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LifeSci Lens

University of Bristol's life sciences magazine

Genetics in Human Health

Drugs in Development

Science in Society

Opinions in Psychology

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Welcome to the first issue of the University of Bristol's new life sciences magazine, written and run by students to celebrate stories, developments and opinions across the diverse and multifaceted field. We believe that the dissemination of free and accessible scientific knowledge is essential to cultivating scientific literacy, and invite readers of all backgrounds to engage with our publication. Our aim is to build a collaborative community which encourages students across different disciplines to share their interests and explore topics outside the scope of their courses. We hope that our writers and editorial team will gain valuable skills and experience from their contributions, and that our readers may be inspired by what their peers have to say.

We would like to say a big thank you to all our writers for their creative and engaging articles, as well as to our teams of editors, proofreaders and designers for their input and diligence, without which this project would not have been possible. While we are still growing as a group, we will continue to work hard to build a successful and enduring publication.

This issue is comprised of four sections split thematically into two halves, beginning with articles that take a deep, technical look at specific aspects of human health and disease and concluding with several broader opinion pieces.

Our first section, Genetics in Human Health, contains articles on several possible features of the human genome and the effects they can have on health and development. The articles look at emerging theories on the role of non-coding DNA, and review the pathology and possible treatments of the genetic disorders sickle cell anaemia and Down syndrome. The following section, Drugs in Development, explores the innovation and complications involved in pharmacological research and development more deeply, delving into the promising but controversial topic of biased agonism, as well as Alzheimer's treatments, old and new.

The Science in Society section then goes on to examine the interplay between science and the modern world, with articles drawing parallels between observed biological phenomena and societal structures, and reporting on the consequences of large pharmaceutical companies prioritising profit over public health, using a recent US court case. The final section has a range of opinion articles from students within the school of psychological sciences, calling for decolonisation in academia, advocating for the potential benefits of incorporating classical philosophy into cognitive behavioural therapy, and sharing the motivations for pursuing a career in neuropsychology.

Ana Miletić and Alex Radlett*, LifeSci Lens Cofounders*

GENETICS IN HUMAN HEALTH

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Cutting Away Anaemia: Using CRISPR to Treat Sickle Cell Disease and β-Thalassaemia

By Zihan Deng

Twelve years ago, the discovery that CRISPR-Cas9, a bacterial defence system that cleaves invasive nucleotide sequences, could be modified to introduce specific breaks in target DNA rocked the scientific world[1]. Today, the technology takes another step forward as it gains first approval as a treatment for two blood-related disorders.

Transfusion-dependent β-thalassaemia (TDT) and sickle cell anaemia (SCD) are both blood-related monogenic hereditary diseases. TDT is caused by a mutation in the human β-globin gene (HBB) that reduces or silences β-haemoglobin production, leading to precipitation of excess α subunits and death of red blood cells (RBC)[2]. SCD occurs when a point mutation (E6V) in the HBB gene gives rise to sickle haemoglobin (HbS) which can aggregate into insoluble polymers that distort the cell, causing chronic pain and triggering vaso-occlusive episodes[2]. Though many treatments have been trialed, there is no complete cure for either. Blood transfusion is the standard method, but to avoid iron overload, it is often coupled with chelation, which can introduce long-term complications such as hepatic and cardiac dysfunction. Though bone marrow transplant has the potential to be fully curative, matching donors are often difficult to find[3]. Therefore CRISPR, with its high specificity and ease of use, holds special promise as a targeted form of treatment.

Foetal haemoglobin (HbF) is a tetramer consisting of two α-globins and two γ-globins (α2γ2). It is the most abundant haemoglobin during gestation, but its production reduces with age, until HbA (α2β2) takes over as the most common form of adult haemoglobin[4]. The hypothesis that SCD and TDT could be cured through artificial reinitiating of HbF production was proposed decades ago, when it was first observed that elevated HbF levels in adults ameliorated SCD symptoms.

However, the main switch controlling HbF synthesis was not discovered until 2008, when Orkins *et al.* revealed a stage-sensitive transcription factor, BCL11A, to be its repressor[5]. Building on these discoveries, the newly approved CRISPR drug, Casgevy, introduces a double-strand silencing knockout in the erythroid-specific enhancer region of the BCL11A gene (*Figure 1*).

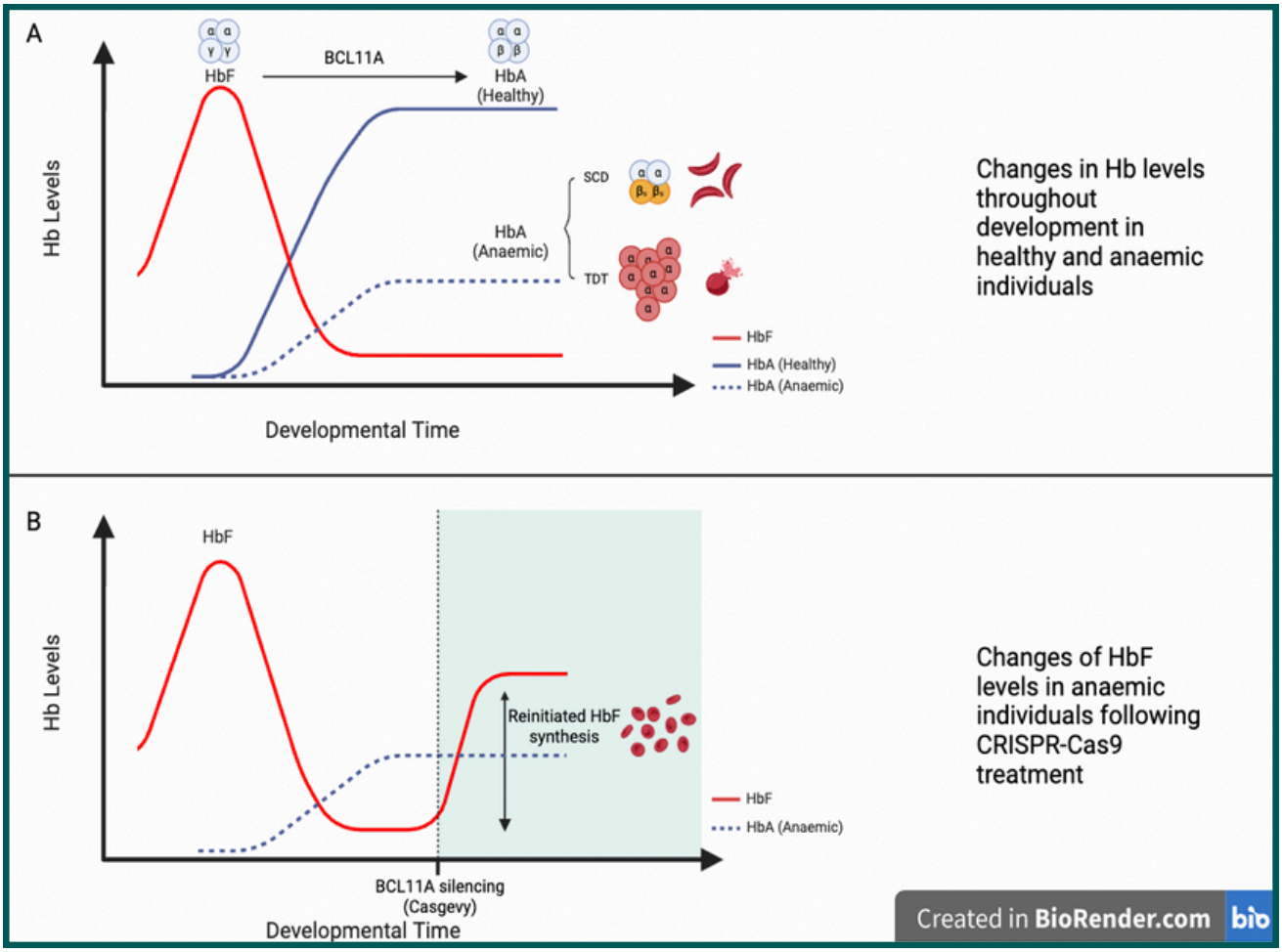

Figure 1. Rescue of erythrocyte synthesis through reinitiation of γ subunit expression. (A) Comparison of HbA levels through time between healthy individuals and SCD/TDT patients without treatment. (B) Increase in HbF levels and rescued erythropoiesis following Casgevy treatment.

To test the efficacy of Casgevy, Frangoul *et al.* performed a study on 2 patients, one with SCD (patient 1) and one with TDT (patient 2). Hematopoietic stem and progenitor cells (HSPC) were harvested from patients' bone marrow, treated with CRISPR-Cas9, then intravenously re-infused. At 21 months after the treatment, neither patient required any more blood transfusions, and patient 1 experienced no more vaso-occlusive episodes. No off-target editing had occurred, and pancellular distribution of BCL11A-silenced RBCs had been observed. These clinical evidence demonstrates the efficiency and precision of Casgevy.

Despite the positive responses from patients, there are still questions that need to be answered. Firstly, the treatment was not without adverse events. Out of the 146 events recorded, five had been classified as serious. Though all had resolved with time and were expected to be connected to the preparations for marrow transplant rather than to the CRISPR treatment[2], a search for gentler methods, or perhaps improvements to the drug that would allow easier delivery, is required. Second, the small sample size makes it difficult to predict the effects of the treatment on the generalized scale, and though 19 more have joined the study, it is yet too early for results. Besides, the recentness of the study means that any potential long-term effects are yet to be seen. Third, though the study has proven CRISPR to be a possible curative strategy for SCD and TDT, the high expenses of the treatment (estimated to be around US $2 million per patient[6]) makes it difficult for the general public to access.

Still, successful treatment of SCD and TDT through CRISPR-Cas9 directed silencing of BCL11A is a landmark achievement, and the first approval of a CRISPR-based treatment could encourage other countries to follow suit, as well as promoting CRISPR's application for other diseases, such as or in other fields, including regenerative medicine[7] or even farming[8]. The search for improved drug delivery methods is also underway, and recently, another CRISPR-Cas9 drug aimed at *in vivo* delivery has entered phase one trial, with positive results, providing hope for easier, less painful treatment[9]. Though still a long way from becoming a standardized treatment, CRISPR's future seems to shine bright.

References

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The Role of 'Junk DNA' in Brain Development

By Saniyah Khan

What is 'junk DNA'?

The Human Genome project, which was completed in 2003, led to the discovery that 98% of our DNA is non-coding, known as introns, and only 1.2% encodes for proteins[1]. Our non-coding DNA can still be transcribed into RNA; however, these cannot be translated into proteins. For this reason, many scientists believed that non-coding DNA was useless. The term 'junk DNA' was officially given to these non-coding regions in 1972[2].

Over half of the junk DNA is composed of motile DNA sequences[3] which can move to different positions in the genome known as transposable elements (TE) or transposons[3]. By shifting exon positions in the genome, transposons can alter gene expression, leading to the development of many organs within the body, primarily the brain; however, sometimes this can result in harmful mutations leading to the development and progression of disease.

Transposons can also influence gene expression by producing non-coding RNA such as microRNA and long non-coding RNA (lncRNA), often pronounced as 'link RNA'[3]. These can bind to targets such as coding RNA to either activate or inhibit translation, thus leading to altered gene expression. Additionally, lncRNA can cause other proteins to bind to chromosomes - hence altering gene expression, without changing the DNA sequence, i.e. epigenetically[4].

