath group decreased on average by 1.7s, the contrast group decreased on average by 2.3s and the passive group decreased on average by 1.8s. It was suggested that if anything, contrast baths help recovery the most, however, a 0.5s difference is unlikely to show a clear difference as it accounts for 0.7% difference between the three. Although being a minor difference, the contrast bath group, as well as having the lowest decline in performance, also had the lowest heart rate in training compared to the others, while having the furthest distance travelled in training. This can be seen in the graph below:



However, alongside these statical results, the players were also asked how they felt after these recovery methods, all players had a negative attitude towards the ice bath and 5/7 of them even went as far as to say they felt stiffer after the bath. While the contrast group reported that they felt more relaxed, had a positive attitude towards them and found it was easier to sleep and rest between activity. Overall, this particular study suggests that short, 5-minute ice baths had little to no difference in recovery and in its conclusion, questions its use in professional sport, while also suggesting that perhaps the ice baths were not long enough, as it was referenced in the study that Arnheim and Prentice (2012) stated that 15 minutes may be needed for vasoconstriction to occur. If ice baths don't work as well as athletes have claimed they do, why do people still use them?

Most people who have taken an ice bath longer than 5 minutes or longer would agree that they are hard, this is backed up by one of the methods of pain tolerance called the cold processor test. The test is simply timing how long someone's hand can remain submerged in ice, proving researchers are well aware of the effect's cold can have. Similar to training and workouts, people assume that if there is pain, or they are leaving their comfort zone, it means that it will benefit them in the long term, people can sometimes associate the pain with long term physical and mental strength.

Pain being associated with success is true to an extent, for example, muscle growth cannot occur without microtears, due to this, people may be under the impression that the best results often come from the hardest workouts, or in this case, recovery methods. "Pain is weakness leaving the body" is a Navy Seals quote. This may not always be the case, as sometimes, pain can be caused by stress, or in the case of ice baths, it comes from the body's shock response system as the body's temperature decreases so rapidly. This shock and pain is a warning, as the sympathetic nervous system kicks in, raising heart rate and releasing adrenaline to help deal with the pain created, this is not a sign of healing.

Another reason why ice baths may be popular is that the theoretical science behind ice baths indicates that they should have very positive effects on recovery after exercise. When the body experiences the cold effects of the ice bath, the muscles vasoconstrict (tighten) and redirect the blood to the core in order to maintain body heat. The opposite happens out of the ice bath promoting blood flow to the muscles again, providing more nutrients and oxygen. This may be why contrasting baths in the rugby study above came out superior. When recovering from an injury or experiencing an injury, although different from normal recovery, it is often suggested that ice is used, it is often described as an anti-inflammatory.

People associate ice with less injury, maybe even healing them, when in fact, a Bellefleur Physiotherapy [3] article suggests that ice itself isn't even an anti-inflammatory, it just numbs the area, easing the pain caused by delayed onset muscle soreness due to anaerobic exercise, only giving a temporary fix. This association with ice helping injury or soreness may also be a reason behind why so many people enjoy the overall experience of the ice bath. (almost no one actually enjoys the bath).

Athletes and researchers remain to be split down the middle. Regardless of universal application, if it works, whether it is a placebo and the athletes simply think it is doing good, or it truly does good, they should by all means continue with it. Problems occur when inexperienced athletes try without guidance from trainers and without access to the top facilities, which may be decreasing their level of performance or having side effects they are unaware of.

There are also more methods of recovery used which have been directly compared against ice baths. Hartono et al [4] (2017) compared ice baths, rollers and massages on how effectively they remove lactate. It was found that ice baths produced the lowest perception of muscle soreness, just head of massages and roller massage being the least effective way perceived by the participants, however the difference was very small and was marked as non-significant in the results.

If they work for individuals, ice baths tend to produce marginal gains rather than huge differences in performance, as it may allow an athlete to fit in an extra workout or training session over the course of the week, however these small gains described may not make much overall difference suggesting that it could be used more beneficial for elite athletes over casual ones, as at the top of their level, elite athletes may have no other area to improve performance whereas casual athletes may have plenty of other options to improve performance in their chosen discipline.

