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Editorial

Editorial

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Welcome to the January 2020 issue of The British Student Doctor!

At the start of this year we look ahead expectantly to a new decade, bringing important milestones in our personal and professional lives; graduations, new jobs, weddings, births, successes and challenges. One of the most complex issues of our generation is the impact of climate change on health. 2019 saw the issue brought to the forefront of our collective societal consciousness and in the guest editorial "Climate action: No time to waste", Professor Hilary Graham from the University of York, calls members of the medical profession to take immediate action for the "climate emergency". The rise in infectious disease is one implication of these events and medical student, Jessica P J Larwood, from the University of Oxford, puts into perspective the realities of a climate crisis.

The impacts of a climate crisis will also impact rates of skin cancers. A case study by foundation doctors Elizabeth Jones and Chantal Patel, along with consultants Dr Vivek Mudaliar and Mr Amir Ismail from the University Hospital North Midlands of a rare case of basal cell carcinoma showing vascular invasion. This article highlights a good example of doctors of all grades working together to advance medical literature.

As climate change will impact the poorest nations first, as will our decisions on future ethical publishing models. Professor Paul Bowman from Cardiff University School of Journalism, Media and Culture, reflects in his editorial on the vital role of diamond open access in the academic community, and the principles that The British Student Doctor Journal endeavours to uphold.

Biyyam Meghna Rao from the University of Liverpool deals with the contentious issue of "Should Obesity Be Considered a Disability?". Given the rise in incidence of obesity, its impact on health and the wider societal impacts of this terminology, this is a debate that will be increasingly important in healthcare in this new decade.

Another contentious issue is an 'Opt-Out system for organ donation', which is explored by Niha Mariam Hussain from the University of Birmingham Medical School and Dhruv Soni from Barts and The London School of Medicine and Dentistry. Continuing with the theme of health controversies, Niha Mariam Hussain and Sanjeev Chaand Sharma from the University of Birmingham discuss the population-level intervention of flour fortification with folate to prevent cases of spina bifida and its complications. Flour fortification has already been introduced in the United States, and the British government will soon be considering its position.

Looking ahead to future advances, Dominic Atraszkiewicz from University College London, summarises the current role of deep brain stimulation in the management

of Parkinson's disease. This novel intervention has the potential for development in the coming decade.

Finally, as healthcare professionals, how do we react to a patient death? Often, we are too busy to process the emotion from the event. In her insightful reflection, Marisol Vasquez discussed the impact that a patient's death can have on healthcare professionals and the role that empathy can play in medical training. We also hope that this is an area that will hold an important position in medical curricula in the 2020s.

As always, we extend our gratitude to our hard working and dedicated editorial team, peer reviewers, faculty advisory board and our publisher, Cardiff University Press. Over the past four years, this team has produced seven issues of The British Student Doctor – and we look forward to continuing our mission to engage medical students in evidence-based medicine and publishing into the years ahead.

We hope you find this January 2020 issue interesting and inspiring, and we wish you and our planet health and success for this new decade.

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Editorial

Guest Editorial : Open access publishing

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There may be truth in the old saying, 'necessity is the mother of invention'. But sometimes it is hard to recognise necessity. For instance, when a small group of us were first pushing the idea of developing a new, free, online, open access, university press, one question we sometimes faced was 'why?'. The sense in some disciplines was that there was no need for such a development – "things were fine as they are". Moreover, sometimes we were told that free online academic publications could and would never catch on within some disciplines, such as medicine and the sciences. This is because such fields are predominantly structured by well-established, well-respected, well-funded and accordingly very expensive academic journals. Nonetheless, once we established Cardiff University Press as 'diamond' open access published, The British Student Doctor Journal quickly joined us.

The word 'diamond' in 'diamond open access' refers to the highest pinnacle of open access publishing. In diamond open access, there are no charges to either readers or authors. It is quite a rare model, because there are many costs involved in publishing – especially costs of time, commitment, professional expertise and technical knowhow. Someone has to bear these costs. So, while more academic publishers now offer content that is free online for readers, they often fund this by charging authors themselves for the privilege of publishing in their pages. Cardiff University Press does not do this, and nor does The British Student Doctor Journal and our other journals.

I regard such an orientation and a commitment as remarkable. When we were first proposing Cardiff University Press to various committees and groups around Cardiff University, we were on occasion laughed at and even somewhat scoffed by those working within from some fields. I never managed to establish the exact origins or orientations of such negative responses to the idea of Cardiff University Press. But I have a theory. This boils down to the mindsets fostered by the publishing models that structure different academic disciplines, and an inability or reluctance to imagine any alternative. After all, some disciplines, such as medicine and the sciences, are often dominated by large, well established and well-funded journals. And these venerable journals seem to serve scholars, researchers and practitioners well. So, why would anyone need to change things? Why innovate? Why invent? Why do anything different? What is the necessity?

To my mind, the reasons are principally ethical, although they are often economic, and sometimes abut with issues that are arguably political.

One of my own first questions has long been: why should academic research and other forms of scholarship be disseminated by commercial publishers for profit? If there are other means available to bypass commercial exchange, shouldn't these means be explored?

Secondly, I have long felt that universities have an ethical obligation to communicate and connect up with other institutions and areas of culture and society. Notice that I did not say "service the needs of the knowledge economy" or anything that might imply that scholarship should be beholden principally (or at all) to economic

imperatives. Rather, I am simply saying: university researchers should be open to communicating as freely and openly as possible with the wider world, for any number of reasons and in any number of ways.

Beyond connecting with our own local communities (however 'local' and 'community' are defined), there are larger considerations too. For instance, although few among us may actually feel wealthy, we must remember the massive disparities in wealth distribution across societies and around the world. Those who work in a university in any country are likely to be comparatively better off than many other people in that same country. But there is also a hierarchy of wealth – if not an explicit 'class' system – across all aspects of university sectors, both nationally and internationally.

Put bluntly, some universities are considerably richer than others. This means that while some universities can pay for access to all kinds of expensive journals, others cannot. Moreover, richer universities can also pay for their staff to publish in the kinds of journals that increasingly require authors to pay for their articles to be published.

This is not the open access model used by Cardiff University Press. The model in which authors have to pay a charge risks entrenching a global class hierarchy of universities, in which research from less affluent institutions is effectively marginalised or even excluded. Rather than this, Cardiff University Press does something very different. We do not charge authors or readers to publish in our journals. Our aim is to be as open access as we possibly can, because we believe this is the best possible model for universities to adopt.

The British Student Doctor Journal is admirably attuned to this ethos. At a time when there was no 'need' to orient itself along such ethical and community-focused lines, the editors chose open access. To me, this speaks directly to the highest principles not only of academic but also medical research integrity. It feels aligned with the founding ethos of the UK's National Health Service, and with the very idea of the university's fundamental obligations to establish and disseminate knowledge freely and openly. The very word 'university' derives from a Latin phrase meaning 'community of teachers and scholars'. Like other open access academic journals, The British Student Doctor Journal is not merely 'servicing the needs' of such a community, but actually helping to invent and sustain it.

Professor Bowman is Professor of Cultural Studies at the School of Journalism, Media and Culture at Cardiff University, as well as a founding member and current Chair of the Editorial Board of Cardiff University Press, the diamond open access publisher of The British Student Doctor Journal.

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Editorial

Climate action: no time to waste

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Conflicts of interest: Hilary Graham is part of the Lancet Countdown on Health and Climate Change and professor of health science at the University of York. She writes here in a personal capacity.

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Modern societies are transforming the planet on which human life depends – and for the worse. BSDJ readers have a key part to play in climate action, both as citizens and as members of the medical profession. In thinking about these dual roles, it is important to remember today's children and those yet to be born lack direct representation in the decisions that will determine their future: in elections, in the structures of local and national government and in policy-making. In all these key public domains, they rely on adults to speak up on their behalf.

Climate change matters to everyone

In the 19th century, the harnessing of fossil fuels drove the industrial revolution in the UK, Europe and North America. In the 20th and 21st century, the development of the global economy has similarly been powered by fossil fuels. The burning of coal, gas and oil produces carbon emissions which increase atmospheric CO_2 and, in consequence, global temperatures. All three - carbon emissions, atmospheric CO_2 and global temperatures – have reached record levels and are continuing to rise. These climatic changes have been combined with other human-induced changes of the planet, including to its oceans, forests and cryosphere (the frozen polar regions, glaciers and mountain icecaps).

Climate change can no longer be dismissed as 'not real'. It is happening fast and having increasing human impacts, particularly on communities – like the small island states – who have contributed least to it. Climate change has many faces, including the spread of climate-related infectious diseases and extreme weather events like droughts, wildfires, storms and floods. In the UK, climate change is making its presence felt through the increasing frequency and ferocity of flooding, an experience taking a heavy toll on people's wellbeing and their sense of security in the world around them.

Time to address what is rightly called the climate emergency is very short. Mean global surface temperature has risen by 1° Celsius above the pre-industrial period, with most of the increase occurring in the last forty years. An increase above 1.5°C would take the human population to a place where people's health and livelihoods are under increasing threat and where we risk bequeathing to today's children a climate system beyond their control. To avoid such a future, global CO_2 emissions need to be reduced by half by 2030 - by the time a child born today reaches their 10th birthday. Emissions need to reach net zero by 2050 – by the time that child could expect to have children of their own.