The Role of Transposons in Brain Development

Researchers (Doctor Christopher Treiber and Professor Scott Waddell Treiber) in the Centre for Neural Circuits and Behaviour in Oxford used the brain of fruit flies to understand transposon activity[4]. The findings from this study were that transposon activity in the brain is not uniform. This is because the level of expression of genes varies leading to differences in cell phenotypes. Insertion of transposons in a highly expressed gene results in high transposon activity. This is displayed as patterns of activity specific

to the cell type. Further analysis by Treiber and Waddell showed that neural genes adjacent to transposons were also expressed[4] highlighting the role of 'junk DNA' in gene expression. Furthermore, transposons play a key role in regulating the differentiation of neuronal stem cells either directly or by the production of microRNA. As seen in figure 1, neuronal stem cells terminally differentiate into neurons, oligodendrocytes, or astrocytes through transposon activity[5].

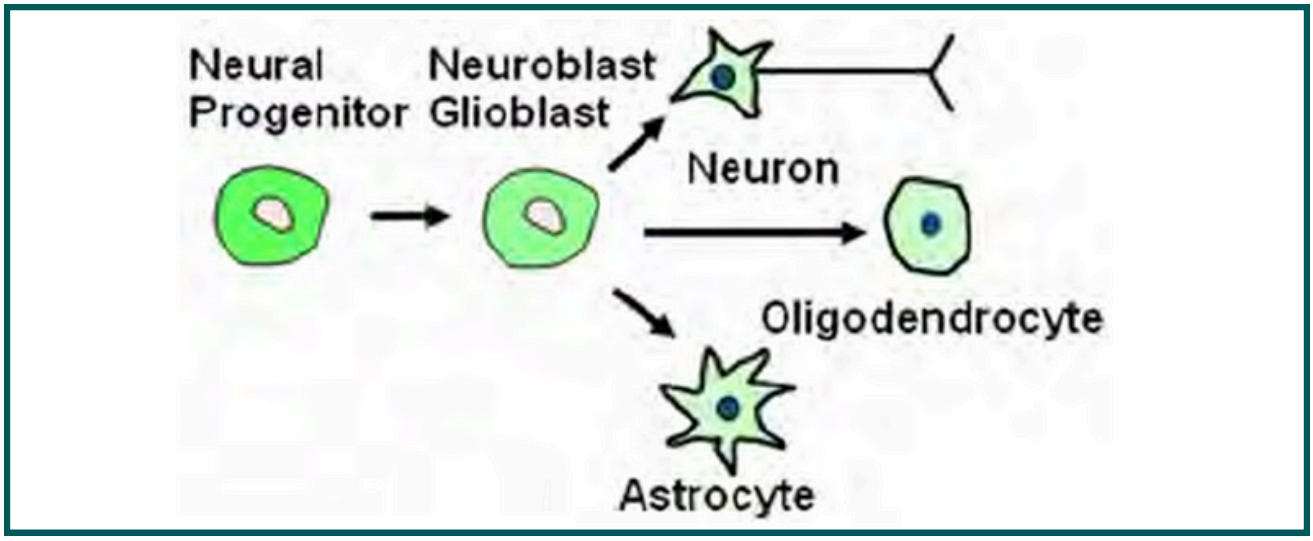

Figure 1. Diagram showing the stages of differentiation in neuronal stem cells[5].

Transposons can act as transcription factor binding sites[6], enabling the upregulation or downregulation of genes which drives differentiation. For example, Neurod2 (a transcription factor) induces neuronal differentiation in neuronal progenitor cells into neuroblasts[6]. A subfamily of transposons known as MER130 are associated with Neurod2[6], implying that they play a role in neuronal differentiation.

MicroRNA produced by transposons are also involved in differentiation. These form a hairpin which can bind to the mRNA, coded for by the 3' UTR (untranslated) region of DNA, leading to the production of different proteins *(Figure 2)*[7]. These proteins alter gene expression, enabling the process of differentiation, whilst giving rise to different cell phenotypes.

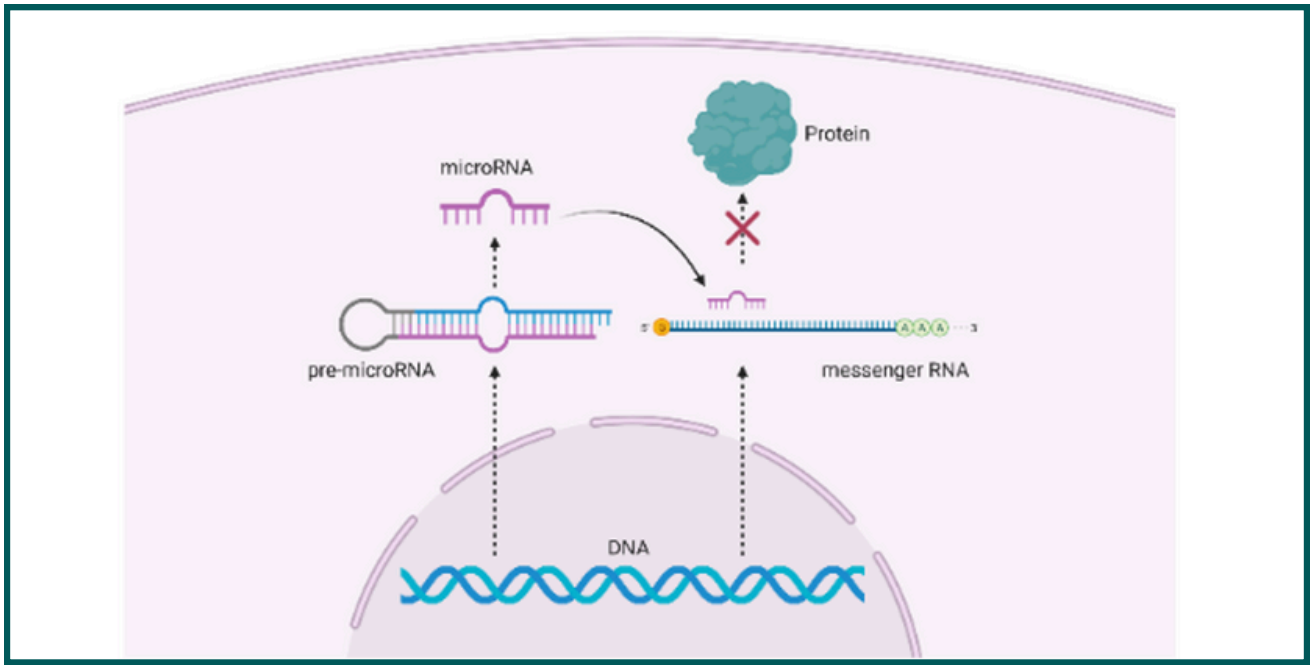

Figure 2. Diagram showing how microRNA alters gene expression[7].

The Downsides of Transposon Activity

Although transposon activity has a significant role in brain development, there are some instances when incorrect insertion of transposons can lead to the expression of harmful genes. This can cause neurodegenerative disorders such as Huntington's disease.

Huntington's disease is caused by the inheritance of a dominant allele[8] which causes the destruction of neurons in the brain[9] leading to many symptoms such as involuntary jerking and depression[8], amongst others. Currently there is no cure, but treatment can be given to reduce symptoms[8].

Alexander Ramos, a PhD student at the University of California, San Francisco, studied the association between lncRNA and the activation of genes[8]. As mentioned above, this occurs epigenetically by the action of proteins binding to chromosomes. Ramos discovered that patients with Huntington's disease shared 88 long non-coding RNA sequences[8], suggesting that lncRNA could upregulate expression of the dominant allele, increasing the severity of symptoms. This could also influence the progression of the disease.

Conclusion

To conclude, DNA previously thought to be 'junk' is becoming an increasingly important area of research. After the discovery of transposons, scientists have been able to start to underpin the molecular changes in the brain leading to correct neural functioning and can use this knowledge to understand neurodegenerative disorders such as Huntington's disease. By knowing that everyone has a unique transposon fingerprint, personalised treatments can be produced for patients with these disorders. As highlighted, further research into 'junk DNA' can lead to advancements in medical treatment, improve understanding of brain development, and many others, making this a growing area of research.

References

Primary Editor: Rebecca Lin
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The Extra Chromosome

By Nisan Kaynar

In honour of March 21st, World Down Syndrome Day, let's shed light on Down syndrome (DS), one of the most common genetic disorders responsible for both intellectual and physical disabilities. DS, also known as Trisomy 21, arises from the presence of three copies of either the entire or a segment of the 21st chromosome within some or all of an individual's cells. DS occurs approximately once in every 700 births[1, 3].

Trisomy 21 is characterised by phenotypic features such as small eyes, short extremities and digits, and a widened space between the first and second toes (*Figure 1*). Individuals with DS also show an elevated risk of various health issues including cardiovascular, respiratory, and urinary system disorders, orthopaedic complications, and immune deficiencies. Although the exact factor triggering the errors leading Trisomy 21 remains unknown, advanced maternal age is widely recognised as a significant risk factor[3, 4].

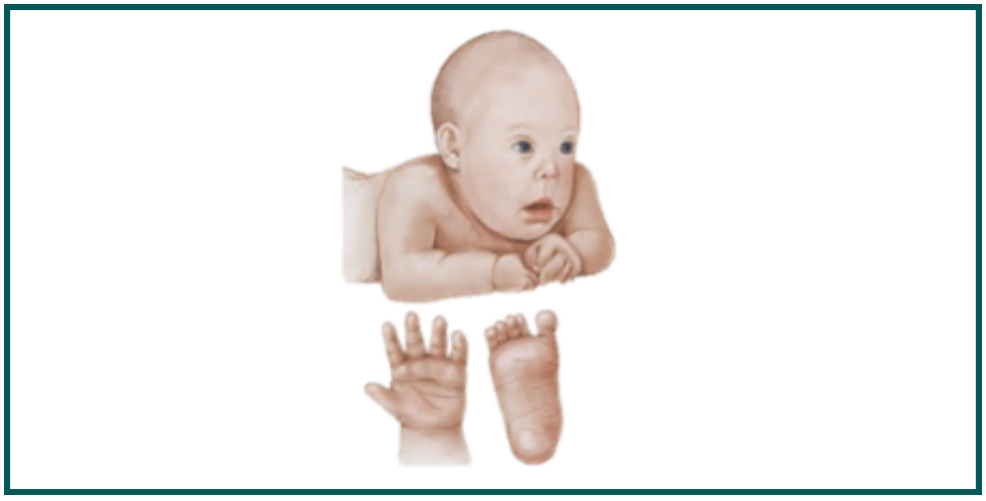

Figure 1. Phenotypic Features of a baby with DS[5].

In cases of pregnancies with DS, it is important to have precise, accurate and rapid diagnosis during the prenatal period to provide families the opportunity to choose between terminating or continuing the pregnancy.

Additionally, diagnosing the condition prenatally is crucial for preparing for postnatal care. Therefore, routine tests for the diagnosis of potential chromosomal abnormalities are recommended by doctors in every pregnancy[6, 7].

Non-invasive screening techniques pose no risk of harm to either the mother or the baby. Measurement of foetal nuchal translucency using ultrasonography during weeks 11-14 of pregnancy is an example of non-invasive screening methods. This test is based on the fact that 84% of foetuses with DS have a nuchal translucency greater than 2.5 mm (*Figure 2*)[7].