Overall, if people feel the positive effects of ice baths, or any recovery method used, they should use them to aid recovery. When trying new recovery methods, a physio visit would be recommended to ensure no damage is being done. All athletes are different and have work at a variety of activity levels within different sports, these all require different recovery and training methods. A simple sentence to summarise would be:

If individuals feel the benefits, continuing would seem to do little harm.

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The Effects of Caffeine on the Human Body

Alex Darvill

Firstly, what is caffeine? *Caffeine is a natural stimulant most commonly found in tea, coffee, and cacao plants. It works by stimulating the brain and central nervous system, helping you stay alert and prevent the onset of tiredness.*

This means that after the consumption of caffeine you will feel a burst in energy and will improve your reaction time to things. Caffeine works quickly, it begins to affect your body immediately and peaks after around 30-60 minutes, meaning it is very fast working. However, it has a half-life of around 3-5 hours, meaning only 50% of the caffeine will be removed from you blood after 3-5 hours.

However, Caffeine is a type of drug that promotes alertness. These drugs are called stimulants. In fact, caffeine is the most widely ingested psychoactive drug in the world. In North America, more than 80% of adults regularly consume caffeine. In Canada, coffee consumption increased from 96 litres per person annually, in 1990, to 106 litres in 2009. Moreover, too much consumption of caffeine makes you dependant on it. Therefore, without it you can experience withdrawal symptoms such as nausea, headaches, and fatigue.

The way caffeine works is that caffeine acts as an 'adenosine receptor antagonist'. Adenosine is a compound in your body that promotes sleepiness, the adenosine receptor (A1 receptor) is found in your brain and once adenosine locks with the A1 receptor, it promotes muscle relaxation and sleepiness. Adenosine itself is produced from physical work and intensive brain use. Thus, over the course of the day you will accumulate adenosine. Caffeine works by blocking the adenosine receptor to keep you from feeling sleepy, this provides you with a jolt of energy and will make you feel more awake, however this can also have a negative impact on your sleep pattern and even cause falling asleep hard which in the long term will make you feel worse as you will not be well rested. Furthermore, caffeine is generally ingested via coffee or energy drinks and these are not pure caffeine therefore it needs to be broken down into the caffeine. Caffeine is metabolized in the liver by enzymes.

Although caffeine has both positive and negative effects on the human body, there are more negative effects. Firstly, there are some positives, for example caffeine is a very effective alerting agent and has a positive effect on your reaction time and metal performance. This is due to caffeine not only blocking the A1 receptor but also the A2A receptor which can promote the release of dopamine and glutamate, which make you feel good after drinking a coffee. Caffeine has also shown to be very effective on athletic performance, benefiting endurance performance, high intensity exercise and power sports. There are, however, many negative effects of caffeine on your body.

Firstly, caffeine can hugely disrupt the pattern and quality of your sleep and a lack of such could cause various other health issues. Secondly, caffeine has a diuretic effect, therefore can cause diarrhoea, and other side effects such as sweating and increased heart rate. Thirdly, due to the addictive drug nature of caffeine it can cause severe withdrawal symptoms when you stop consuming caffeine, such as headaches, bad moods, low energy levels, and sleepiness.

The recommended, maximum amount of caffeine per day, for healthy adults, is 400 milligrams which is approximately four or five cups of coffee. This amount, although "healthy", will eventually reduce your tolerance to caffeine causing it to have less of an effect on you as you have built up tolerance to it.

Overall, in my opinion, the negative effects that caffeine can cause are far greater than the positive effects, and also the effects of caffeine and the implications it can have on your body are not as widely recognized due to the increase in caffeine consumption.

What Effect Does Physical Activity Have on Mental Health and Mood?

Ben Lloyd Taylor

What affect does physical activity have on mental health and mood?

There's lots of evidence to prove that taking part in physical activity can have a positive impact on mental wellbeing. Being physically active can improve mood, decrease the chance of depression and anxiety and lead to a better and more balanced lifestyle.