Climate change matters to the medical profession

Safeguarding human health is at the heart of medicine. General Medical Council (GMC) guidance on Good Medical Practice spells out the doctor's fundamental duty to 'protect and promote the health of patients and the public'. The same duty underpins Faculty of Public Health (FPH) guidance for those seeking a career in public health. As people's anxieties about climate change increase, the GMC guidance on 'listening and responding to patient concerns' and the FPH's requirement that 'you must respond, when and where you are able, in emergencies' take on new and deeper meanings. Doctors for Extinction Rebellion (1) and the climate-focused work of Medact (2) are two examples - among many - of how members of the medical profession are responding to this call. In support, the BMA and the Royal College of Physicians have issued declarations of a climate emergency.

There are further reasons to support the medical profession's engagement in climate

action. The first is the large carbon footprint of the healthcare sector, a footprint which itself adversely affects people's health. A recent report estimates that the global healthcare sector is responsible for 4.4% of global net emissions and concludes 'if the health sector were a country, it would be the fifth-largest emitter on the planet' (3). The report lays out actions to enable the sector to achieve net zero emissions before or by 2050, a goal integral to Health Care Without Harm (HCWH), the international NGO which co-authored the report. HCWH supports the Global Green and Healthy Hospitals Network (4) that provides local entry-points for healthcare workers (for example, via UK hospitals and NHS Trusts) to be part of the climate movement.

Secondly, the medical profession is a trusted authority. Along with nurses and pharmacists, doctors are consistently rated highest for their honesty and ethical standards. In contrast, recent decades have seen declining public trust in governments and politicians and, in the UK, a widespread perception that neither the government nor the media present official statistics honestly. In this context, the medical profession are among the few trusted 'truth speakers'. As part of their duty to protect everyone's health, they have become active partners in public debates about climate change, for example via the Lancet Countdown on Health and Climate Change (5).

2020 is widely regarded as crunch time for effective climate action. In November, the countries signed up to delivering the 2015 Paris Agreement on climate change will be meeting in Glasgow (6) to review their ambitions to reduce their carbon emissions by 2030. Strengthening these ambitions – by a factor of five - is required to keep the global temperature rise below 1.5°C. Public engagement is absolutely essential to build and sustain pressure on governments to act now and act decisively to keep their populations safe. As citizens and as health professionals, BSDJ readers have a vital role to play.

Hilary Graham is part of the Lancet Countdown on Health and Climate Change and professor of health science at the University of York. She writes here in a personal capacity.

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Discussion

What is the impact of climate change on infectious disease?

DISCUSSION

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ABSTRACT

The world is warming at an alarming rate; in October 2018 the Intergovernmental Panel on Climate Change reported a 1°C human-induced warming since the pre-industrial period and a current rise of 0.2°C per decade. The UN secretary-general stated that 'climate change affects every aspect of society, from the health of the global economy, to the health of our children'.

Many in the field hypothesise that the changing climate will lead to an increase in the size of vector-borne disease transmission zones, an appearance of tropical disease in temperate regions and the emergence of native species that have the capacity to transmit tropical pathogens. Although a large proportion of the discussion surrounding climate change and infectious disease focusses on malaria, concern exists surrounding other vector-borne diseases such as tick-borne encephalitis and Lyme disease, and water-borne and respiratory infections. The true effect of climate change on infectious disease is elusive and heavily debated; a comprehensive model including not only temperature, but precipitation, humidity, and extreme weather events is needed to properly evaluate the impact of the warming climate on communicable disease. Whilst the intricacies of the climate and infectious disease is not fully understood, it is important to remember that those most vulnerable to communicable diseases are those living in poverty, so any climate induced increase in transmission will only seek to worsen the already apparent health inequality worldwide.

Introduction

The relationship between climate change and infectious disease is a topic of polarising debate, especially when it comes to human pathogens - socioeconomic drivers, vector-control methods, antimicrobial treatment, and infrastructure can all mask the true climate effect. The relationship between climate and infectious disease is non-linear, with certain factors increasing disease transmission and others limiting it, making the true trajectory difficult to elucidate.

The life-cycle and transmission of many pathogens is tied to climate, whether that be an increase in water-borne disease after extreme weather events or the seasonal cycle of flu outbreaks. Climate has a greater association with disease caused by pathogens that spend part of their lifecycle outside of the host, exposed to the environment, whilst disease transmitted directly between humans has fewer climate associations. (1) A recent assessment of over 150 high-impact European pathogens concluded that 66% have at least one climate affected variable that impacts disease occurrence and up to 37% of disability-adjusted-life-years arise from human infectious disease sensitive to climate. (2) Nonetheless, the method used to prioritise pathogens for inclusion in this assessment has a number of limitations, including under-representation of newly emerging diseases and bias in results due to trends in interest in diseases. Evidently, there is a relationship between many infectious diseases and the climate, but how a warming climate will impact these pathogens is up for debate. A seminal review published in Science in 2002, by Havell et al, concluded that warming can increase pathogen development, survival rates, disease transmission, and host susceptibility; (3) however, these conclusions were drawn from data on both marine and terrestrial biota with cholera the only human disease included. Since the publication of the Havell et al review, numerous studies have explored the impact of a changing climate on individual infectious diseases or mechanisms of transmission, but there is still no consensus on the overall impact of climate change on infectious disease within the human population.

Vector-borne disease

Vector-borne infections are the focus of research when it comes to climate change and infectious disease, and dominate the conversation surrounding the topic. Broadly, there are three expected threats from vector-borne disease under a warming climate: increased risk from endemic disease due to changes in temperature and rainfall, change in geographic range of vectors, and the appearance of exotic diseases in temperate regions due to increased climatic suitability. (4) Although much attention is focused on the threat of invasive species, there is also a risk from native species which may have the potential to become vectors for tropical disease. The endemic UK mosquito, O. Detritus, has been shown to be a capable vector for exotic flaviviruses (a genus that includes West Nile Virus and Zika) when under specific temperature conditions. (5) Limitations of this study include unrealistically high temperature conditions that do not mimic current UK climate and a small sample size. Nevertheless, it is an early contribution to knowledge on the competence of native vectors. Understanding the risk posed by native species in the transmission of exotic pathogens is essential in predicting climate-mediated change, especially in temperate regions, such as the U.K, where the impact of vector-borne diseases is currently relatively small.

Malaria is already a great concern to public health. The WHO predicts it is likely to be the vector-borne disease most sensitive to long-term climate change. (6) Malaria is caused by the Plasmodium parasite, a group of single-celled organisms that use mosquitos as mobile vectors, ,infecting the human host via the mosquito feeding. Plasmodium Falciparum accounts for approximately 75% of human malaria cases and has a high rate of mortality, whilst Plasmodium Vivax accounts for a further 20% of cases and is traditionally thought to cause a milder form of disease. Due to its prevalence in lesser-developed regions, P. Falciparum is often diagnosed clinically; the potential for over-diagnosis can therefore make the true pattern of transmission hard to elucidate.

Malaria is intertwined with many aspects of climate. Research from endemic areas demonstrates clear seasonal variation in disease transmission and analysis has shown that the malaria epidemic risk increases five-fold in the year after an El Nino event, although this may be confounded by human behavioral changes or infrastructure inadequacy. (7) The prevailing forecast for the trajectory of malaria transmission is global expansion, particularly into regions of higher altitudes. (7) However, an alternative approach, using statistical modelling rather than historic biological data, suggests that overall change to malaria transmission due to climate change is likely to be relatively small and any expansion in disease range would be offset by contraction in other geographic locations. (9) A major disadvantage of these models is that they only account for malaria caused by P. Falciparum and neglect malaria caused by other species, including P. Vivax which was once endemic to Northern Europe and requires much lower temperatures for transmission. Therefore, the risk of malaria in a warming climate may be vastly underestimated in areas where P. Vivax poses the greatest risk. Additionally, evidence suggests recent invasion of other mosquito-borne diseases in temperate regions, such as Chikungunya, Dengue fever and West Nile Virus in Europe. It is likely that even if there is no net change to the size of the area suitable for mosquito-borne disease transmission, the impact on previously unaffected communities will be significant. (1)

Mosquitos are not the only vector thought to be vulnerable to climate effects; the possible increase in cases of tick-borne encephalitis (TBE) in Europe is also cause for concern. Viral transmission of TBE occurs between cofeeding larval and nymphal ticks, and synchrony of this feeding is associated with milder winter climates. (10) It is therefore thought that by increasing tick synchrony, climate warming may increase rates of transmission and promote the selection of more virulent strains. (10) This theory is claimed to explain the increased incidence of TBE in Sweden since the 1980s, with a prominent study published in the Lancet reporting a significant relationship between two consecutive mild winters and an increase in disease. (11) However, authors do not account for an increase in TBE vaccination since the mid-1980s or the increase in education and awareness surrounding ticks, meaning the links between climate change and disease incidence may be underestimated. Unsurprisingly, there is division amongst researchers as to whether climate change is the true cause of the increased incidence of TBE in Europe; alternative explanations include changes in land-use, increase in human population in tick-endemic areas, wild-animal population

changes, and increased tourism. Another tick-borne illness with an increasing incidence in Europe is Lyme disease, the most common vector-borne disease in temperate climates. (1) The field is similarly divided as to whether climate change is solely responsible for the increase and poleward spread of disease. Increased surveillance programmes and predictive modelling is needed to better assess the threat from tick-borne infection.