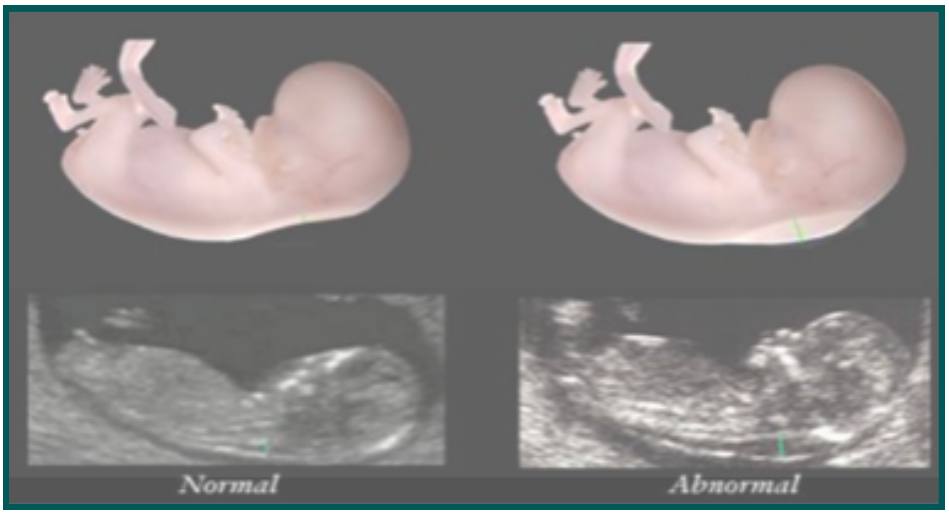

Figure 2. Difference between normal and abnormal foetal nuchal translucency demonstrated using ultrasonography[5].

Blood screening tests called “quadruple test” and “combined test” are also used currently in the UK by NHS[8]. The quadruple test is a method applied during the second trimester by evaluating the risk value created by maternal age together with human chorionic gonadotropin (hCG), alpha-fetoprotein (AFP), unconjugated estriol (uE3), and inhibin A levels in maternal blood. Low AFP and hCG, and high uE3 and inhibin A are signs of a foetus with DS. On the other hand, the combined test is applied during the first trimester by evaluating ultrasonography results and the risk value created by maternal age together with hCG and PAPP-A (pregnancy-associated plasma protein-A) levels in maternal blood. Low levels of both hCG and PAPP-A are signs of a defective pregnancy[6, 7, 9, 12].

DS can also be diagnosed prenatally using invasive methods. Invasive methods involve direct intervention with the foetus and its appendages. These methods include preimplantation techniques, foetal biopsies, chorionic villus sampling, cordocentesis, and amniocentesis (*Figure 3*). The samples obtained are used for karyotyping, thus these tests provide precise diagnosis. However, using interventional procedures can lead to infections and even miscarriages in 0.5%-3% of the cases. Therefore, invasive diagnostic methods are only recommended in pregnancies that are in the high-risk group, according to screening test results[6 13 14].

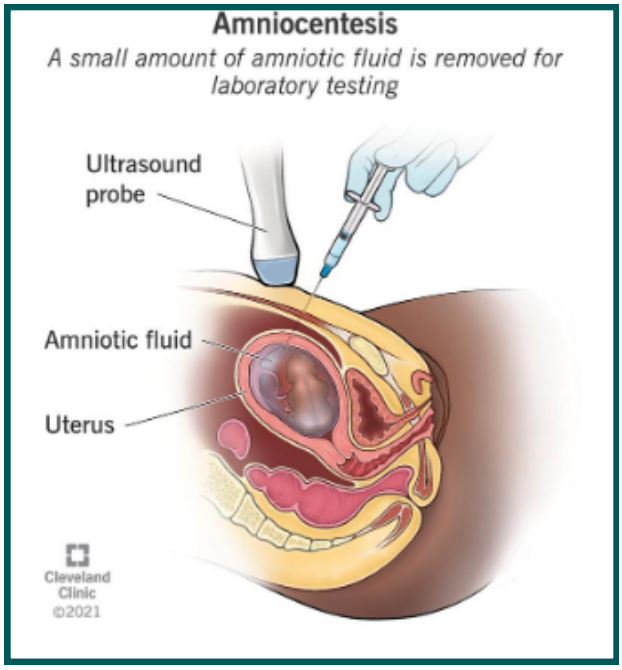

Figure 3. Amniocentesis procedure[15].

Free foetal DNA (cell-free foetal DNA / cffDNA) analysis, which is a non-invasive test, has gained popularity in recent years. It is considered an alternative to invasive tests to prevent complications. This test is performed by measuring the amount of free foetal DNA in maternal plasma starting from the 10th week of high-risk pregnancies. DS can be detected based on the amount of DNA obtained. cffDNA analysis is a highly reliable method with a specificity of 99%[6, 14].

As mentioned above, the exact cause of trisomy 21 is unknown. But this "unknown factor" leads to errors in the cells which then cause Trisomy 21. Most cases arise due to errors during the meiosis of oogonium or spermatogonium. When the mitotic checkpoint fails, homologous chromosomes in Anaphase I or sister chromatids in Anaphase II fail to separate, resulting in the formation of disomic gametes. DS can occur due to the fertilization of a disomic egg with a healthy sperm, or a disomic sperm with a healthy egg. However, almost 95% of cases have a maternal origin[3].

Alternatively, errors during mitosis of somatic cells in prenatal development can lead to improper segregation of the 21st chromosome, resulting in the formation of trisomic and monosomic cells. While monosomic cells cannot survive, trisomic cells proliferate alongside healthy cells. This results in 'Mosaic Down syndrome' where some cells have Trisomy 21, while others have a normal chromosome count[3 5].

Lastly, "Partial Down Syndrome" cases occur when only a segment of the 21st chromosome is triplicated. This can result from the breakage and translocation of a part of the 21st chromosome, with the additional copy being fused with other chromosomes. Alternatively, an extra copy of a segment of the 21st chromosome may arise during DNA replication[3].

In conclusion, prenatal screening and diagnosis methods for DS provide families with vital information for informed decisions and better preparation. Integrating these procedures into routine care enhances support for individuals and families affected by DS.

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Primary Editor: Fahad Al-Dainy
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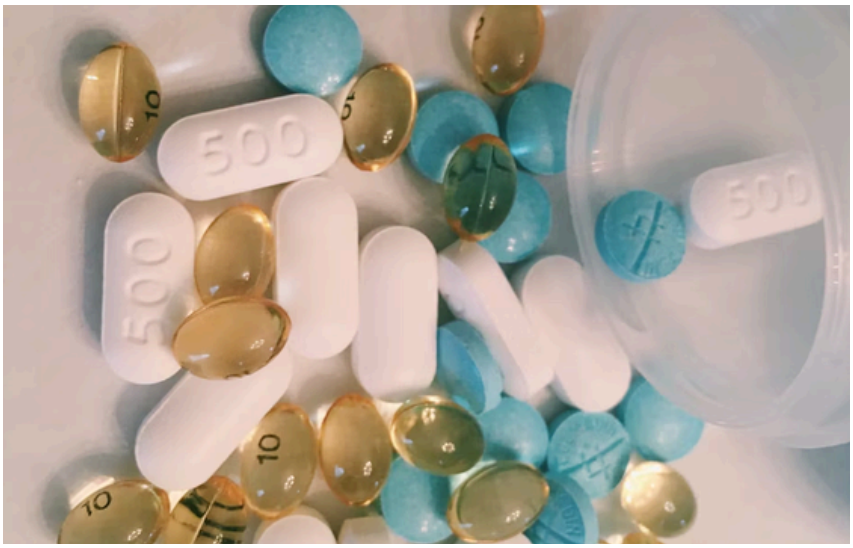

DRUGS IN DEVELOPMENT

The Controversial Nature of Biased Agonism in Drug Discovery

By Thomas Lonsdale

Since its beginning, pharmacology has aimed at designing drugs that show an improvement over currently available treatments[1]. One avenue of research that has shown a lot of promise, and controversy, in the development of improved therapeutics is biased agonism.

In pharmacology, agonism refers to the ability of a molecule to activate a receptor to evoke a response[2]. Receptors are proteins that can induce a myriad of signalling cascades in response to activation by a molecule or drug[3]. Biased agonism in turn refers to the ability of an agonist to specify which signalling cascade the receptor signals via[4], and this has many implications for drug discovery. For instance, it could lead to the generation of opioids that do not cause dependency[5], or antipsychotics that have greater activity[6].

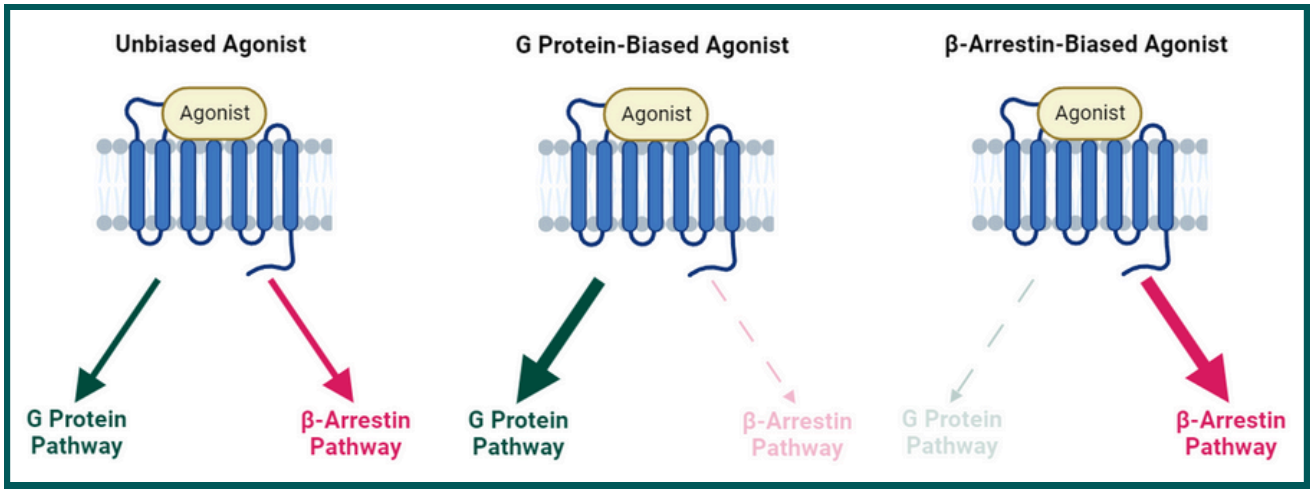

Figure 1. The differences between unbiased and biased agonists at a GPCR. An unbiased agonist signals with equal preference between the G protein and β-arrestin pathways, whereas a biased agonist preferentially signals via one of the pathways[4].

Much of the focus on biased agonism is on the G protein-coupled receptors (GPCRs), because they are the largest and most therapeutically targeted receptor family[7]. Many household drugs such as antihistamines, opioids, and β-blockers act on GPCRs. GPCRs can cause various signalling events via the G protein pathway[8] and can also couple to other proteins called β-arrestins to induce other distinct signalling events[9]. Most agonists acting on GPCRs are unbiased, meaning they induce signalling events via G proteins and β-arrestins in equal amounts (*Figure 1*).