When you exercise, your body releases chemicals such as dopamine and endorphins in your brain that make you feel happy. Not only is your brain producing feel-good chemicals, but exercise also helps your brain get rid of chemicals that make you feel stressed and anxious.

Exercise increases your heart rate, which pumps more oxygen to the brain. It aids the release of hormones which provides a great environment for the growth of brain cells. Exercise also promotes brain plasticity by stimulating growth of new connections between cells in many important cortical areas of the brain. A study by the Harvard medical school showed that people who moved more/did more exercise had a significantly lower risk for major depressive disorder — the exercise was only measured using a tracking device, not when people self-reported how much exercise they performed making the study more reliable. Even by doing 15 minutes of high intensity exercise, such as running, or an hour of low intensity exercise, such as walking, can heavily reduce depression this is generally because of the feel-good hormones that are released and how it heavily increases your self-esteem.

Exercise can help by getting your sleep patterns back to normal and getting enough sleep can protect the brain from damage. Intense exercise reduces the time for you to fall asleep and decrease the amount of time you lie awake at night. Being active can drive the want for sleep. A study in 2006 on the effects of mental health by Ashish Sharma, Vishal Madaan and Frederick D. Petty stated that Aerobic exercises have been proved to reduce anxiety and depression. These improvements in mood are proposed to be caused by exercise-induced increase in blood circulation to the brain and by an influence on the hypothalamic-pituitary-adrenal axis which has a connection to the limbic system which controls motivation and mood. They also stated that exercise has been found to alleviate symptoms such as low self-esteem and social withdrawal.

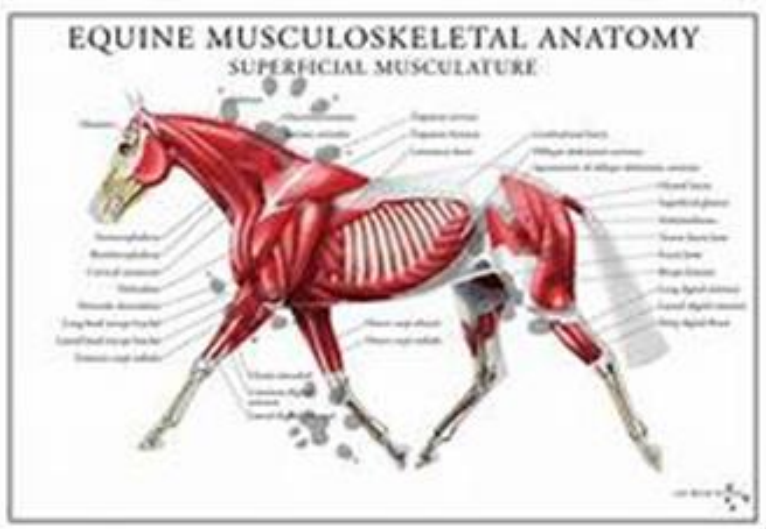
Health benefits from regular exercise that should be emphasised by every mental health professional to their patients include: improved sleep, better endurance, stress relief, improvement in mood, increased energy and weight reduction.

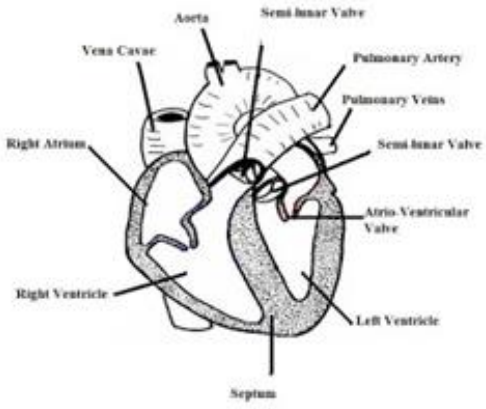
Animals:

The Circulatory System of a Horse

William Evans

The Circulatory System of a Horse





Similar to mammals, horses have a four chambered heart: left and right atrium, as well as the left and right ventricles. Similar to all mammals, horses have valves within the heart chambers which open and close as the heart muscle relaxes and contracts to ensure blood flows in the correct direction. The two pumping chambers are the left and right ventricles, and the two receiving chambers are the left and right atria. The left ventricle is larger than the right ventricle. Though in contrast to most mammals the average horse heart weighs around 1% of its bodyweight, roughly 3.6-4.5kg; in humans on average the heart weighs 0.5% of bodyweight, roughly 0.25-0.3kg. Horses have a proportionally larger heart as their heart's maximal heart rate can be as high as 240 bpm, in comparison a human's maximal heart rate is roughly 220-their age (so for me 220 – 17 = 203). Interestingly a horse's resting heart rate would be around 20-30 bpm, which is far lower than that of a human: 60-100 bpm. The fact that a horse is able to have a maximal heart rate around 10 times as large as their resting heart rate is a contributing factor to their athletic superiority. Although some studies have found that in thoroughbreds that the proportion of skeletal muscle exceeds 50% of body weight, and so the energetic capacity of the muscular system far exceeds the capacity of the cardiovascular system to deliver oxygen.

Interesting Fact:

A horse of average size has approximately 28 litres of blood circulating through its system every 40 seconds! Whereas in humans there only roughly 5 litres of blood in the body

One important feature of the horse heart is its heart wall which consists of three layers: the epicardium (external layer), the myocardium (middle layer) and the endocardium (inner layer). The epicardium is the thin, transparent outer layer of the wall and is composed of delicate connective tissue. The myocardium, comprised of cardiac muscle tissue, makes up the majority of the cardiac wall and is responsible for its pumping action. The myocardium is very thick, in order to cope with the load it is put under. The endocardium is a thin layer of endothelium overlying a thin layer of connective tissue. It provides a smooth lining for the chambers of the heart and covers the valves. Similarly, the thickness of the four chambers varies in accordance with their function.

The atria are thin walled because they deliver blood into the adjacent ventricles and the ventricles are equipped with thick muscular walls because they pump blood over greater distances. Even though the right and left ventricles act as two separate pumps that simultaneously eject equal volumes of blood, the right side has a much smaller workload. This is because the right ventricle only pumps blood into the lungs, which are close by and present little resistance to blood flow. On the other hand, the left ventricle pumps blood to the rest of the body, where the resistance to blood flow is considerably higher. Consequently, the left ventricle works harder than the right ventricle to maintain the same blood flow rate. This difference in workload affects the anatomy of the ventricular walls; the muscular wall of the left ventricle being significantly thicker than that of the right.

Perhaps the biggest difference in human and horse anatomy would be that the horse has a shock absorber on its hoof which plays an important role in circulation called a “Frog.” The frog pumps blood up the horse's leg each time the frog contacts the ground. The blood flows down the horse's leg into the digital cushion, a fibrous part of the inner hoof located just above the frog which contains a network of blood vessels. The horse's weight then compresses the frog on the ground, squeezing the blood out of the digital cushion, and pushing it back up the horse's legs. This is one of the reasons a horse must have their hooves regularly cleaned.

Evidently a horse's metabolic requirements are far higher than that of human, simply due to the glaring size difference. The metabolic requirements of a horse also greatly vary from horse to horse depending on its activity rate, for example between a pony and a thoroughbred racehorse.

Table 1. Daily energy and protein requirements for a 1,100-pound horse

	Intake (% BW) lbs	Digestible energy Mcal	Crude protein g
Adult at average maintenance	22 (2%)	16.65	630
Adult at high maintenance	22 (2%)	18.15	720
Pregnant 8 months	27.5 (2.5%)	18.49	759
Adult moderate working	22 (2%)	23.31	768
Nutrients supplied by high-quality alfalfa or grass hay			
Alfalfa hay	22	26.4	2,118
Grass hay	22	20.0	1,076
From NRC, 2007			

Interestingly a horse has a proportionally very small stomach, and the digestion process takes roughly 48 hours and depends not only on the right amounts of food at correct times, but also on an adequate supply of water and plenty of exercise. If these requirements are not met than the horse's sensitive digestive system may become upset raising the risk of indigestion, impaction, formation of gas or even sudden colic attack.