It is difficult to elucidate the impact of climate change on vector-borne disease due to challenges in modelling the multiple possible effects of a changing climate on pathogens, vectors, and host susceptibility, with climate warming often increasing some elements of transmission and decreasing others. During an outbreak of P. Vivax malaria in Greece in 2012, spatial modelling was used to highlight areas of susceptibility based on land temperature and elevation, and ultimately helped to guide the public health response. (12) The major limitation of this technique was the fact it only accounted for environmental suitability, rather than incorporating actual data from to vector surveillance or disease incidence. The success of this approach does however demonstrate that even rudimentary models can be useful in directing healthcare responses, initiating vector control, and increasing awareness amongst at-risk populations. Although the outbreak reported in Greece was amongst economic migrants from malaria endemic areas, the spatial modelling demonstrated may be a useful tool in mapping changes in climate suitability over time. Socioeconomic and public health factors such as vector control strategies, vaccination initiatives, inconsistent diagnostic methods, and human migration may mask true patterns of vector-borne disease transmission.

Water-borne disease

Research surrounding vector-borne disease and climate change focusses on a temperature change as a possible driving force behind an increase in disease transmission, however, a warming climate will also affect precipitation, humidity, and the frequency of extreme weather events. Climate change is expected to alter the water cycle and - water-borne enteric diseases are among the expected health implications of this climatic shift. (13) Diarrheal disease already accounts for 10-12% of all deaths in children under the age of five, so even a small increase in diarrhea risk will have a substantial impact on the global disease burden . (13) The WHO estimate that climate change could be responsible for between 20,000 and 86,000 deaths in children globally between the years 2030 and 2050, under a range of socioeconomic growth models. (1) This assessment does not account for the likely co-morbidity of water-borne infection and malnutrition, or the different temperature profiles of individual pathogens. Despite these limitations, it does begin to expose the possible devastation climate change could cause via diarrheal disease.

The first systemic review of water-borne disease and climate change in 2016 showed that heavy rainfall and flooding significantly increase the rate of water-borne disease outbreaks, often due to contamination of the drinking water supply. (13) Additionally, it demonstrated that an increase in temperature may precipitate increased outbreaks of bacterial diarrheal disease whilst having a negative correlation with viral diarrheal disease. This tendency to promote bacterial and inhibit viral disease is possibly

explained by the vulnerability of viruses to higher temperatures compared to more complex survival mechanisms employed by bacteria, including increased bacterial load in hosts and expression of virulence genes. (13) Despite these convincing results, reporting bias - with over-representation of certain geographic regions and surveillance programmes - limits conclusions that can be drawn. Unlike the impact of temperature and precipitation, the impact of drought on water-borne disease is unclear, with sparse and variable epidemiological data. The research is mixed, with some studies demonstrating a clear association between drought and diarrheal disease, possibly explained by increased concentration of pathogens in water sources, though other groups reject this claim. (14) (15) Variability between drought events may explain these inconclusive results; as such, it may be useful to stratify data based on water source used during the drought, length of drought, amount of rainfall at the end of the drought period, etc. Though temperature, flooding, and heavy rainfall are all risk factors for water-borne disease, more research is needed to fully understand the relationship between drought and water-borne infection.

Cholera, a disease caused by the water-borne bacteria Vibrio Cholerae, is of heightened interest in the conversation surrounding climate and water-borne disease as it is highly contagious and can be fatal within hours in the most severe cases. V. Cholerae is naturally present in estuaries, rivers, and coastal bodies of water, forming a commensal relationship with plankton for its survival and replication. Coastal cholera infection has been associated with plankton blooms, increased sea surface temperature, and extreme storms. (10) Moreover, analysis of monthly data points for cholera cases in Dhaka, Bangladesh between 1980 – 1998, showed a variability in incidence correlating with the frequency of the El Nino weather pattern. (16) However, this is not sufficient evidence to conclude that increased temperature directly increases cholera transmission and alternative explanations consider changes to Himalayan snowpack melting, sanitary conditions, and human interactions with water sources. (16)

The increased risks of cholera in endemic areas is one concern, but there is also evidence of poleward spread of Vibrio outbreaks in cold and temperate regions, such as Chile, Northwest US, and Spain. (17) Vibrio bacteria preferentially grow in warm, low salinity sea water; increased precipitation reducing salinity in estuaries and wetlands and an increase in temperature due to climate warming may explain how new areas of suitability are emerging in high latitudes. (17) The Baltic sea is of particular interest in the study of Vibrio diseases, it is one of the fastest warming marine ecosystems worldwide and long-term warming and extreme heatwaves have been related to an increase in Vibrio infections. (17) Predictive models suggest that for every 1°C increase in sea surface temperature, cases of Vibrio illness in the Baltic regions could increase two-fold. (17) Despite clear changes to the patterns of Vibrio infections, conclusive evidence of a climate related cause remains contentious. This is in part due to lack of full epidemiological data and the possible attribution of cases of Vibrio infection in high latitudes to sporadic cause. Cholera and other forms of Vibrio infection appear to be susceptible to climate change and further research is needed to exclude alternative drivers such as changes to human interaction with water sources and changes in coastal population density. (17) Looking to the future, it would be helpful to

establish a centralised reporting system for Vibrio infections that is consistent between geographic areas and allows analyses alongside climate data, with the ultimate aim of devising an early warning system to advise public health measures.

Respiratory infection

Respiratory infections often follow seasonal cycles of transmission, but whether climate change will impact transmission patterns is purely speculative, with insufficient evidence to draw meaningful conclusions. Pneumonia and influenza are significant contributors to the global burden of disease, with severity and transmission increasing in winter months. Therefore, as suggested by the European Respiratory Journal, climate change could actually have a beneficial effect, with warmer winters reducing disease frequency. (18) Interestingly, an Australian study showed that the most important variable in determining frequency of childhood pneumonia is the temperature drop between neighboring days, suggesting that oscillations in temperature may have the potential to drive increased transmission of respiratory infections. (19) Any conclusions drawn on how respiratory infections are affected by climate change are currently limited and lacking in robust evidence; extensive epidemiological analysis is needed to elucidate true patterns of disease transmission, as well as consideration of other direct and indirect confounding factors such as air pollution, risk of flooding, and changes in human behavior. A better understanding of the relationship between a changing climate and respiratory infections is essential, as such diseases can spread rapidly and cause a huge burden on public health.

A pathogen may emerge as a new public health concern due to changes in its transmission or life cycle, or mutualistic microorganisms may become pathogenic due to changes in host susceptibility to infection. Although there are many causes of new pathogen emergence, it is important to consider the implications of a changing climate on the development of new diseases. Parachlamydia Acanthamoebae is an emerging human respiratory pathogen that relies on warming for the transformation from endosymbiotic to lytic within host amoeba in the human nasal passage, and ultimately conversion from a commensal to pathogenic species. (20) Despite having a temperature component for pathogenesis there is currently no research to determine whether climate change has an impact on disease transmission. Predicting emergence of new diseases is virtually impossible, but it may be useful to develop a database of emerging pathogens with climate dependency in order to increase preparedness for unexpected disease patterns and outbreaks.

Global health

It is important to remember that one of the biggest risk factors for infectious disease is poverty and that any changes to infectious disease burden due to climate change will disproportionally affect the poor. Developing nations are already most at risk from climate change due to their geographical locations, their high dependency on natural resources, and their limited ability to adapt to climate changes. An increase in infectious disease transmission would therefore compound existing adversity. Over 1 billion people live in poverty; in order to protect these communities and alleviate health inequality we need urgent development of intervention strategies and public health initiatives, and continued research and investment to establish the true potential

impact of climate change on infectious disease. (21)

Conclusion

Given the evidence for the sensitivity of many pathogens to climate, it is highly likely that at least some diseases will be affected by climate change. As it stands, the most conclusive evidence is on the link between increased frequency of diarrheal disease and climate warming. The most divided debate surrounds the changes in transmission pattern of vector-borne disease, although many argue there is strong evidence supporting a climate-related cause. Epidemiological data relating climate change and respiratory infection is currently lacking, as is evaluation of the potential of native species to transmit infections, and predictions surrounding the emergence of new pathogens. Additionally, there is a pressing need to develop a model that encompasses all possible climate related diseases and considers not only changes in temperature, but also precipitation, humidity, extreme weather events, and indirect factors like loss of land, migration, and air pollution. The true effect of climate change on infectious disease is notoriously elusive and demands careful consideration of all of the socioeconomic, geographical, and meteorological variables.

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Discussion

Should obesity be considered a disability?