At the turn of the millennium, a series of studies performed in mice administered with morphine suggested that the adverse effects of this opioid, like dependency and tolerance, may have been mediated by unwanted signalling through the β-arrestin pathway[5, 10]. It was thus hypothesized that compounds that selectively signalled through the G protein pathway (i.e. G protein biased) would have an improved therapeutic efficacy and lower incidence of side effects[5]. This led to the generation of the G protein-biased opioid, oliceridine, which was approved by the U.S. Food and Drug Administration (FDA) in 2020 after a series of promising clinical trials. These trials demonstrated that it had a reduced side effect profile compared to morphine whilst being similarly effective[11, 13].

This biased agonist, the first of its kind to be approved by the FDA, has sparked the interest of others into researching and developing biased agonists for other receptors.

Therapeutic targeting of the adenosine A_1 receptor has long been sought after for its protective role against cardiovascular diseases, central nervous system disorders, inflammation, and cancer[14]. But so far, no selective agonists for the adenosine A_1 receptor have made it to market[15], partly because activation of this receptor also induces unwarranted effects, such as lower blood pressure and slower heart rate[16]. It is surprising then that in 2022, a study reported the discovery of a compound for the adenosine A_1 receptor that could elicit cardioprotective effects without its cardiorespiratory adverse effects[17]. The compound, benzyloxy-cyclopentyladenosine (BnOCPA), demonstrates strong G protein bias (particularly for the GoB protein which is found at very low levels in the

heart)[17]. Because of this, BnOCPA has minimal activity at the heart, explaining its absence of cardiac side effects. Although BnOCPA is yet to be tested in human clinical trials, the existence of this biased agonist demonstrates the great potential biased agonism might have for the future of pharmacology and drug discovery.

Despite the promise of biased agonists in potentially revolutionising the field of GPCR research, they have not been without controversy. Firstly, attempts to replicate the findings of earlier studies[5, 10] were unsuccessful in reporting that the adverse effects of morphine and other opioids were a result of β-arrestin signalling[18, 21]. Secondly, PZM21 – another G protein-biased opioid – was still capable of producing adverse effects[22], contradictory to past studies[23]. Thirdly, one study has gone so far as to say that many of the supposedly 'biased' agonists are not in fact biased at all[24]. These findings severely hinder the scope of impact that biased agonism might have on drug discovery and the generation of safer agonists acting at GPCRs.

Biased agonism has long been a well-known phenomenon in pharmacology, and many have tried to exploit this to generate agonists with an improved therapeutic efficacy and reduced side effect profile. But there has been varied success in achieving this goal, with attempts to find biased opioids coming up short of their desired outcome. There has been success in other receptors, however, and it is possible that within the coming years that new biased agonists might be discovered.

References

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An Update on the Progression of Alzheimer's Disease Treatments

By Erin Johnston

Alzheimer's disease (AD) is a neurodegenerative disorder characterised by disruptions to memory and emotional dysregulation. Currently, there are very few treatments for AD and so an ageing population has led to a drastic increase in incidences of AD globally[1].

AD can be caused by genetic mutations- some common risk loci are PSEN1, PSEN2, APOE, APP[2] and the Trisomy 21 gene which is linked to AD in Down's syndrome[3]. However, it is commonly thought that AD is caused by abnormal aggregations of the proteins amyloid-β (Aβ) and tau[4]. These proteins are broken down and processed by faulty mechanisms, then they bind and anneal to themselves, eventually forming clumps that situate inside and outside the neuron[4]. The aggregations prevent neuronal signalling between one another causing dysfunction to normal cognitive functioning and manifesting in the symptoms we see in AD patients[5]. For instance, post-mortem investigation has demonstrated larger ventricles and a reduction in brain volume and shrinkage in AD patients as seen in Figure 1 below.

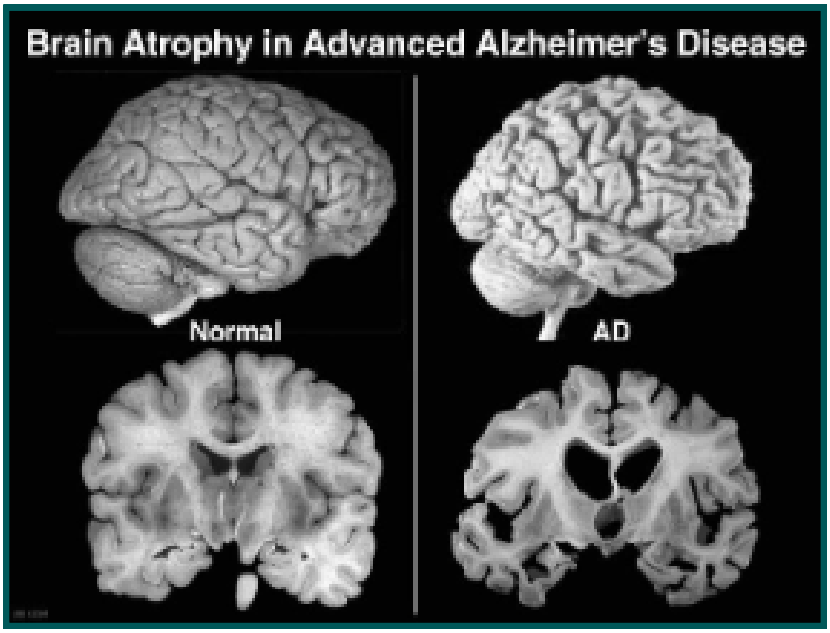

Figure 1. Healthy brain compared to an Alzheimer's disease brain[6].

Recently, the FDA approved two drugs that target AD: Aducanumab and Lecanemab[7]. Aducanumab was approved by the FDA in June 2021 with strong evidence citing its efficacy and thus was suitable for over-the-counter use[8]. Following this, Lecanemab was given accelerated approval in January 2023 and FDA in July 2023[9]. These drugs are monoclonal antibodies that are intravenously injected and work by targeting Aβ and amyloid plaques[7]. They have been hailed as 'game changers' in modifying AD and are promising for the future of AD treatment. Whilst these drugs are not 'miracle drugs' and cannot cure AD, they have been shown to slow cognitive decline[7].

However, despite being supported by some, they have been widely criticised by others. These drugs come at a price, with Aducanumab costing 56,000 USD annually. Further, some contend that the FDA was too quick in approving these drugs as there is controversial evidence regarding their efficacy[10]. These drugs are not currently available in Europe as Lecanemab is still under assessment. This was in part due to a side-effect: amyloid-related imaging abnormalities (ARIA) have been identified in numerous patients treated with these drugs[10]. ARIA can lead to swelling of the brain, haemorrhages or even death.

On the other hand, tau treatments are still in very early stages and there are currently no on the market tau-targeting drugs. However, microtubule stabilisers, kinases, phosphatase activators, immunotherapies, and antisense oligonucleotides are currently in pre-clinical and clinical phases[11]. BIIB080 is the first anti-tau drug to successfully remove tau tangles from brain cells[11] - this is promising for the direction of future research. However, there is mixed support for tau-targeting therapies. Ultimately, they have not been approved due to toxicity or a lack of efficacy. This is a large pitfall in AD treatment research as some researchers argue that tau pathology correlates better with cognitive dysfunctions seen in AD than Aβ[12].

In the last two decades, 98 experimental AD drugs failed in late-stage human trials. This is attributable to a few factors.

AD is a neurodegenerative disorder meaning it is largely captured by the brain. The brain possesses one of the best and worst mechanisms, the

blood-brain barrier (BBB)[13]. The BBB is a tightly regulated mechanism that filters and controls what materials can enter the brain through blood vessels. This is excellent for preventing pathogens from the wider blood circulation entering the cerebral vasculature. However, this poses an incredibly difficult challenge when trying to treat disorders of the brain, as many drugs are too large to cross the BBB[14]. Furthermore, AD diagnosis may be occurring too late. Post-mortem examination is currently the only way to be 100% certain a patient had AD[15]. Therefore, more attention needs to be directed towards discovering biomarkers for earlier diagnosis.

Future directions for AD should involve continuing to improve Aβ-targeting drugs and strive for further research and successes in tau-targeting therapies. We should hope that the future will present us with a cure to AD, but in the meantime, we need to push for disease-modifying drugs with a high clinical and post-clinical success.

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Primary Editor: Imogen Joseph
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Snake Venom as a Novel Treatment for Alzheimer's Disease

By Poppy Firchau

Alzheimer's disease (AD) is a neurodegenerative disease characterised by progressive impairments to cognitive function and behaviour, producing various deficits and particularly affecting memory[1]. The underlying pathology is complex, primarily resulting from an accumulation of amyloid-beta plaques, neurofibrillary tangles composed of tau, and a loss of cholinergic neurones *(Figure 1)*[2]. Unfortunately, current treatments are only symptomatic and have short-term, limited effects[3]. Novel drugs are desperately needed to improve the quality of life of the 24 million patients suffering worldwide[1], and such a drug may be derived from snake venoms[4].

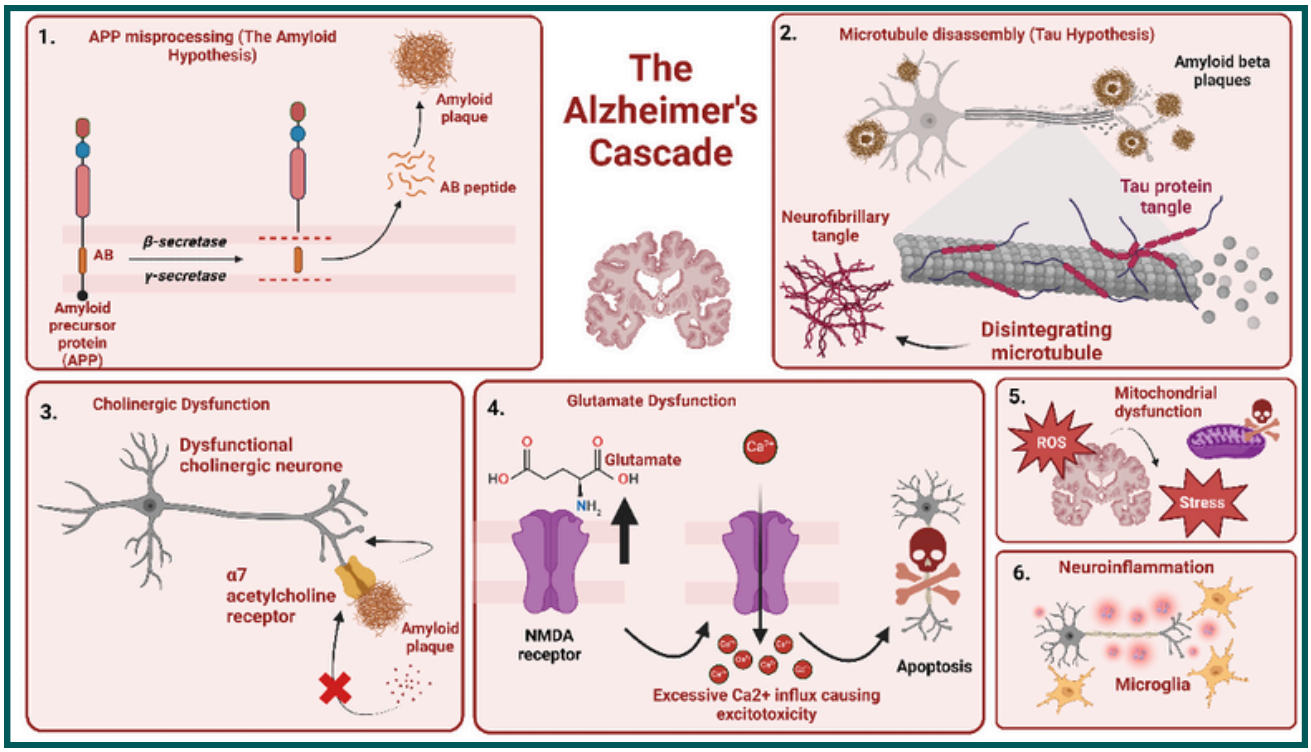

Figure 1. Amyloid-beta (Aβ) is produced in varying lengths depending on the sequential cleavage of amyloid precursor protein[3]. α-secretase favours the non-amyloidogenic pathway producing shorter forms of the Aβ protein, whilst β- and γ-secretase favour the amyloidogenic pathway promoting more neurotoxic forms of Aβ. The amyloidogenic pathway is favoured in AD as longer protein isoforms have a greater tendency for self-aggregation, forming plaques. These plaques disrupt neuronal function, causing apoptosis directly, as well as facilitating