One way a horse gets around having a proportionately small stomach, particularly important for racehorses, is the storage of glycogen (a vital fuel source) in muscle (90%) and to a lesser degree in the liver (10%). The horse eventually breaks down this glycogen to lactic acid through glycolysis and can be triggered by an increases in adrenaline which would obviously happen to a horse during a race.

An individual animal's metabolic rate is based on many factors and ultimately determines how much sustaining dietary energy it requires. Body size is a major determinant of metabolic rate. For instance, a smaller animal has a higher surface area to volume ratio and so has more area for heat loss. Therefore, a mouse generally will have a higher metabolic rate per unit weight than an elephant. But within the same species, a heavier animal typically will have greater energy requirements than a smaller animal. There also appears to be breed-dependent differences, as some breeds are easier to look after, due to a less sensitive digestive system than others.

For example, many gaited breeds and pony breeds are considered easier to look after and have a slower metabolic rate, while other breeds such as Arabians and Thoroughbreds are harder to look after as their digestive systems are more sensitive. Another determinant of metabolic rate is ambient temperature. Temperatures within a certain range do not require metabolic rate to change simply to maintain body temperature. Interestingly this range changes throughout the year (hence why 130c feels cold in summer yet warm in winter), it is also different for different horses and depends on factors such as hair coat thickness. In summary, as ambient temperature decreases a horse's metabolic rate will increase to maintain body temperature, thus increasing his dietary energy needs.

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The Effects of Increased Human Pressures on the Environment and sustainability in relation to Mountain Gorillas

Nabeel Johar

Introduction:

Mountain Gorillas are one of two subspecies of the Eastern Gorilla. Around 50% live in the Virunga Mountains, bordering Uganda, Rwanda and the Democratic Republic of Congo. Specifically, they can be seen near multiple extinct volcanoes. The rest of the Mountain Gorillas are in the Bwindi Impenetrable National Park in Uganda. These Mountain Gorillas are found in high-altitude forests, at elevations of 8,000 to 13,000 feet. They have many adaptations to the environment such as very thick fur, which allows them to withstand extreme cold temperatures. They are also one of human's closest relatives. However, humans are also their biggest threat as a result of political instability, human invasion and forest degradation. Despite these human pressures, the population of Mountain Gorillas have increased. In the essay below I will discuss the effects of human pressures on the environment and sustainability in relation to the Mountain Gorillas.

Increasing human pressures:

Logging, deforestation and climate change:

The first pressure that impacts gorillas is logging. Logging is the activity or business of cutting down trees and preparing the timber or pulp for sale. Logging is one of the major forms of deforestation around the world. Forest ecosystems are an important in maintaining biodiversity as they contain the greatest number of different species compared to any other ecosystem and, in total, they cover 31% of land on Earth. 7 countries can be held accountable for 60% of the total deforestation on Earth, which includes the Democratic Republic of Congo in Africa, home to around 50% of the Mountain Gorillas. Logging can have detrimental effects on wildlife and the environment. For example, a major impact is the reduction of the overall biodiversity. Since many species have habitats within forests, when logging occurs in these areas, species will have lost their habitats and major food sources. Furthermore, if these species lose their shelter and primary food sources, it can lead to extinction. In addition, logging can also add to the growing carbon footprint on Earth. This is because trees store carbon, so when the activity of harvesting forests occurs, the carbon is released into the atmosphere in the form of carbon dioxide. This is a greenhouse gas as it traps heat, contributing to global warming. Moreover, when trees are cut down in numbers, it can lead to deforestation. Again, there will not be many trees to release oxygen and intake the greenhouse gases. Therefore, global warming will greatly increase.

The resulting climate change means that, as the Mountain Gorilla is a mountainous animal and is highly restricted by temperature in their habitat, they have nowhere else to go that has an equally high altitude and a cool atmosphere. Therefore, they cannot escape from the warming conditions that are lower down the mountain, which will result in the extinction of the *Gorilla beringei*. Furthermore, the Mountain Gorilla population live within the protected areas, which surround human civilisation. As a result, they are not able to migrate to any other area.