DISCUSSION

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ABSTRACT

Obesity is a growing concern in the 21st century. With almost a three-fold increase in incidence since 1975 worldwide, it is important to address a new concern, should obesity be classified as a disability? This raises a series of ethical and practical issues that need to be taken into consideration when exploring the best way to provide treatment and protection in society for obese individuals. This begins with the very definition of obesity itself. It is equally important to consider how to define a disability; several models have been suggested, which further adds to the complex nature of the problem. These include the biological model, the psychosocial model and the medical model. There are many arguments for and against ruling obesity as a disability.

Should Obesity Be Considered A Disability?

According to the World Health Organization (WHO), obesity is defined as an abnormal accumulation of excess fat that presents a great risk to the health of an individual. A BMI of over 25 classes an individual as overweight, whilst a BMI over 30 considers them obese. (1) Worldwide, the incidence of obesity is increasing, having nearly tripled since 1975. (2) In 2016, more than 1.9 billion adults were classed as overweight, with over 650 million considered obese. (2) The growing incidence of obesity therefore highlights the need for more discussion around whether or not obesity should be termed a disability.

A disability is defined under the Equality Act 2010 as a physical or mental impairment that has a substantial negative effect on a person's ability to complete normal daily activities, for over 12 months, where impairment is described as an abnormality in the structure and function of the body. (3) Obesity fits in with this definition of a disability, and gives rise to various arguments for and against this classification. In 2014, the European Court of Justice ruled that severe obesity could be classed as a disability if a person's ability to perform in the workplace is limited. This mainly includes the morbidly obese, defined as those with a BMI of over 40. (4, 5) This ruling followed the case of Karsten Kaltoff, a Danish child-minder who believed he was unfairly dismissed for being 'too fat' after working for the Municipality of Billund (Denmark) for 15 years. (4) After bringing a case of discrimination against his employers, the European Union Court of Justice ruled that factors that hinder "full and effective participation at work" could be treated as a disability, and therefore these individuals are protected under the European Equal Treatment Framework Directive. (4) This suggests that attitudes are already changing, with more organizations seeing obesity as a disability. By raising awareness of this ruling, we will be able to reinforce that it is unlawful to discriminate against those who are obese.

Models of Disability

The term disability can also be defined through various models, most notably, the medical model and the social model. The medical model states that a disability is a result of a disease, health condition or trauma that interferes with an individual's cognitive function or physiological ability to perform activities of daily living. (6) This definition therefore looks for a way to 'fix' the problem or at least manage it as best as possible to improve the patient's quality of life. (7)

The social model, on the other hand, is a model that has been developed by the disabled that states that the definition of a disability is not identified by the medical condition but more the attitudes of society, where there are many social barriers in place that essentially 'disable' people more than the medical condition itself. (8) The social model was developed in the 1980s and aimed to address the failure of society in considering the needs of those less able. (8) It was therefore more widely accepted by the individuals that it affects.

A newer model of disability termed the biopsychosocial model has been introduced, stating that the medical and social models are not sufficient in defining disability. It

offers a more complex classification and posits that a disability encompasses biological, psychological and social factors with complex interactions between these. (9) It is therefore argued that this is the model of disability that we should be adopting in order to provide multi-dimensional care to the affected as it combines elements from both the medical and social model and puts the patient first.

Obesity as a Disability

One of the main arguments for the classification of obesity as a disability stems from the assertion of the 2010 Equality Act that any condition that physically or mentally impairs an individual for over 12 months should be considered a disability. (3) Using this definition, obesity impairs the ability of an individual to complete their daily tasks such as tying shoelaces or climbing stairs. These difficulties last longer than 12 months and significantly hinder daily life. By this definition, obesity can be defined as a chronic condition and much like most traditional disabilities; cannot be 'cured' overnight.

Obesity as a Self-Inflicted Condition

A major argument against the classification of obesity as a disability is the claim that obesity is a 'self-inflicted' condition. This stems from the belief that overweight individuals are 'lazy' and 'undisciplined' and should not be encouraged to continue as they are. This belief may have originated from the portrayal of the obese in the media and further worsens the stigma associated with the condition. The combination of a sedentary lifestyle and an increased calorific intake accelerates the onset of obesity. Some argue that it would be unfair to classify obesity as a disability when the obese individuals have not made efforts to prevent or control their condition. By improving lifestyle factors, such as diet and exercise, obesity in most cases can be prevented or managed, although this is not an option available to those with other more classically defined physical disabilities. In addition, if individuals with other 'self-inflicted' conditions such as alcoholics and heavy drug users are not considered disabled, why then should the obese? By starting to accept obesity as a disability, we may open the gate to the classification of other 'self-inflicted' conditions as a disability, increasing their societal acceptance. This complicates an already complex topic, fuelling debate.

However, obesity is not always a 'self-inflicted' condition. For example, there are certain medical conditions where weight gain is a common side effect or presenting complaint. These include binge eating disorders, Cushing's disease and polycystic ovarian syndrome. (10) Side effects to many medications also promote weight gain and an increased appetite, including insulin, anti-psychotic medications and anti-depressants, which can all be used to treat conditions associated with an increase in weight themselves. (10) There may also be rare genetic causes, for example Prader-Willi syndrome in which obesity and Type 2 Diabetes are the most common presenting features. Moreover, patients with musculoskeletal disorders may be physically challenged and find it difficult to exercise and keep fit. Immobility puts these individuals at higher risk of becoming obese; a factor that is not necessarily within their control. In addition, those with psychosomatic disorders have a higher chance

of overeating, resorting to comfort eating, with low motivation for physical activity, acting almost as a form of self-harm.

In addition, obesity can be described as a heritable trait influenced by the complex interaction between genetics, epigenetics, metagenomics and the environment. (11) According to John Wilding, a professor of medicine at the University of Liverpool, and Vicki Mooney, executive director of the European Coalition for People Living with Obesity (EASO), 40-70% of the variability in weight is inherited. This evidences the theory that obesity is strongly influenced and controlled by epigenetics, where body weight, fat distribution and the risk of complications are not necessarily self-inflicted. (11) External factors, beyond an individual's control may be to blame for their becoming obese. Because of these factors, obesity should be classed as a disability as it is not enough to class it as a 'self-inflicted' condition alone.

Stress and Obesity

Increasing appetite and weight gain can also be the result of societal pressures. Stress and emotional brain networks result in some individuals not being able to control their food intake. Stress stimulates the release of glucocorticoids and insulin, where glucocorticoids increase the motivation for food and insulin promotes food intake, and therefore, obesity. (12) This promotes an unhealthy relationship with food and increases the chance of a 'food addiction'. (13) This addiction has been compared to that of drug users struggling to cope with their drug use, where foods high in fats and sugars stimulate similar reward centers in the brain in the same way that common illicit drugs such as methamphetamine and cocaine do. (13) This merely suggests that affected individuals need help and support in the same way others suffering from addictions do. These results have led to the argument that obesity is not always a self-inflicted condition and so should be classed as a disability.

Changing Lifestyles and Obesity

Moreover, in today's society, many people feel that their busy lifestyle do not allow them to cook wholesome nutritional meals at home. Of 2,287 young adults surveyed in a study by Escoto et al., long working hours (> 40 hours per week) were associated with a greater number of time-related beliefs and behaviors regarding healthy eating, particularly in young adult men. (14) As a consequence, the diets of these men consisted of fast food and ready meals, both of which are high in sugars and fats.

According to a study by the Centre for Diet and Activity Research in 2014, the consumption of food outside of the home has risen by almost a third. (15) This, combined with an increase in the number of fast food shops, has contributed to an 'obesogenic' environment where individuals are easily able to turn to an unhealthy alternative to healthy foods. (16) However, this study only focused on the association between the rise in fast food shops and obesity in one geographical area, and not in the country as a whole. It is important to take this into consideration when drawing conclusions.

A busier lifestyle also likely results in less time for exercise. Studies have shown that both sedentary and active individuals have reported time as being one of the biggest barriers of regular exercise, ahead of money or knowledge. (17) These arguments suggest that certain factors contributing to obesity are not within our control. Protection of these individuals would therefore create a fairer society and avoid discrimination against those affected. The classification of obesity as a disability may also motivate individuals to work harder to improve their lifestyles and avoid being classed as disabled.

Complications of Obesity

Another argument against the classification of obesity as a disability is that obesity itself is not the disability, but rather the many complications that arise from obesity lead it to becoming one. For example, according to the International Diabetes Federation (IDF), 80 per cent of people with Type 2 diabetes worldwide are overweight or obese at the time of diagnosis. This explains why obesity is considered the largest modifiable risk factors for Type 2 diabetes. (18) In addition, a study by Zheng and Chen showed that overweight and obese patients were 2.45 and 4.55 times more likely to develop knee osteoarthritis respectively. (19) Obese individuals are also more likely to develop hypertension, sleep apnea, gout, metabolic syndrome, cardiovascular incidents, gallbladder disease, gynecological problems amongst others. (20) These complications are the disabling features of obesity; therefore some argue that obesity itself should not be considered the disability. However, by recognizing obesity as a disability, interventions can be put into place earlier, before the development of further complications.