tau misfolding and neuroinflammation, furthering degeneration through interrelated cascades[3]. The selective loss of cholinergic neurons also contributes to cognitive decline[4]. Of note, is the loss of the α7 acetylcholine receptor (α7AChR) due to high-affinity binding by Aβ, causing receptor internalisation and accumulation of AB-α7AChR complexes, and eventually resulting in apoptosis. Whilst high Aβ concentrations produce allosteric antagonism, low concentrations alter function through action as both a low-efficacy agonist and a negative modulator[4]. These pathologies have varying levels of contribution to AD, and many cascade components influence other elements through their action.

Snake venoms have shown promise in interfering with AD mechanisms. α-neurotoxins are derived from venom, they can bind to the α7AChR and interrupt acetylcholine transmission[4]. In silico modelling revealed structural similarities between Aβ and α-neurotoxins and showed that Aβ binding to the α7AChR may be inhibited with the application of α-neurotoxin[5]. Fonar *et al.*[4] furthered this by investigating a modified α-neurotoxin in a battery of tests. Modification with phenylglyoxal significantly reduced toxicity. In silico modelling suggested that modified toxin (mToxin) functioned as a weak competitive modulator, preventing Aβ binding, and thus enabling greater acetylcholine transmission with α7AChR. Additionally, a TUNEL assay was utilised, measuring the rate of apoptosis occurring in a population of cells by detecting DNA degradation. TUNEL positivity was analysed in rodent hippocampal dentate gyri (an area critical for memory formation targeted by AD pathology), and mToxin was found to reduce apoptosis in this region after treatment with mToxin. Behavioural paradigms (*Figure 2*) were assessed in 20 female, triple-transgenic AD mice administered the mToxin intracerebroventricularly – injected into the spaces of the brain filled with cerebrospinal fluid[4].

Whilst this study includes a robust battery of tests, there are still points for improvement. This drug was only administered to the mice for 4 weeks, and perhaps functions similarly to the Parkinson's drug Levodopa and have fluctuating efficacy over time[6]. The transgenic model used is associated with early-onset AD, so perhaps the toxin application may not be as applicable to sporadic AD. The mToxin was also applied at 8 months of age, by which point dense and diffuse Aβ plaques were already extensively distributed.

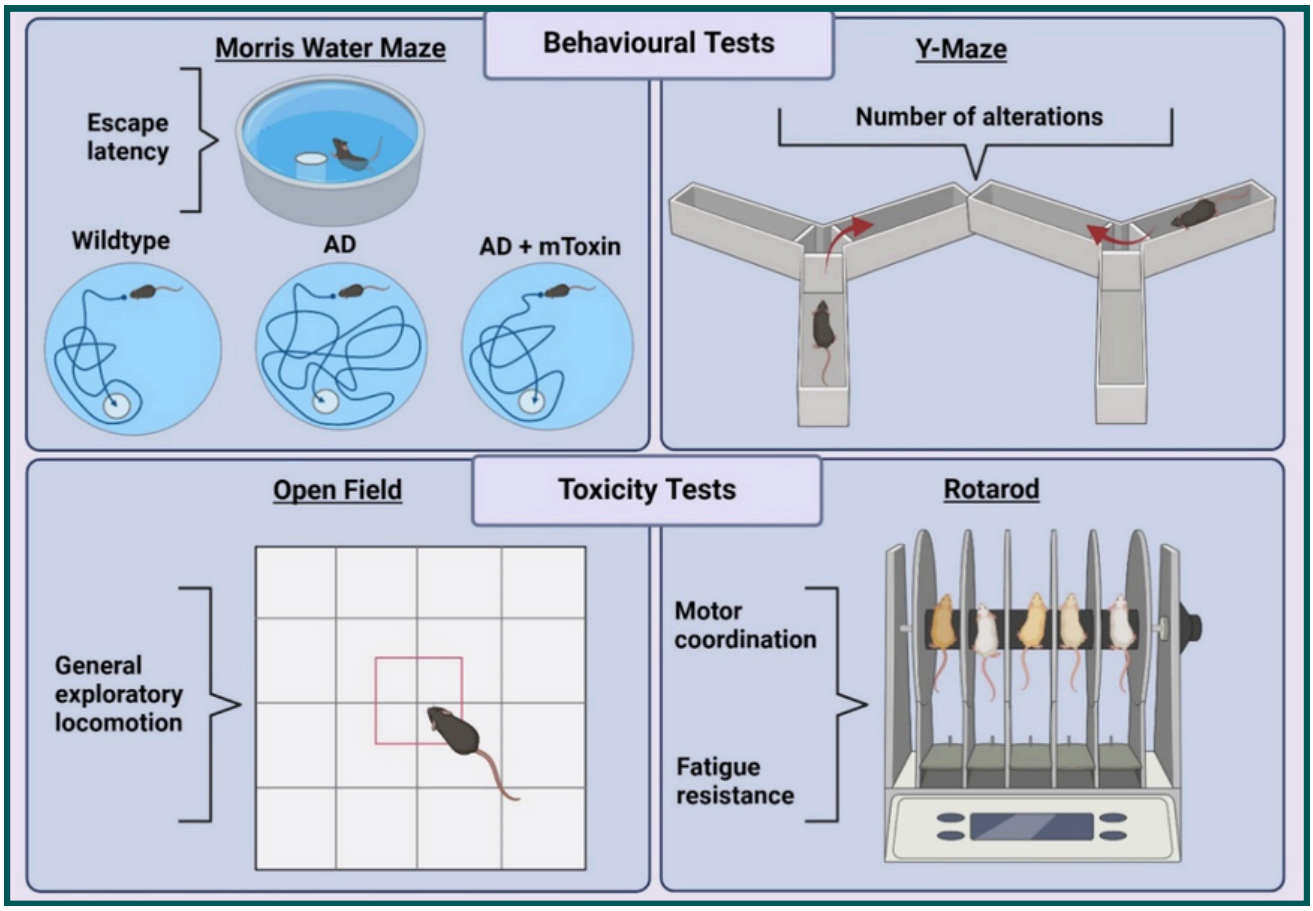

Figure 2. Behavioural tests included a Y-maze to assess spatial working memory and a Morris water maze to evaluate short-term memory and spatial working memory. These tests revealed that mToxin doesn't influence memory formation or recall in wild-type mice but improves short-term memory in the AD models. Toxicity testing involved the open field test and the rotarod test. They found all animals survived toxin injection, no observable changes in appearance or behaviour, and locomotion wasn't inhibited in either test[4].

There may be greater efficacy if this drug was applied earlier in the stage of pathology when brain damage is less extensive. However, this study still provides a novel therapeutic proposing significant efficacy. Research has also uncovered neuroprotective benefits against Aβ in rodent hippocampal neurones[7] and found snake venom metalloproteases inhibit AB secretion in human cell cultures[8]. This supports Fonar's therapeutic discoveries, albeit in different snake species.

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SCIENCE IN SOCIETY

Evolution, Cancer, and Symbiosis: How Biological Theories Influence Society

By Amy Cotterell

Take a unicellular organism and look at the pathways that encompass its most basic functions. Zoom in further, to a single protein and try to count its possible conformational states[1]. Then, count the years its ancestors have lived and find that life originated an estimated 3.7 billion years ago[2]. There is knowledge within this ancient complexity; what can it teach us about organising complex human societies?

Evolution: Building Complex Systems

Enzymes can be used in chemical synthesis to increase the rate of a desired reaction (e.g., in production of pharmaceuticals). These enzymes often need to have a better rate, specificity, or stability than natural enzymes[3, 4]. *De novo* design aims to build an enzyme based on a rational design of its structure and mechanism[5]. While directed evolution, improves an existing enzyme by generating a library of mutants from the 'best' enzyme, allowing the process to be repeated through multiple rounds until a sufficiently improved enzyme is gained[6, 7] *(Figure 1)*. It's normally better to improve an enzyme by directed evolution because it doesn't rely on the scientist knowing the best solution.

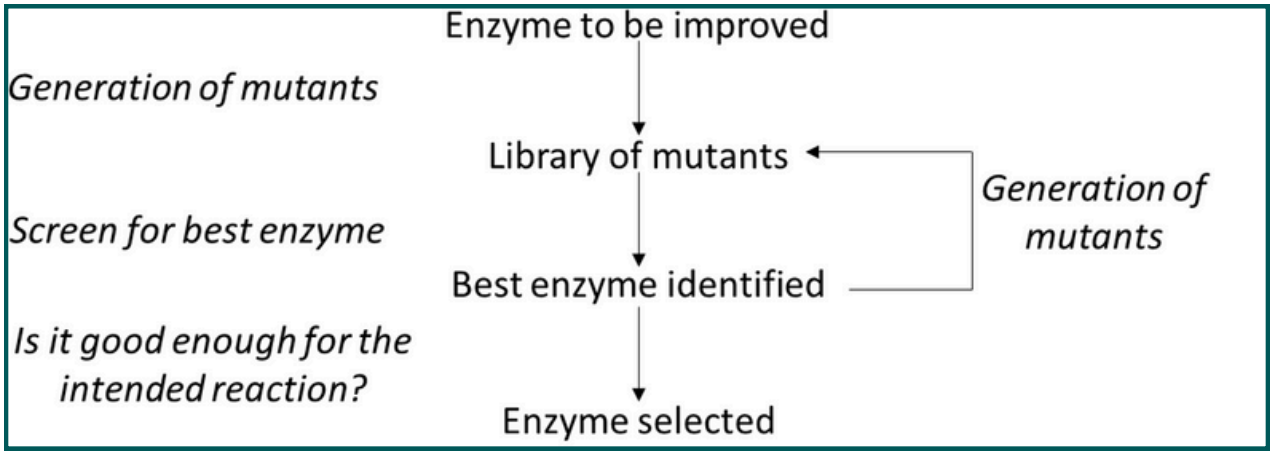

Figure 1. Directed evolution.

When a society undergoes a revolution and rebuilds itself within an idealised image, often the end result is not how it was initially imagined. The same applies to when a city is built from scratch, like the UK's new towns. Whereas gradual change can lead to a society better adapted to its citizens' needs. The same applies to a city that builds up gradually over a long period of time. Evolution is a humble model for building something too complex to understand.