There are many ways to reduce the amount of logging done on Earth, and this can be used to conserve many endangered species, such as Mountain Gorillas. For example, the main purpose of logging is to prepare pulp and timber. Therefore, if the governments of countries invest their spending into researching better ways of recycling paper and they incorporate the use of plantation forests, less resources will be needed from these natural forests. Therefore, the amount of logging used will significantly decrease. This will mean that less habitats will be destroyed, due to less forests being cut down. Consequently, species such as the Mountain Gorillas can live for longer as they will have a larger food source.

Human migration:

Another human pressure is migration. Over time, humans have moved towards and into the Mountain Gorilla habitat. They have cleared a devastating amount of land for personal use, such as agriculture and

livestock. A major example was in 2004, where illegal settlers cleared 3,700 acres of gorilla forest in the Virunga National Park. As more and more humans have been settling in areas where the Mountain Gorilla live, it is more common for them to come into contact. Consequently, Mountain Gorillas are more likely to contract diseases that humans normally get. For example, the Mountain Gorillas may be impacted by influenza more severely than humans, in the form of death. On the other hand, researchers have undergone studies and established that the Mountain Gorillas that are visited regularly by tourists and researchers have survived better than the gorillas that have not been visited at all. This could be because the gorillas benefit from the increased protection from those who monitor the gorilla habitats regularly. The mountain gorillas are able to survive for longer as they can receive the veterinary help they need from humans if they are sick or injured.

Furthermore, as most Mountain Gorillas are located near Rwanda, which is the second most populated country in Africa, their living space has been massively reduced due to the sheer amount of people in that location. Therefore, the Mountain Gorillas are isolated to only the high-altitude areas. In addition, the natural resources used by humans are used unsustainably, causing more strain on the gorilla's environment.

Charcoal making:

Additionally, another human pressure is through charcoal making. This occurs after a tree is cut down, the large branches of those trees are made into a dome, which is then covered in mud and ignited. Through using mud, the wood burns more vigorously and, instead, charcoal is formed. The charcoal can then be used as a fuel source for heating and cooking. Via this illegal process, many Mountain Gorilla habitats have been destroyed.

Poaching:

Although it is illegal in almost all Congo Basin countries, Mountain Gorilla poaching is still a growing problem, due to the lack of enforcement of national and international laws. The commercial trade for bushmeat is one of the biggest human pressures and one of the biggest threats to gorillas. Although gorillas only accounts for a small number of species killed for bushmeat trading, they are still very easy targets and, in some cases, are preferred over other prey as they are much bigger, therefore their meat weighs more, making it more expensive and profitable.

Rwanda civil war:

Lastly, the Rwanda civil war, and many years of civil unrest in the Democratic Republic of Congo, have sent many refugees into areas such as the Virunga Mountains, where at least 50% of the Mountain Gorillas live. Therefore, as more refugees move into this region, the habitats of the Mountain Gorillas get destroyed. Additionally, the population is in grave danger of being poached for bushmeat. As well as this, many parts of the Virunga Mountain Park that are inhabited by gorillas have been taken over by rebels, resulting in surveys and conservation efforts being hindered due to how dangerous the area has become. The World Wildlife Fund have stated that since 1996, 140 Virunga rangers have been killed in the line of duty.

Why Mountain Gorillas have such importance:

Like any other animal, the Mountain Gorillas play a vital role in the environment we live in. Without them, the natural balance in the food chain would be disrupted. This can be detrimental for the other wildlife in those areas, and also the people who depend on that environment for food and water.

Mountain Gorillas are also essential for the local population, as they create a form of income through ecotourism. The Oxford definition of ecotourism is tourism that is directed towards exotic, often threatened, natural environments, intended to support conservation efforts and observe wildlife.