Protection of Obese Individuals

The incidence of workplace discrimination continues to increase. A recent study from Yale University has shown that there has been a 66% increase in job discrimination, where the obese are less likely to be hired when compared to other factors including ethnicity, physical disability or sexual identity. (21) Moreover, the same study showed that the obese are less likely to be promoted regardless of their skillset. Carr and Friedman found that those with a BMI over 35 were 84% more likely to report job-related discrimination as a person of average weight. (22) Moreover, several studies have shown that the obese earn lower wages than their normal-weight counterparts, especially in women involved in jobs with customer interaction. (23) By classifying obesity as a disability, individuals would be protected in the workplace under employment and discrimination law. This may reduce the stigma associated with obesity. However, the rise of an obese workforce creates a hidden cost burden from losses in productivity. According to a recent study by Tatiana et al., absenteeism due to obesity accounts for 6.5% to 12.6% of total absenteeism in the workplace, with up to 1.1 to 1.7 extra days missed annually compared to normal weight employees, contributing to an estimated $8.65 billion per year in lost economic value in the US. (24) Further work needs to be done to protect the obese but also ensure that this loss in productivity is controlled.

On the other hand, with obesity becoming a disability, groups such as the International Size Acceptance Association and Fat Acceptance at Every Size have expressed concerns that it may open those affected to further discrimination, (25) and may hinder a person's inclination to improve their lifestyle, as it may negatively affect their mental health and increase acceptance of their condition to view it as something that they cannot change. This is one of the main problems with using the social model of disability in the case of obesity. By adopting the social model, once society has accepted that these individuals are obese, they are less likely to change their behaviour, and are more likely to carry on living an unhealthy sedentary lifestyle. This further adds to the growing problem by increasing the incidence of obesity in those it already affects. One could argue that advocates of the social model have no desire to improve their health and are therefore using this model to shift the blame on to others. By reducing individual responsibility, more individuals are likely to follow this pattern and contribute to increasing pressures in society. Moreover, a recent study by Luck-Sikorski et al. explored the opinions of 1,000 obese individuals in Germany and reported that only 38.2% agreed that obesity should be classed as a disability, where heavier participants more strongly agreed. (26) These findings support the European Court of Justice's ruling where only severe obesity should be considered a disability. However, as less than half of the German population affected agree, one could argue against the classification of obesity as a disability as it may not be in the best interest of those it affects. However, this study showed a snapshot of opinions from one European country; international studies should be conducted before any definitive conclusions are drawn.

Conclusion

Increasing numbers of individuals are being classed as 'obese' according to the World Health Organization (WHO). Nowadays, there is much debate over whether obesity should be classed as a disability with reasonable arguments both for and against the case.

In current circumstances, it is important to ensure obesity is accepted and people are not discriminated against for being obese. However, it is equally important to encourage and promote healthier lifestyles that improve individual health, since at the heart of all of these arguments, individual health should come first. This is additionally important with the need to reduce some of the strain on the NHS. By classifying obesity as a disability, we would be able to protect obese individuals in the workplace and in daily life by creating a fairer society. It would also reduce the negative connotations around obesity and may motivate individuals to further improve their lifestyle. Moreover. the European Court of Justice has already classified obesity that is severe enough to limit performance in the workplace as a disability, (4) suggesting that only those classed as morbidly obese should be protected under employment and discrimination law on a case dependent basis. As this has only been ruled in 2014, it is too soon to tell whether the right decision was made, however it is a start in recognizing obesity as the disabling condition that it is. Overall, in the coming future, it will be interesting to see where attitudes of society lie and whether a firm ruling on this debate will arise.

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Education

Max and Keira's law: a discussion surrounding the advantages, disadvantages and alternatives to an opt-out organ donation system in the UK

EDUCATION

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ABSTRACT

Relevance:

To increase the number of organ donors in England, the government will implement Max and Keira's Law: all adults over the age of 18 living in the United Kingdom become potential organ donors after their death, unless they choose to opt out. The law will be employed by spring 2020. Despite there being presumed consent for the retrieval of organs, families of the deceased will still be contacted to recheck consent, and ensure that family wishes are upheld.

Summary:

Despite definite implementation of the law, there have been concerns over the presumed consent given for retrieving organs from the deceased; ignorance and lethargy from certain members of the public may mean that true informed consent can never be obtained when collecting organs. To combat this, expensive national campaigns would need to be launched to make the public aware of the new process, as well as educating them on how to opt out of the process if necessary. Regardless of these challenges, there are many advantages to the new law. Advantages include an increase in successful organ donations and transplant, as well as potentially an increased availability of organs for use in medical research, drug development and university teaching.

Take Home Messages:

Based on the advantages, the move to the opt-out system appears to be a sensible method to increase the number of organs available for use in medicine. Proposed alternatives such as xenotransplantation and 3D bioprinting have the obvious benefit of providing an almost infinite supply of organs. However, these alternatives remain in the preclinical stages, with ethical challenges and infection risks that need to be overcome before they can be used in hospitals.

By Spring 2020, the UK government will implement 'Max and Keira's Law, commonly referred to as an opt-out system. Everyone over the age of 18 in England will be assumed to have agreed to be an organ donor when they die. (1) The new system would not presume consent for the retrieval of organs whilst a person is still alive; however, individuals may still opt to be a living donor. All adults living in England will be on the organ donor list unless they have opted out by recording their decision not to donate, or are a part of a group excluded from organ donors. Excluded groups would include those who have or are suspected of having conditions such Creutzfeldt-Jakob Disease (CJD), Ebola, an active malignancy or are HIV positive. (2)

Currently, all countries within the UK except Wales have an opt-in system, where people are not considered as organ donors unless they sign up to the register, and express consent to donate. The opt-out legislation, which was first proposed in 2015, has been supported by several health regulatory bodies in the UK, most notably from the British Medical Association (BMA), who have supported the change by advising local MPs through parliamentary briefings about the positive impact that this life-saving change in law could bring. (3) Those excluded from having given assumed consent include minors, those who lack the mental capacity to understand and act on the new law, visitors to England and those who have lived in England for less than 12 months prior their death. Moreover, if a deceased individual has not opted out, family members will still be contacted and asked if they knew of any unregistered objection. (4) If there is a known objection from the deceased, or it becomes clear that the individual would not have consented, the organ donation will not go ahead; donation despite objections would ruin the trust between a doctor and the family and could reduce donation rates in the long term. Organ donation involves legal consent from the donor, which can be obtained when the donor is alive or dead with the assent of their next of kin. (5) Donation may be for research or transplantation into another person as a part of an operation to either save or improve the recipient's quality of life.

The main aim of an opt-out system is to overcome the shortage of organ donors currently available for transplant operations in the UK. Statistics taken from the 31st March 2019 show that there were 6077 patients in the UK waiting for a suitable organ on the active transplant list, yet only 1600 deceased donors listed in the UK. A further 1039 living donors are also listed. (6) Although it is possible for a single donor to donate multiple organs, the demand for certain organs over others, such as a demand for kidney and liver donors, would limit the number of organs retrieved per donor. In cases where an organ is available, challenges such as family refusal, poor condition of a donated organ, incorrect blood type or tissue match and adverse immune reactions leading to the body's rejection of an organ, may prevent a successful transplantation.

The proposed system would generate a greater number of potential organ donors, leading to a larger selection of organs that surgeons can use in operations, thus increasing the likelihood of finding a suitable match for someone who needs a transplant. (7) This could lead to a reduction of complications post-surgery, which benefits both the patient's health and the NHS financially, as less money would be spent in treating the complications of surgery, providing alternative treatments or arranging palliative care for someone with a life-limiting condition. This paper aims to discuss some of the advantages, disadvantages and alternatives to the implementation of 'Max and Keira's Law' in England.

The opt-out organ donation system has already been trialed in several European countries, including Austria, France, Greece, Italy, Spain and Sweden. Spain has the highest rates of organ donation in Europe, due to their implementation of presumed consent, along with additional non-legislative measures, such as financial incentives for those who do not choose to opt out. (8) Overall, when other determinants of donation rates are accounted for such as GDP per capita, literacy rates, religion and causes of death of donors, presumed consent countries have roughly 25–30% higher organ donation rates than opt-in countries. (9, 10)

Not all these countries have opt-out organ donation systems. Some countries such as Israel use a donation-allocation system to motivate individuals to donate organs. Israel's Organ Transplant Act 2008 introduced a priority point system, rewarding those who are willing to donate an organ with preferential status as a recipient of a donated organ. A person can gain priority points by signing a donor card, making an organ donation during their lifetime, being a first-degree relative of someone signing a donor card or by consenting to donate organs after death. (11) The act has led to a record number of signed donor cards and there has been a significant increase in the numbers of transplants in Israel.

Perhaps the greatest advantage to an opt-out system is that an increase in donated organs available for transplant would lead to more successful operations. Successful transplant allows patients to have a greater quality of life and return to their normal routine prior to their illness. For example, if someone required a kidney transplant, but was unable to find a suitable donor, they would have to undergo haemodialysis for multiple hours weekly. The average patient receives dialysis 18 hours a week, which extrapolates to the patient losing one month of every year out of their normal routine on dialysis alone. (12) Exhausting processes such as dialysis, can be eliminated through successful organ transplantation, and significantly improve patients' quality of life.