The danger of treating theory as fact

When Darwin came up with his theory of evolution, liberalism and capitalism were beginning to take shape[8]. Darwin was influenced by this and borrowed concepts and phrases from economists such as 'survival of the fittest' from Herbert Spencer, who believed in unrestrained capitalism during the Industrial Revolution and opposed laws in aid of the poor, workers, or those he determined 'genetically weak'[8]. Given this, it's not surprising that Darwin's theory of evolution was used to justify the eugenics movement, which influenced Hitler, and led to the forced sterilisation of 64,000 people in America[8]. Here, Darwin's theories were treated as facts and so could be used to validate social theories.

Symbiosis

New theories are changing the narrative that life is a 'bitter struggle for existence' between competing individuals[9]. For example, the complex cells of eukaryotes are thought to have come about through endosymbiosis, in which bacterial cells living inside cells eventually became organelles, such as the mitochondria or chloroplasts[10]. Symbiosis does not discount competition, early eukaryotic cells would have gained a competitive advantage through collaboration, but it tells a more complex story of interconnectivity. Gaia expands on this by describing the earth as a self-regulating system, similar to a complex organism, which maintains artificial conditions desirable to life, such as an oxygen-rich atmosphere[11]. If biology is an interconnected collaborative web, then theories such as the selfish economic man who acts rationally based on their own interests, no longer seem an effective way of modelling human behaviour or of running a society[12].

Cancer

Six hallmarks characterise cancer[13]. They also describe a capitalist society:

- **'Sustaining proliferative signalling, enabling replicative immortality, and evading growth suppressors':** Cancer and capitalism are both processes of dysregulation. There's this idea that growth can continue forever and that nothing should be put in place to limit growth.
- **'Resisting cell death':** The narrative that ageing and death are processes we should prevent at all costs.
- **'Inducing angiogenesis':** The development of extending trade routes and roads into new areas to grow expanding civilisations.
- **'Activating invasion and metastasis':** Capitalism spreads leading to a vast, globalised system of wealth extraction[13].

In other words, cancer is where a set of cells in the body become dysregulated and seek endless resources and growth regardless of the consequences to the rest of the body. Capitalism seems to follow a similar pattern of endless growth at the cost of the rest of the world. In cancer, the cancer cells die with the rest of the body as the fine balance required for survival collapses. Earth's own life-supporting systems are shutting down. What will that mean for us?

Sequence Landscapes

A protein can exist in many different structures, some of which are highly disordered, while others are neatly folded. The structure a protein is most abundant in is its lowest energy state and it reaches this state by sampling steadily lower energy states through a folding funnel[14] *(Figure 2)*. The binding of another protein or a change to the environment can change the energetics of the protein so that this seemingly static structure suddenly switches into another. This is only possible, however, if there is enough energy to cross the free energy barrier. Society can feel unchangeable until a shift over an energy barrier leads to another seemingly fixed conformation.

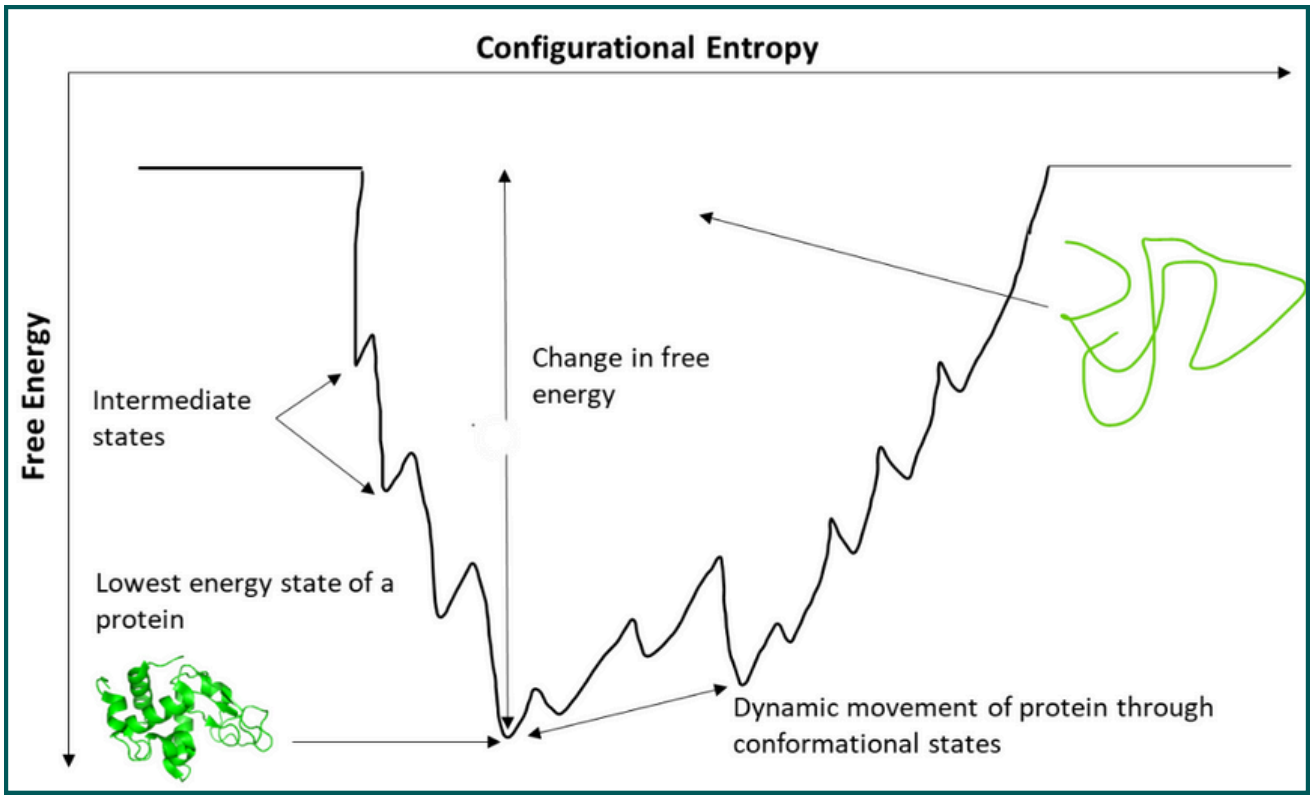

Figure 2. Folding funnel of a protein.
Protein structure taken from PDB (1DPX)[15].

Studying biology

Looking at society through the lens of biology helps us to understand ourselves and how we organise. It also shows biological research, and the communication of this research is important. However, science is not the only approach to understanding biology. Professor Robin Wall Kimmerer talks about the different ways of knowing: mind, body, emotion, and spirit; she says that Western science only uses the body to serve the mind[16, 17]. Leaving space for people to communicate their own understanding of the natural world, as well as pushing for access to wild spaces so that we can gain greater connection, means that a broader spectrum of the bountiful knowledge of biology will be understood and used. What connections could you find?

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Primary Editor: Malintha Hewa Batage
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Johnson & Johnson's Great Legal and Biological Talc Scandal

By Uthra Mandi Jayaram

Would you believe that a multi-billion-dollar company produced a product that caused cancer in over 70,000 mothers?[1] Johnson & Johnson (J&J) was initially accused in 1999 of producing carcinogenic baby powder[2]. J&J were thought to have been producing their talc powder from impure sources that contained traces of asbestos[2]. Whilst J&J denied this, they still conducted at least three tests which were positive for asbestos[2]. Moreover, biopsies of pelvic tissue from 11 patients suffering from ovarian carcinoma revealed that the same size of talc particles were also present in talc particles found in J&J baby powder[3]. This indicated that the J&J baby powder may have had some involvement in the formation of the cancer. This triggered additional ethical implications because the people most affected by the baby powder were new mothers at a very vulnerable stage of their lives.

Asbestos fibres are minerals found naturally in rocks that have been proven to cause cancer[4]. Some people thought that the talc mining process was not regulated enough, which allowed the mined talc to be contaminated with asbestos. In 1972, research performed by the University of Minnesota into the contaminants revealed that tremolite (an asbestos mineral) was found in their sources of talc[5]. Very small traces of asbestos can cause lots of health problems in some individuals years after exposure[4]. Asbestos can enter the lungs via respiration, this results in inflammatory responses in the lung tissue due to its very sensitive nature[4]. The prolonged disruption of lung endothelium can cause lung cancer. Asbestos is also known to cause reproductive issues *(Figure 1)*; asbestos can induce a similar inflammatory response in ovarian tissue and promote the development of cancer[6]. However, it is still unknown how asbestos reaches the reproductive system to cause these implications.

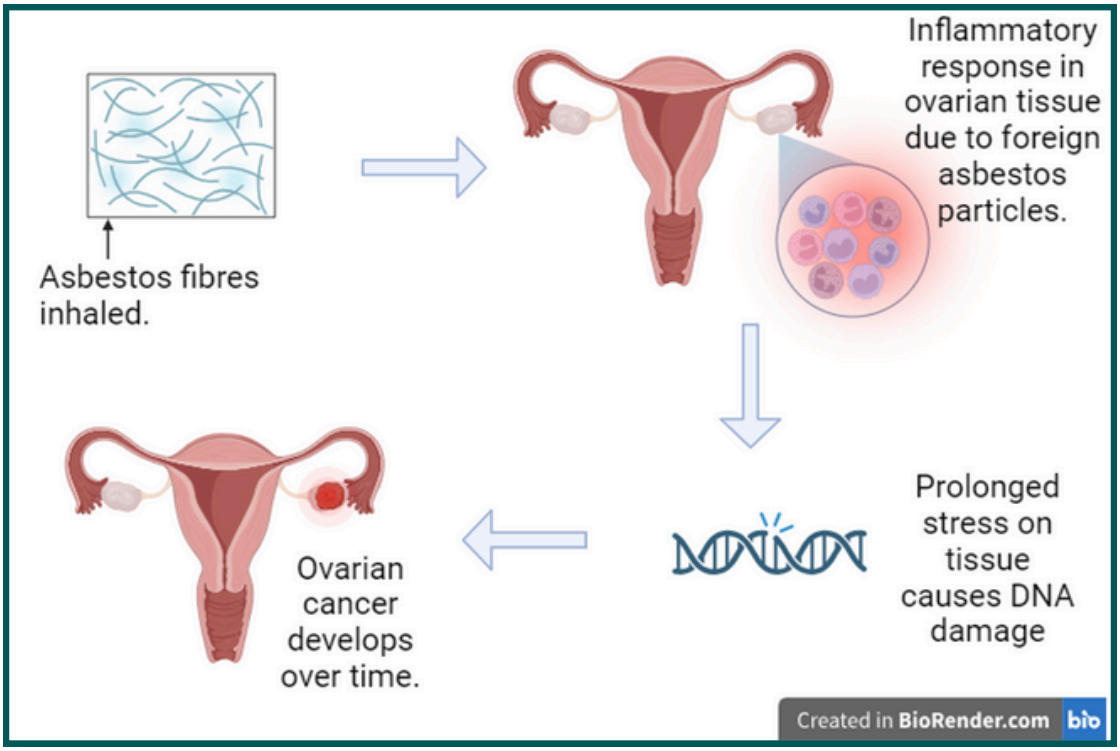

Figure 1. Development of cancer in ovary due to asbestos exposure.