Environmental monitoring and how to protect gorillas:

There are many ways to measure the number of Mountain Gorillas within an area. One method is to count the number of individuals seen. However, this is not always possible, as they may not all be present within the time of the census being carried out. Therefore, instead of counting the number of individuals, the evidence was monitored. For example, every 5 years, the WWF work through the International Gorilla Conservation Programme to census remaining Mountain Gorilla populations. The WWF website reveals that:

"*To carry out the census, teams of people hike through the forest no more than 500m apart, combing the area for gorilla signs and nests (gorillas make nests to sleep in every night from leaves and branches, either on the ground or in the trees). In the most recent censuses, these 'sweeps' have been performed twice to help ensure accuracy, collecting gorilla faecal samples from every nest they encounter, which are sent off to a lab for DNA testing to make sure each individual gorilla is counted only once.*"

The WWF website concludes:

"*In the Virunga volcanoes , the population rose from an estimated 380 in 2003 to an estimated 480 in 2010 – although this was partly due to a change in census methodology. And, we're hoping the results of the latest survey, to be released in 2017, will continue this positive trend. The population in Bwindi Impenetrable National Park increased from an estimated 302 in 2006 to an estimated 400 in 2011. Again, this is partly due to a change in methods used.*"

Another study divided their research into 3 time periods. The first of 6 complete censuses of the Virunga mountain gorillas was done in 1971, and it was concluded that the population of Mountain Gorillas decreased from 275 gorillas to 254 gorillas. This is because of the dangerous number of poachers in the area. Although they were not hunting for specifically Mountain Gorillas, they may have been caught in traps set up for other animals. Contrary to this, by 1989, the number of gorillas had increased to 320. This is because of increased local conservation education, law enforcement and veterinary programs. During the 1990s, the number of gorillas may have dropped due to the Rwanda civil war and civil unrest, however, by 2003 the number of gorillas had increased to 380. This is due to the high level of monitoring. Approximately 70% of this population is used for ecotourism or research. In 2008, approximately 20,000 tourists visited these groups, which led to a generated amount of $8 million.

How to protect gorillas:

International non-government organisations, such as the Worldwide Fund for nature (WWF), help protect these Mountain Gorillas. For example, they also support efforts to reduce the human-wildlife conflict. They have helped residents to create a buffer zone between the areas where the Mountain Gorillas are situated and human civilisation. This is done through instituting tea plantations. This is because gorillas are not interested in the taste of tea, therefore, they are less likely to move towards the towns. Citizens can also help protect these endangered Mountain Gorillas by donating to non-profit organisations, as they work their hardest to conserve and preserve these Mountain Gorillas.

Additionally, people can make life choices which may reduce the amount deforestation that occurs around the world. For example, we can eat food, sourced sustainably, consume less and choose products that are made from certified sustainable softwood. Furthermore, we can support companies that adopt a forest-friendly policy. Also, educating others about the impacts of deforestation and logging on other species such as the Mountain Gorilla can be extremely impactful as this may influence others to become more environmentally conscious. Many have already adopted a plant-based diet as this reduces deforestation from animal agriculture practices.

Lastly, by travelling to the Virunga Mountains, in Uganda, Rwanda and the Democratic Republic of Congo, you provide incentive to protect the Mountain Gorillas. For example, governmental bodies have kept the volcano habitats off bounds to human agriculture, as this hotspot provides a large amount of revenue for the government through tourism. Therefore, if tourism suddenly stops, the government will have no incentive to preserve the Mountain Gorilla habitats, therefore they will be in danger of extinction.

Conclusion:

Overall, the main human pressures have been deforestation, poaching and logging, also political pressures such as the Rwanda Civil War from 1990 to 1994. This has been damaging for the *Gorilla beringei* because it has resulted in their endangerment. However, many solutions have been found and utilised to increase their safety and protection in the current environment. In addition, many scientists will have different views as they may have collected or even researched different data, therefore, their conclusions will be different to others. For example, the WWF collect a census every 5 years, whereas other organisations may collect a census every 2 years. There have also been issues surrounding the collection of data. For example, simply counting the number of Mountain Gorillas is insufficient and unreliable as they can vary with the time of day, or they may have collected data in the wrong season. A way researchers have overcome this is by counting their nests and then looking at faeces. The faeces can then be tested in a laboratory to make sure each individual gorilla is only counted for once. Lastly, no firm conclusion can be made whether the human pressures have been entirely positive or negative because most of the data collected have fluctuating figures, therefore various scientists will interpret the data differently to others.