Organ donation may provide closure and consolation for the family of someone who has passed away suddenly or in a tragic manner. Normally, families would only be contacted if the deceased had signed up to the organ register; however, an opt-out system would mean that if the deceased's organs were needed, the family would be contacted in order to seek consent for the organs to be used.

Opening this new avenue for families who had not previously considered organ donation may provide some relief and alleviate their own guilt, as they know that their relative's death was not in vain.

Further satisfaction could be received as the family of the lost individual may also have the chance to connect to new individuals who were saved due to the organs of their loved one. A 1987 descriptive study that examined donor families' overall feelings about their organ donation experience found that of the 83% of families who returned a survey, a majority of donor families had positive feelings about organ donation because of their desire to help someone else and make something good come from their loss (13). It is important to note that not all families would feel consolation knowing that their loved ones' organs are being used to treat another individual. Families may grieve in different ways and the idea of organ donation may prolong the family's grieving period. In such cases, it would be important for clinicians to provide social and emotional support for families experiencing the organ donation process, and communicate sensitively when asking for consent. (14, 15)

An opt-out system would increase the number of organs collected for medical research or teaching purposes—when an organ is unsuitable for transplant or if a specific tissue type of organ is desired for research. Organ use in research could contribute to providing vital information about the pathology of a disease; and assist in the development of more efficacious drugs with improved safety profiles, as they would be tried on a donated organ before risking the safety of a participant in a trial. (16) Moreover, due to higher volumes of organs available, medical students have the potential to learn anatomy and human physiology using human specimens. Thereby allowing medical students to forge stronger links between anatomy and the pathologies observed during clinical placements. (17)

One of the main reasons for organ shortage is due to insufficient education on organ donation. (18) An opt-out system may engage the public on the issues surrounding organ donation, as the government would accompany the new law with a large awareness campaign to educate and assist people in making an informed choice. A study analyzing 383 medical students showed that prior to a specific lecture on organ donation, the request for further information about organ donation was significantly higher amongst students without a donor card compared to card carriers ($P < 0.0001$). However, after the lecture, the number of students requiring further information decreased to just 19% of the cohort ($P < 0.0001$). (19) Exposure to donated organs during teaching, and a specific lecture about donation significantly decreases the request for further information on organ donation and improves students' attitude to organ donation. With such teaching, students could share the information with friends, families and colleagues, thus helping to reinforce a positive attitude to organ donation from the general public. Hence, contribute to fewer people opting-out. (19)

Though a majority are in favour of organ donation, (20) the proposed system relies on the assumption that the public are informed about the process, and can decide what happens to their organs after death. This ignores the possibility that some members of the public remaining ignorant or lethargic with regards to finding out about donation; some would still be accustomed to a process where consent is given actively, rather than as a result of inaction. (21) This would ultimately result in several organs being retrieved without true informed consent, which may compromise the trust patients have in doctors and the NHS.

To ensure that most organs are donated with true informed consent, the government would have to spend more educating the public via national campaigns. In 2016-2017, the NHS Blood and Transplant (NHSBT) spent approximately £5 million on campaigns encouraging mainly those who are less aware of the need and the opportunity to save lives to donate. (22) A change in systems would mean that the NHSBT would have to spend a greater sum annually to address the entire population, rather than just targeted groups. The public would need to be informed that they are organ donors by default, and would need to be given the relevant information on how to remove themselves from the register if they choose to opt out. This information is too vast to be conveyed solely via social media; more expensive traditional media campaigns and expensive television and print advertising would be required. Therefore, requiring a larger budget to be allocated to the NHSBT from the government.

Another concern regarding the shift to an opt-out system is that an increased rate of organ donation does not necessarily equate to a proportional increase in successful organ/tissue transplants. Conditions such as osteopenia, obesity (due to inactivity/diet changes), cancer and autoimmune tissue rejection could develop in individuals after a transplant, and would negatively impact an individual's quality of life. (23) A study measuring the incidence of malignant tumours post-transplant operation showed that out of 674 solid-organ-transplant recipients (305 renal, 307 heart, 54 lung, 8 heart/lung), 79 malignancies were detected, representing an overall cancer frequency of 11.7% in recipients of organs which would further complicate their health. (24) Therefore, it could be argued that rather than shift to an opt-out system, the NHS should instead focus on preventing post-operation complications, and providing further care for organ recipients post-transplant.

As the opt-out system has already been accepted and will be enforced in the UK, future discussions will likely turn to how the new law can be successfully implemented, rather than whether the law is needed in the first place. Nonetheless, it is still worth exploring some of the more unfamiliar alternatives to organ donation such as xenotransplantation, genetic engineering and

3D Bioprinting organ tissue. All three alternatives offer an almost unlimited source of organs. Scheduling transplant surgery would no longer be dependent on the unpredictable availability of a donor human organ. This would allow clinicians to intentionally time the harvesting of an organ for immediate transplantation, as well as allocate immunologic pre-treatment of the recipient if necessary. (25)

Xenotransplantation involves transplanting tissues or organs between members of different species. Most xenotransplantation activity is still in the preclinical stage. Currently, there are significant ethical concerns surrounding xenotransplantation as it could mean livestock would be reared solely for organ harvesting, as well as the threat of spread of infectious diseases. Xenotransplantation would be accompanied with heavy immunosuppressive therapy, which can lead to fatal infections such as Hepatitis B and HIV in patients. (26) These challenges would have to be overcome before xenotransplantation can compete with organ donation.

A printed organ is an artificially constructed structure designed for organ replacement, produced using 3D bioprinting techniques. 3D bioprinting seems to be a feasible alternative compared to xenotransplantation. However, 3D bioprinting is relatively expensive due to a lack of equipment and resources, and needs to be further developed before it can be commonly used in hospitals. Another option is genetic engineering. Genetic engineering involves the modification of the phenotype of a living organism by manipulating its genetic material. The exact tissue type and blood type of an organ can be engineered, resulting in a much lower chance of rejection by the body of the recipient. (27) Since no humans or animals are used to obtain the organ, there are fewer ethical difficulties that need to be overcome when using genetic engineering. However, practicality and expense still remain an issue.

The UK's move to an opt-out system in 2020 means that all adults over the age of 18 living in the UK become potential organ donors after their death. Despite there being presumed consent for the retrieval of organs, families of the deceased will still be contacted to recheck consent and ensure that family wishes are upheld. Challenges to this new system include the possibility of true informed consent never being fully achieved. Advantages include an increase in successful organ donation and transplantation, as well as potentially an increased availability of organs for use in medical research, drug development and medical teaching. Based on the potential benefits, as well as the fact that proposed alternatives to organ donation are still in the preclinical stages, the move to the opt-out system appears to be a sensible method to increase the number of organs available for use in medicine.

Summary:

- The opt-out system will be implemented in Spring 2020 by in England.
- Those over 18 will be assumed to have given consent to be an organ donor unless they have opted out or are part of a group excluded from organ donation.
- The main aim of an opt-out system is to increase the number of organ donors available for transplant in UK.
- Countries with opt-out systems have around 25-30% higher donation rates than opt-in countries.
- Opt-out systems may also help facilitate research and teaching, providing information about pathology of a disease and drug development.
- Challenges of an opt-out system involve lack of true informed consent due to members of the public remaining ignorant or lethargic with regards to finding out about donation.
- Increased rate of organ donation does not always mean the number of successful organ and tissue transplants increase.
- Alternatives to an opt-out system include xenotransplantation, genetic engineering and 3D printing.

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Education

Mind over matter: an analysis of the mechanism of deep brain stimulation in the treatment of Parkinson's Disease

EDUCATION

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ABSTRACT

Relevance:

In a population of increasing longevity, neurological disorders are becoming more prevalent - placing a large strain on NHS resources and funding, as well as an emotional burden on those affected and their families. One such example is Parkinson's Disease (PD). This neurodegenerative disorder of the basal ganglia is characterised by a progressive loss of nigrostriatal dopaminergic transmission, commonly presenting as tremor, bradykinesia, rigidity, postural instability, akinesia, and impairments in cognition. Deep brain stimulation (DBS) has proven a successful approach to treating PD despite its mechanism of action being unclear.

Summary:

Three main problems of counteractive outcomes present when identifying a common mechanism of DBS within targets. Firstly, contrasting actions of DBS are required to explain DBS between targets, such as the GPe and GPi. Secondly, conflicting studies have reported both excitatory and inhibitory action of DBS within the same targets. Finally, the treatment has also paradoxically proven effective in treating hyperkinetic disorders, such as Dystonia. There remains no conclusive model for the treatment's mechanism.

Take Home Messages:

To deliver effective treatment and care, it is important for doctors to understand the mechanism of action of procedures they are performing. Hence further investigation into PD aetiology and DBS action is required.