To combat the damage to J&J's finances through legal trials for individual plaintiffs, J&J created another company called LTL to which it passed all its legal liabilities to this subsidiary[7]. LTL was a smaller company with less capital than J&J; they attempted to use this to their advantage in the bankruptcy courts to allow them to halt all the trials and instead offer each victim compensation and use capital to "restructure"[8] their business rather than fund each trial. These types of schemes are controversial as firms that support this type of bankruptcy scheme state that this system will allow all victims to get equal compensation that will reach them quicker without the requirement to go through complicated legal processes[9]. However, this can cause distress in victims because they are denied the right to trial at court which could also prevent their personal damage from being addressed – it could be argued that the course of justice is being manipulated. The bankruptcy scheme would have been beneficial to J&J because they could have saved capital, and they also could have ignored allegations of asbestos contamination of their baby powder. However, the bankruptcy court denied their claims twice which meant J&J had to proceed with mass tort court trials (separate trials with all the individuals that were harmed by

the same product)[1]. This resulted in J&J compensating each individual plaintiff. For example, a court in Missouri ordered J&J to pay $4.7 billion to 22 women[10], this was later reduced to $2 billion[11].

Due to loopholes in the legal system such as the "Texas-two-step"[9] (used by J&J), large companies can split into smaller companies that handle all legal liabilities. As a result, it is suggested that pharmaceutical companies may not face fair consequences from such tort allegations. J&J have lost over $3.5 billion in plaintiff settlements, which also led to a decline in their brand reputation that promoted the safety of mothers and babies[11]. Therefore, in 2020, J&J altered the ingredients of their baby powder to contain corn starch instead of talc in an attempt to regain their consumer demand[11]. However, J&J's talc baby powder is still available for purchase everywhere (excluding North America)[12]. Overall, it is agreed by many that pharmaceutical companies should test their products more thoroughly to protect the health and well-being of the public.

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OPINIONS IN PSYCHOLOGY

The Ghosts of Colonial Past: Why We Need to Re-evaluate Modern Psychology

By Fiona Chung

By the twentieth century, the majority of the world had at some point been colonised by Europe[1, 2] *(Figure 1)*. Colonisation – the forcible seizure of one nation or state by another – leads to violence and exploitation against indigenous populations and the imposition of the coloniser's ways of thinking and being[3]. In psychology, this has led to an overwhelming focus on 'Western', particularly European and North American, perspectives and paradigms, and the erasure of indigenous knowledge and practices[4].

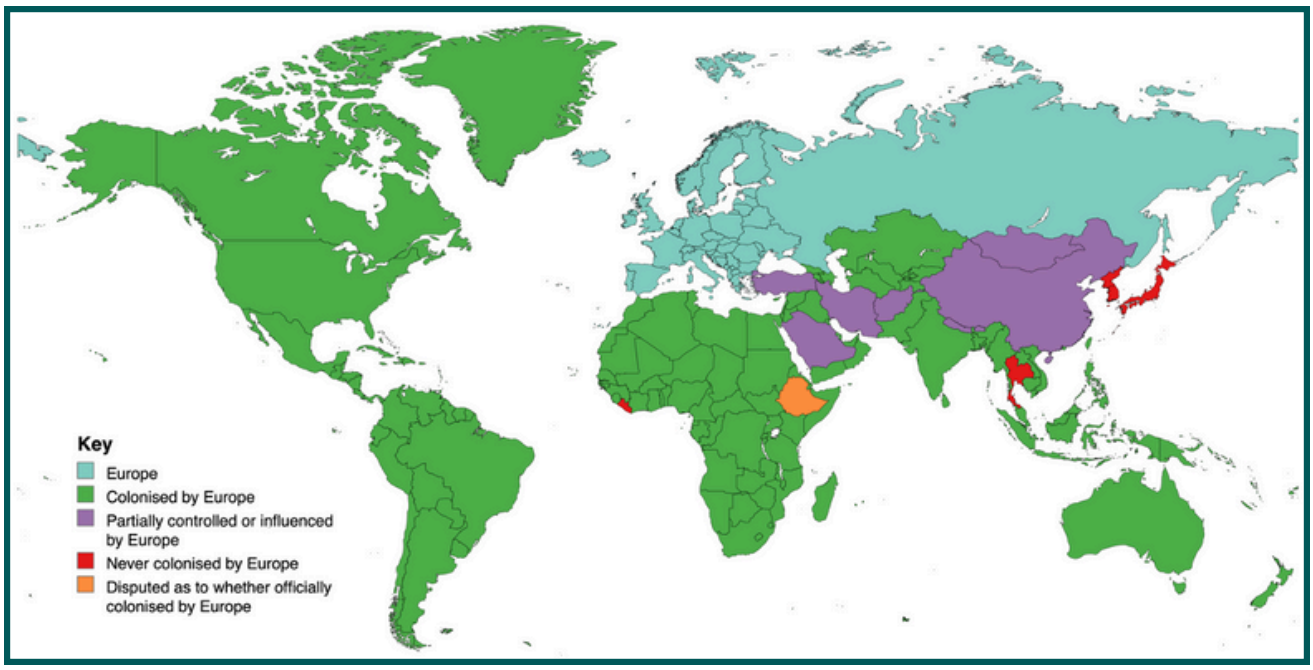

Figure 1. Map illustrating the extent of European colonialism. Five countries have officially never been colonised by Europe: Japan, Thailand, North and South Korea, and Liberia. There is dispute regarding Ethiopia, which Italy took control of in 1935 and annexed in 1936, lasting until 1941. Some consider this part of the fascist expansionism of World War II and separate from colonialism, whereas others consider this a form of colonialism. In some countries, European powers would declare exclusive rights, rule through proxies, or occupy only certain regions and are, therefore, considered partially colonised or within the European sphere of influence[1, 2].

Psychology has a history of racist and culturally insensitive research, often being used to justify maltreatment of and prejudice towards racialised ethnic groups in the twentieth century[4]. Today, the university curriculum is dominated by research by White men – in some cases, you are more likely to find reading materials by White men named John/Jon than by Black, Asian, and Minority Ethnic (BAME) individuals of any gender or name[5]. This imbalance has spurred protests worldwide, including the 'Why is my curriculum White?' protests in the UK in 2015, calling to decolonise the curriculum[6].

Decolonisation is the process of ending colonial power and privilege and restoring rights and autonomy to colonised populations. For psychology, this would involve diversification to include more research and perspectives from marginalised peoples as well as recognising indigenous knowledge and promoting inclusive and equitable research practices[4].

Current psychological research is Western-centric[7] *(Figure 2)*, but what arises is generalised to the rest of the global population.

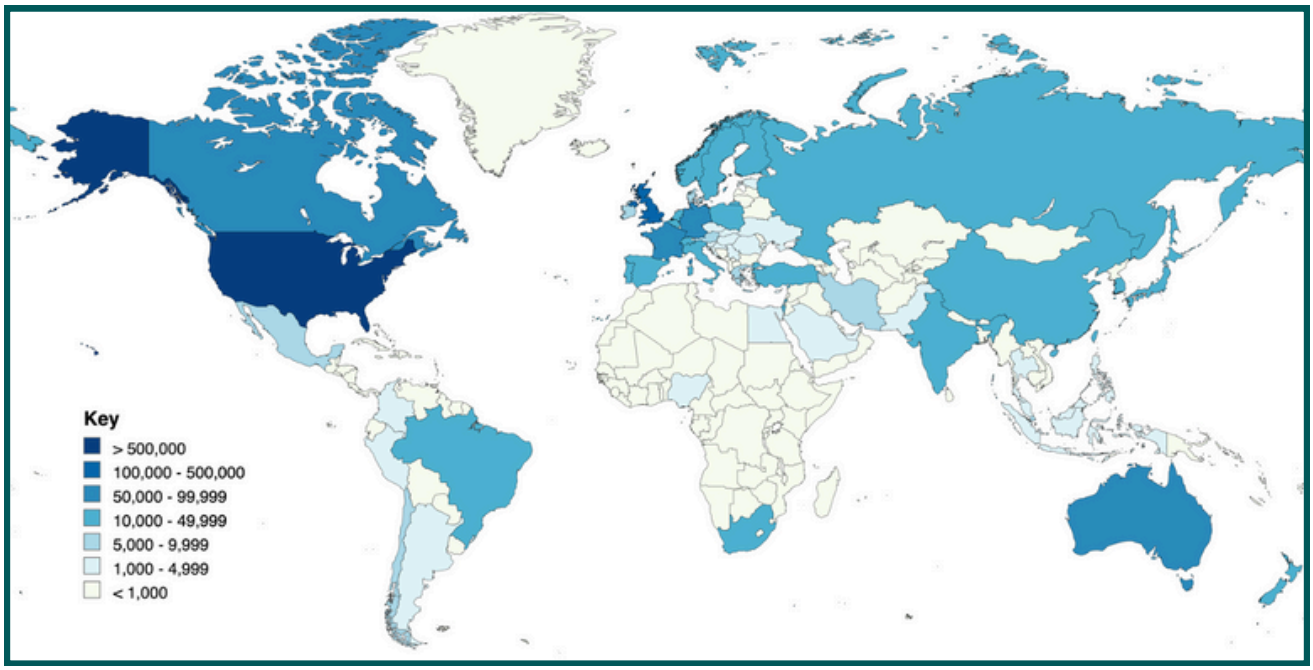

Figure 2. Map illustrating the number of citable psychology documents published per country (1996-2022). Most current psychology research comes from the USA, the UK, Germany, Canada, Australia, and France. Data from Scimago Journal & Country Rank[11].

A major consequence of this relates to psychiatry: services that are not culturally informed do little for marginalised groups experiencing difficulties with their mental health and wellbeing[8]. For example, psychosis can be attributed to supernatural or religious-spiritual explanations amongst Asian, African, Latin, and Māori cultural groups. However, Western mental health services focus on bio-psychosocial models. This can lead individuals from these groups to delay seeking treatment over concerns of professionals being dismissive[9,10].

Moving towards a decolonised psychology is a complex process that involves more than including more diversity in research. Much of our foundational psychological knowledge was established through a very narrow lens[4]. Thus, our pre-existing understanding of psychology as a discipline is already biased. Passively including more diverse groups in research does little to address their prior exclusion if we continue to view them and the world through this biased lens[12].

One way to broaden the lens of psychology is to engage with other schools of thought that focus on different perspectives. For example, Black psychology focuses on the experiences of individuals of African descent to address their wellbeing and needs[13]. Indigenous psychology rejects 'Western' psychology as universal and aims to establish more contextually relevant psychological theory[14]. Critical social psychology highlights the importance of power dynamics with the aim of ending the oppression of marginalised groups[15]. Liberation psychology focuses on taking practical steps to advance social justice and emphasises the importance of community and collective good over the individual[16]. Engaging with these schools of thought provides space for different voices and allows us to think more critically about how we understand the world.

Beyond updating what is taught, it is also important to consider how psychology is taught. 'Problem posing education' is a form of pedagogy that positions both student and teacher as dynamic beings in a dynamic world, from which knowledge and understanding is co-created. This is in contrast to 'bank deposit education', through which education is a one-directional transmission of knowledge from teacher to student. Shifting towards problem posing education allows for greater reflection, prompting us to engage in tackling oppression[17].

Steps are currently being taken to decolonise the psychology curriculum. In 2020, the British Psychological Society (BPS) set up a Taskforce on Diversity and Inclusion, which addressed the need to decolonise the curriculum[18]. Additionally, specific resources are being created to inform both staff and students about decolonisation, with a focus on the voices of the marginalised and oppressed[19].