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Animal Testing: Cruel or Beneficial?

Adi Sachdeva

Animal testing is a major and just one of the many components that go into research procedures, such as testing the effectiveness of new medicinal products, learning about the fundamental knowledge of an organism and genetic modification, just to name a few. This form of testing has advanced our knowledge in so many different areas. Without it, the progress we have made in disease prevention and the creation of all medications would simply just not be possible. But, have you thought about the cruelty and inhumane nature of stealing the souls of hundreds of millions of animals each year. The ruthlessness behind taking each individual spirit from its body. Is it worth it to subject these innocent little animals to potentially damaging chemicals and medicines with absolutely no guarantee that they will survive and live to see another day.

Each year, 115 million animals across the world suffer and die in cruel tests carried out for a wide range of research. Sadly, only 3% of animals survive testing in lab experiments which is absolutely obscene even to think about. The cruelty extends to chemical, drug, food and cosmetic tests as well as medicinal training exercises and curiosity driven medical experiments at universities, which lead to testing on millions of innocent lives, knowing that they have a 97% likelihood of never breathing again. This completely unethical practise wouldn't be allowed for humans, so why is it allowed for animals. Do they not eat, breathe and have emotions in the same way as humans?

Each life that we subject to this inhumane and harsh treatment has a family, has a role in the ecosystem, has a goal to complete in their life just like humans so what gives us the right to take this away? Examples of these abhorrent tests include forcing mice and rats to inhale toxic fumes, force-feeding dogs pesticides and dripping corrosive chemicals into the sensitive eyes of rabbits. The worst part is even for the 3% that survive these brutal attacks, it's not guaranteed that the chemical will be safe to use in humans. Is this worth it? Is it worth putting millions of living, feeling beings through tests where they are almost certainly going to die for medications that may not be able to be used for our benefit?

On the other hand, animal testing has brought about many medical benefits such as the development of penicillin, treatment of tuberculosis, asthma, meningitis, breast cancer, Parkinson's disease and the ability for kidney transplant just to name a few. Penicillin has revolutionised the ability to treat bacterial infections which were a major cause of death. Before the discovery of penicillin, it was thought that death was inevitable after being affected by a bacterial disease. There was simply no cure. However, in the 1940s, eight mice were infected with a deadly dose of bacteria and four of them were injected with penicillin. The ones injected survived whilst the others died. Without these early animal studies on toxicity and effectiveness, penicillin would not have developed further, preventing millions of lives being saved, both human and animal.

Another illness that animal testing has helped overcome is breast cancer, 1 in 11 women in the UK are affected with around 40,000 affected each year. Animal studies show that breast cancer is caused by hormone changes which lead to the development of tamoxifen, which blocks the growth of the hormone causing breast cancers. This is now the second most survivable female cancer, with 77% five-year survival rate. Following the increased awareness of tamoxifen there has also been a 30% fall in death rates. Without animal work, it may not have been possible to show that the cell culture results were relevant and reliable. The research on animals is critical for biomedicine as mice share more than 90% of DNA with us. Animals are susceptible to the same problems as humans and as they have a shorter lifespan, they are more easily studied across several generations. There are also laws in place that require nonhuman animal research to show the safety of new treatments which allows us humans to benefit from this research and testing but also can help animals live longer, happier and healthier lives. To add to this, 95% of all animals necessary for biomedical research in the United States are rodents and larger animals are far less frequently used.

Overall, the benefits for animal research testing, such as the development of many new medications saving millions of animal and human lives, vastly outweighs the disadvantages. It is detrimental in protecting and saving the lives of billions and when speaking ethically, the lives of humans are slightly more valuable than rodents such as mice and rats.