In his 1817 Essay on the Shaking Palsy, James Parkinson first described the symptoms of the eponymous disease - distinguishing resting tremor (a pill rolling action) from essential and intention tremors. It was not until the turn of the twentieth century that attempts were made to target Parkinson's Disease (PD) via surgical intervention; however, many were unsuccessful due to hemiplegia often being induced. In 1940, Russell Meyers pioneered basal ganglia lesioning in PD treatment, reporting improvement of both rigidity and tremor. In 1947, Ernest Spiegel and Henry Wycis lead a shift of treatment towards electrical coagulation procedures on the basal ganglia and thalamic nuclei. And in 1952, the implanting of electrode contacts into subcortical nuclei began. (1) This would ultimately become deep brain stimulation (DBS).

However, this work was soon overshadowed by the discovery of dopamine's modulatory effects by Arvid Carlson and colleagues in 1957. Three years later, a deficit in striatal dopamine concentrations was crucially implicated in PD aetiology by Oleh Hornykiewicz, who then went on to pioneer Levodopa (L-DOPA) therapy which remains a first line treatment for the disease. In 1963, an application of DBS to PD was pioneered by Bekthereva and colleagues. (2) Via use of pacemakers, it became the first controlled and reversible PD therapy and met FDA approval in 1997 for the treatment of PD and idiopathic tremor. DBS also proved useful experimentally as it allows for double blind trials. As summarised in Figure 1, three basal ganglia pathways have been implicated in the control of movement. Multiple structures involved in these pathways are approved targets for DBS, including: the subthalamic nucleus (STN), globus pallidus Internus (GPi), and the ventral intermediate nucleus of the thalamus (VIM). The globus pallidus externus (GPe), subthalamic nucleus/Substantia nigra pars reticulata (STN/SNr) combined, and GPe/GPi combined DBS have also proven successful in treating the disease within laboratory conditions.

Despite its mechanism remaining unclear, DBS replaced lesioning therapies as the most common surgical option for PD patients who, though still responsive to pharmacological management, suffer from periods of severe motor complications or dyskinesia. To this day, PD medications can only alleviate symptoms; none stop or delay the degeneration of nigrostriatal neurons. Furthermore, there is at current a 50% chance of patients with early onset PD developing drug-induced dyskinesias within 5 years of pharmacological management. (3) DBS offers a reversible alternative with fewer reported side effects.

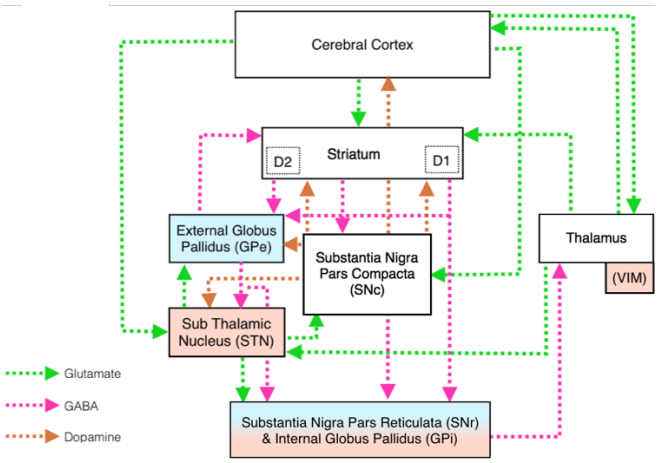

Figure 1: Diagram of basal-ganglia connections. Pink nuclei denote approved DBS targets for PD and blue shaded structures are those which have been successful in experimental studies. Note Direct (cortico-striato-nigral), indirect (cortico-striato-pallido-subthalamo-nigral), and hyperdirect (cortico-subthalamo-nigral) pathways.

Models of Parkinson's Disease

At present there are three leading models for the progression of Parkinson's disease.

The first is changes in SNr/GPi Firing Rates. Here depleted concentrations of dopamine result in both a reduction of tonic inhibition of the indirect pathway and excitation of the direct pathway. Cumulatively, this results in reduced striatal inhibition of the SNr/GPi output nuclei. This model explains bradykinesias and akinesia. Conversely, increased SNr/GPi activity may explain hyperkinetic disorders such as Dystonia. However, tremors are poorly accounted for.

PD tremors have instead been suggested to be result of oscillatory GPe-STN-GPe activity. (4) Here reduced dopaminergic modulation of the indirect pathway results in a continuous cycle of GPe inhibition, STN disinhibition, reciprocal glutamatergic GPe excitation, STN inhibition, and the cycle continues. This model is supported by DBS electrode recordings of PD patients showing oscillatory local field potentials in the basal ganglia. (5)

A third, rather elegant model suggests that temporal differences of activity in direct, indirect, and hyperdirect pathways induce GPi/SNr 'dynamic activity' to alter thalamic input in a centre-surround formation. This is supported by triphasic GPi responses of early excitation, inhibition, and subsequent excitation. (6) Initial thalamic motor commands are reset by hyperdirect pathway action, then the direct pathway disinhibits centre thalamic field to execute

a motor command. Lateral inhibition maintains suppression of surrounding commands. Finally, delayed indirect pathway activity diffusely inhibits all commands. In PD, a deficit of dopaminergic transmission increases the ratio of indirect: direct pathway firing. The consequent temporal shortening and spatial narrowing of GPi inhibition, helps explain the PD symptoms of bradykinesia, akinesia, and rigidity. This broad thalamic disinhibition increases probability of competitive motor commands being generated, resulting in involuntary movements: tremors.

DBS Configuration

The modern-day DBS system consists of three components:

- A lead containing electrode contacts at the tips (often Tungsten) which create a cylindrical contact with the surrounding tissue to stimulate the target.

- An extension wire passing under the skin of the head, neck, and shoulder.

- A pacemaker, often subclavicular, generating a controllable pulse of stimulation to the lead.

DBS leads are commonly one of two variants: monopolar or bipolar. The former involves implanting a cathode contact within the targeted structure. The pacemaker acts as the anode, creating a spherical stimulation field at the cathode. As current flow is greatest at proximity to the cathode, anodal implantation is not performed during monopolar DBS. Bipolar DBS involves both contacts within a single lead being inserted and connected to a pacemaker in the chest cavity. These contacts, less than 1mm apart, create elliptical stimulation fields allowing for a more precise targeting of tissue. Alternative 'multipolar' methods of DBS are under research to assess whether they may offer greater therapeutic benefit. One such example is tripolar DBS with two cathodes and one anode. (7)

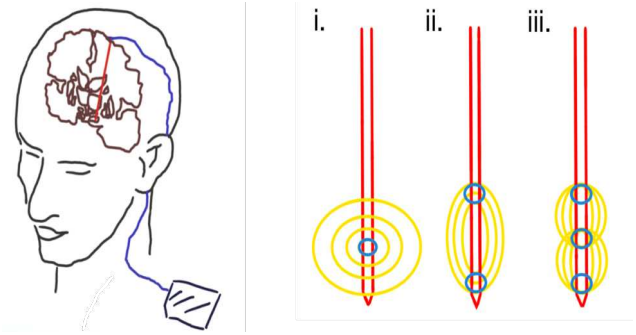

Figure 2 : Left: Diagram of DBS components: the electrode (here targeting the STN) is shown in red and is connected via a lead (blue) to a subclavian pacemaker (grey). Right: Not-to-scale representation of DBS electrode variations and their respective stimulation fields (i. monopolar, ii. bipolar, and iii. tripolar).

Monopolar DBS is the most popular as it requires a lower level of stimulation to attain identical therapeutic benefit to bipolar DBS as the space between contacts is greater, therefore a larger volume of tissue is activated. Hence, battery longevity is greater and fewer operations to replace batteries are required.

The pacemaker system itself can also be one of two types: voltage-controlled stimulation (VCS) and current-controlled stimulation (CCS). (8) Adapted from cardiac pacemakers, VCS is the traditional approach. However, as the immune system targets the foreign electrode, tissue builds up at the contacts. This results in impedance changes and consequently current fluctuations and charge accumulation, ultimately leading to over-stimulatory side-effects. To counter this, and maintain a constant output, a parallel arrangement of capacitors absorbs surplus charge and discharges when needed. This increases pacemaker size and mass, making implantation more invasive. The uniform flow of electrons in CCS overcomes these issues. However, this requires a large output headroom and a lower voltage swing compared to the near 100% attained by VCS. The amount of charge supplied, and its rate of delivery can be controlled by adjusting the pulse width, current/voltage supply, and the frequency of stimulation. As current fluctuations are absent in CCS, it is easier to control pulse width than in VCS.