These are only a handful of the issues that need to be addressed and psychology has a long way to go to shed its colonial past. We must look beyond surface-level changes and aim to tackle the root of the issue. Euro-American ideals have been ingrained in our culture and must be addressed before psychology can be truly decolonised.

This article is adapted from a short communication written for MSci unit Advanced Creative Communications.

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Becoming a Stoic Student: How Ancient Wisdom Can Benefit Student Wellbeing

By Alexandra Papadaki

16% of university students in 2023 reported having a mental health condition or challenge, which is three times higher than in 2016[1]. The transition to university poses many personal, emotional, and academic challenges. Consequently, student wellbeing and academic performance are at risk of being affected. Stoicism is an ancient Greek and Roman philosophy, the most well-known follower of which was Roman emperor Marcus Aurelius.

Figure 1. Marcus Aurelius was a prominent Stoic and the author of 'Meditations'[2].

Today, 'stoic' describes someone that is rational, detached, and does not express their emotions. This characterisation is associated with unhappiness, less overall pleasure, and a reduced sense of meaning and purpose in life[3]. The original teachings of Stoicism do not align with modern connotations. Instead, the philosophy advocates for the processing of negative experiences through emotional awareness, understanding what you can and cannot control, and gratitude.

The Stoic principle that appraising an event can alter your emotional experience exists in Cognitive Behavioural Therapy, and this is explicitly stated by its founder[4]. The Stoics did not believe that emotions were inherently bad. Rather, they believed that ideal emotions are grounded in rational thought and reality, and that emotions based on false interpretations of events should be relinquished[5].

Therefore, psychologists want to know if Stoicism can improve the wellbeing of students. Brown *et al.* employed a Stoic training programme on 24 medical students in their clinical placement year[6]. This sample was

selected due to the prevalence of burnout in third-year medical students. The training lasted 12 days, involving independent completion of various short Stoic exercises. These included students having to predict misfortunate events that may happen and preparing for such events. Students also engaged in reflective journalling every evening *(Figure 2)*.

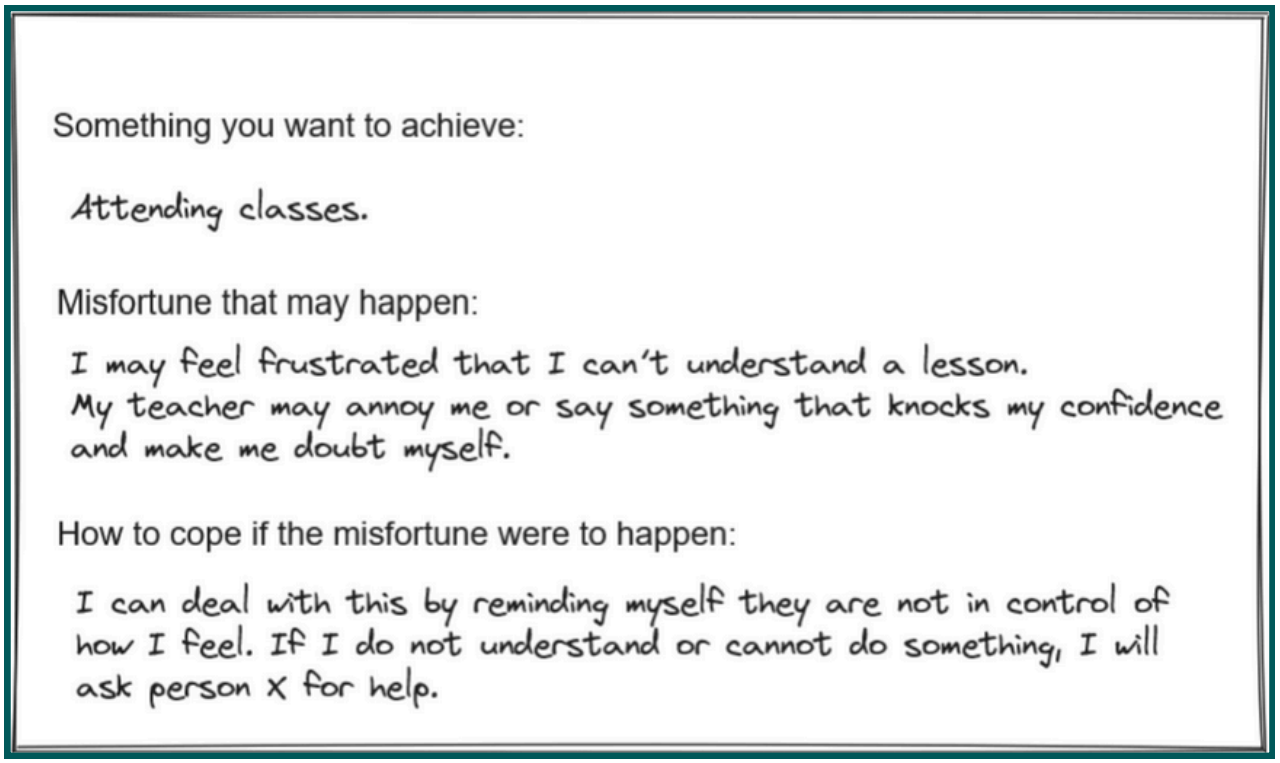

Figure 2. Example prompts given to students to practise predicting misfortune. Adapted from Brown *et al*. (2022)[6].

Post-training interviews revealed that students had increased empathy towards their patients, felt more prepared for negative situations, and felt more aware of their feelings and thought processes. Self-report questionnaire scores for Stoic tendencies, resilience, and empathy all increased, and the qualitative results from the interviews showcased themes of improved wellbeing and meaningful changes in their lives, even after 2 months following the training.

Student resilience is positively correlated with subjective happiness and negatively correlated with depression and anxiety[7]. Brown *et al.*'s research illuminated the potential of Stoic training as a tool for student wellbeing[6].

Medical students are not the only ones who suffer from burnout and face adversity. Students across all disciplines are challenged by the transition from school to higher education. Resilience in first-year students is associated with increased wellbeing, better academic performance, and increased employability[8]. Implementing resilience-building interventions in the university curriculum could yield wellbeing and academic benefits.

My dissertation project investigated if a shorter online Stoic practice intervention could increase the academic resilience of university students. The intervention required students to read quotes from prominent Stoics and answer relevant questions to prompt reflection on Stoic themes.

The self-discipline exercise asked students to reflect on how they could practically achieve their goals, encouraging planning and taking pre-emptive measures.

The locus of control-themed exercises prompted students to focus on the aspects of their lives that they could directly control. Similar to the growth mindset[9], this theme advocates taking a proactive approach to improving performance.

Exercises on the Stoic theme of emotional regulation asked students to focus on the present and be aware of judgments they had made on situations and people. Verbalising emotional experiences can reduce the intensity of distress caused by events[10].

The theme of virtue required students to reflect on how they view and interact with others, encouraging a sense of empathy for their community.

Before and following the Stoic practice intervention, the students completed self-report questionnaires to measure their Stoic tendencies and academic resilience. A paired samples t-test will be conducted to test for a statistically significant difference between pre- and post-intervention scores.

Implementing Stoic practice into the university curriculum could be a cost-effective way to build resilience in the student population. Academic resilience is likely to provide a protective effect against the mental health risk factors that students experience. Could students benefit from wellbeing exercises being implemented in the curriculum? For students who feel the pressure, Stoicism might be the answer.

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What is Neuropsychology?

By Prisha Sharma

Often when I tell people that I study neuropsychology, the response I usually get is, “Oh, will you be a doctor/neurologist?” So, for starters, no, we aren’t doctors, and no, we don’t hold a degree in medicine.

Two arms outstretched by Youssef Naddam[1]

‘Neuro’ signifies the study of the brain, and ‘psychology’ delves into the intricate realm of the mind and its manifestations in behaviour. When these two realms intertwine, an extraordinary discipline emerges — neuropsychology — a branch of scientific inquiry deeply rooted in the biopsychosocial paradigm. Within this framework, neuropsychologists formulate therapies by navigating the interface between a patient’s biological, psychological, and social facets of their life. For instance, a patient presented with a history of a right posterior brain tumour treated by surgical resection would experience low mood, anxiety, fatigue, word-finding difficulties, and issues with balancing[2]. In this scenario, the guidance of a neuropsychologist becomes indispensable, as the oncologist seeks their expertise to conduct comprehensive neuropsychological assessments and discern interventions based upon evaluation of test scores and observations. We don’t cure the condition itself; neurological conditions are extremely challenging to resolve easily. However, we are the guiding force in ensuring the patient's well-being is intact through various forms of therapy, providing awareness through psychoeducation, and directing them to the right professionals for further assistance.

Neuropsychologists are the anchors to people's cognitive abilities and daily functioning. Whether it's mild depression, a brain tumour, or brain inflammation, neuropsychologists identify and recover behavioural and cognitive deficits of patients afflicted with neurological diseases and emotional difficulties. In doing so, they illuminate the path towards recovery, instilling hope and rekindling the flame of resilience within their patients.

Neuropsychology has a contemporary focus on 4 elements:

1. diagnostic decision-making,
2. understanding an individual's cognitive status or level of functioning,
3. surgical planning, and
4. planning and evaluation of treatment and rehabilitation[3].

When patients initially contact their general practitioner with cognitive deficits such as memory issues, poor verbal fluency, and difficulty with visuospatial reasoning, they are referred to the neuropsychologist for a clarified diagnosis. It is then the neuropsychologist's responsibility to understand the patient's present cognitive status and devise strategies to recover the deficit through therapies.

Photographed by Camila Quintero Franco[6]

Such therapies include acceptance and commitment therapy, which uses acceptance and mindfulness techniques to change one's negative perception of their situation, or cognitive behaviour therapy to reduce symptoms pertaining to anxiety or depression[4]. In severe cases such as Parkinson's or epilepsy, where surgery might be necessitated, a neuropsychological pre-evaluation is performed using tests to measure pre-morbid functioning of the patient[5]. This is then used to compare their performance once they recover from surgery.

If the test results suggest that the surgery would impact certain cognitive abilities negatively, a multidisciplinary team involving neurologists, specialist nurses, and neuropsychologists is assembled to determine the efficacy and need for the surgery.

To become an established neuropsychologist, a bachelor's degree in psychology or neuroscience is ideally required[7]. For psychology students in the UK, you're already accredited for graduate membership by the British Psychological Society (BPS). Should one choose neuroscience, a Master of Science (MSc) in Neuropsychology must be accredited by the BPS, and if not, then an MSc in Psychology (conversion course) would be required. Having transversed these initial stages, an MSc in Neuropsychology is the ideal program to get into, in which you can flex the fact that you now think like a saint and understand why your friend lashed out at you. After the master's degree, 1-3 years of clinical work experience is required. Finally, the zenith of this educational pilgrimage ends by attaining a Doctorate in Clinical Psychology (DClin) which takes place for 3 years in the UK.

The arduous education journey required to become a neuropsychologist surpasses the limitation of what words can fully convey in this article. It demands unwavering dedication and focus; however, it also bestows me with a great sense of fulfilment and pride. Embarking on this path grants me the privilege of tending to the intricate workings of people's minds and healing the human spirit.

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Peer-reviewers: Georgia Grogan, Akanksha Pai & Serena Lee

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Figure 1: Created by Zihan Deng using BioRender

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