'Excitation vs. Inhibition' Debate

As there is no unanimously accepted PD model, it is unsurprising that contradictory effects of DBS action have been reported in PD treatment. This paper will now explore DBS action within individual targets.

i. GPi-DBS

GPi stimulation was shown in 1996 to alleviate rigidity and bradykinesia in MPTP treated monkeys. (9) As pallidotomies were a successful approach in the 1990s, GPi-DBS was long accepted to act via inhibiting neurons. However, a reduction of activity in 77% of sampled, responsive thalamic neurons (mostly VA and VLo) in an awake macaque monkey indicates that the GPi is instead excited by DBS. (10) Only 16% of the thalamic neuron pool were shown to have a higher rate of firing during GPi stimulation. The decrease in thalamic activity was suggested to obstruct abnormal firing patterns causative of PD. Additionally, increased thalamic activation has been explained by antidromic current propagation during GPi-DBS treatment of Dystonia patients. (11) The excitation model is further

supported by recordings of decreased primary motor cortex activity during GPi-DBS. (12)

GPi stimulation is often performed at 130-185Hz, 60–90μs pulse width, and at a constant voltage of 1-3.6V – parameters optimal for exciting GPi axons rather neural soma. (6) Hence GPi-DBS action may be due to downstream excitation via GPi efferent neuronal current spread, despite a reduction or no change in the activity of the GPi itself. However, this is further complicated by GPi-DBS studies on PD monkeys reporting multiphasic responses of both excitation and inhibition. This may be due to activation of both GABAergic and glutamatergic terminals. (13)

ii. STN-DBS

As lesioning of the STN significantly reverses PD symptoms in MPTP treated monkeys (14), initial studies hypothesised STN-DBS to act via inhibiting STN activity. (15) This was thought to be via a depolarisation blockade; however, voltage gated channel inactivation has also been recently proposed. (16) Later studies reported that 44% of STN neurons inhibited by high frequency stimulation exhibited both early inhibitory and rebound excitatory phases; thus indicating a role of hyperpolarisation. (17) Furthermore, VL neuronal activity increases during STN-DBS, indicating inhibited STN-GPi input (18)

Conflicting studies report increased GPi and GPe activity of MPTP treated monkeys during STN-DBS. (19) Additionally, a trial on 10 PD patients showed SNr activity to be increased during and 10 minutes after 130Hz STN stimulation. (20) Hence it is likely that if STN neurons are excited during local DBS, they consequently stimulate GPe, GPi, and SNr neurons via efferent glutamatergic projections.

An explanation for this confliction is that STN-DBS inhibits the soma of STN neurons while simultaneously exciting their axons, resulting in downstream stimulation of interconnected basal ganglia nuclei. (21) This explains unchanged activity in GP neurons despite reduced STN activity and firing rates in other nuclei being similar to stimulation pulse rate. Additionally, this mechanism has been proposed to incorporate antidromic activation of GPi-STN efferents, though their presence is inconsistent with other anatomical studies. (22).

A study has also suggested STN-DBS to both inhibit and excite different populations of STN neurons. (23) These effects were attributed to stimulation of glutamatergic and GABAergic afferent axon terminals. Stimulation also increased SNc activity, possibly explained via STN-SNc efferent activation.

iii. GPe-DBS

GPe stimulation alleviates bradykinesia and akinesia in Parkinsonian monkeys. (24) This induces a repeating cycle of GPi suppression, brief activation, and 5ms latent prolonged suppression, restoring SNr/GPi firing rates to those seen in non-Parkinsonian monkeys. Additionally, oscillatory GPe and STN activity is reduced, hence supporting all three PD models.

GPe-DBS has also been shown to excite and inhibit different GPe neuronal groups. (6) GPe neurons receiving single-pulse stimulation exhibited either a biphasic neuronal response of initial inhibition and subsequent excitation or prolonged inhibition with no excitation. Repetitive stimulation produced both excitatory and inhibitory effects.

Biphasic activity of neurons may be due to post-hyperpolarisation rebound spiking. Differing effects between neuronal groups can be explained in line with the excitation model of DBS: variances in densities of neurons projecting into the GPe induce differing responses to GPe stimulation. (25) This is supported by injections of GABAA antagonist Gabazine eradicating inhibitory response to stimulation and combined administration of AMPA and NMDA channel blockers NBQX/CPP abolishing excitatory effects. The Oscillatory Firing Pattern model of PD also explains the biphasic recordings: an inhibition of the GPe during DBS would decrease activity of GPe-STN GABAergic neurons, in turn disinhibiting the STN and increasing activity of STN-GPe glutamatergic neurons. This would result in phases of inactivation and activation of the GPe in an oscillatory manner.

iv. Combined DBS

A trial has recently investigated the therapeutic benefit of GPe-DBS, GPe/GPi combined-DBS, and pharmacological PD management in patients who had previously undergone GPi-DBS. (26) GPe-DBS was more effective than GPi-DBS. However, combined DBS was by far the most effective treatment, suggesting a synergistic mechanism. GPi-DBS was more effective treatment in the long run. As observed earlier, excitation of GPe and inhibition of GPi best explain the effects of DBS in line with the firing rate and oscillatory firing pattern models. GPe/GPi combined-DBS evidently presents a paradox. I suggest that these contradictory effects may be explained by activation of glutamatergic afferents in the GPe and GABAergic terminals in the GPi. However, this specificity of DBS targeting is contradicted by many of the aforementioned observations of mono GPe- and mono GPi- DBS. Combined GPe/GPi-DBS doesn't fall in line well with the dynamic activity PD model.

Additionally, a double-blind study suggested STN/SNr combined-DBS as a novel treatment in alleviating PD refractory gait disturbances. (27) This is supported by SNr (mono)-DBS alleviating forelimb akinesia in hemi-Parkinsonian rats. (28)

v. VIM-DBS

The ventral intermediate nucleus (VIM) of the Thalamus receives input mainly from the cerebellum and projects to the primary motor cortex to aid in the coordination of movement. Bypassing the basal ganglia entirely, unilateral VIM-DBS was as beneficial as, and produced similar side-effects to, unilateral thalamotomy. However, stimulation is reversible and also safer to use on elderly patients. It was hypothesised that the mechanism of this is via inhibiting neurons of a transcortical reflex loop. (29) A 6-year multicentre follow up study showed monopolar VIM-DBS to significantly reduce contralateral tremor with p-values of < 0.00001. (30) Additionally, a $> 60\%$ decrease in average contralateral tremor scores in the 'off-state' was observed compared to baseline figures, suggesting that VIM-DBS induces permanent physiological changes in alleviating tremor. The nucleus remains a DBS target in alleviating upper extremity tremor and is easier to surgically access than the STN.

Disruption Hypothesis

Following their work identifying GPi-DBS to inhibit both artificial cortical response and spontaneous discharge via activation of GABAergic afferents, Chiken and Nambu hypothesised a third DBS mechanism: GPi-DBS activates afferent axon terminals and dissociates them from efferent projections, hence 'blocking' the flow of information through the output nucleus. (6) The mechanism for this is in essence synaptic fatigue; stimulated neurons excessively release neurotransmitter and so cannot respond to further action potentials as their transmitter stores have been depleted.

A disruption model of DBS action would fall in line with all three PD models as any abnormal PD basal ganglia activity - be it firings patterns, rates, or dynamic activity changes - passes through the GPi. The mechanism may also explain the counterintuitive efficacy DBS has in treating dystonia: involuntary movement commands, as explained by the dynamic activity model, are blocked by GPi stimulation. Based on reports of direct pathway inhibition of the SNr not being affected by STN stimulation (31), it was also suggested that STN-DBS 'blocks' hyperdirect and indirect pathway excitation of the SNr. This would explain the treatment's ability to alleviate bradykinesia and rigidity in PD patients.

Discussion

Depolarisation blockade, voltage-gated channel inactivation, and GABAergic afferent activation have been suggested to explain inhibitory effects of DBS action. Axonal stimulation, particularly of glutamatergic afferents, has also been proposed to account for DBS's excitatory effects.

Evidently there is a contradiction in action of DBS. Based on the disruption hypothesis, this review suggests that these observations are in fact not antagonistic but rather synergistic in nature. Observed effects vary due to glutamatergic and GABAergic neuron pools being investigated, but in either case excessive transmitter release reduces abnormal information flow in the stimulated nucleus.

I also suggest that this hypothesis may explain the sustained effects of DBS when stimulation is turned off. That is, prolonged stimulation of afferent axon terminals may instigate a long-term depression mechanism due to excessive bouton polarisation. A reduction of neurotransmitter release sites on the presynaptic membrane would decrease response to action potentials, essentially 'blocking' information flowing through. Support for this comes from hippocampal GABAergic synapses exhibiting a long-term reduction of GABA release probability as result of presynaptic NMDA-mediated calcium influx. (32)

GPe-DBS is likely explained by an increase in GPe activity or the activation of GABAergic efferents projecting to the STN. However, GPe-DBS may also be explained by a disruption mechanism. As the GPe has been shown to have high intrinsic activity (33), stimulation disrupting GPe input would result in greater inhibition of the STN and output nuclei. This falls in line with Vitek and colleagues' study explored earlier. (24) Additionally, tremor symptoms may be alleviated due to reduced GPe-STN oscillatory firing.

However, the disruption hypothesis raises some issues. Firstly, in the STN and GPi the suggested effects are near indistinguishable with those supporting the inhibition hypothesis. Secondly, reduced direct pathway activity, as a result of nigrostriatal neurodegeneration, is not compensated for by GPi-DBS in this hypothesis. If anything, the remaining direct pathway input to the GPi is too being blocked by this mechanism, along with hyperdirect and indirect pathways, resulting in intrinsic GPi firing. As PD symptoms are drastically reduced to near-normal values of symptom scores, this hypothesis undermines previously held views of the role of the basal ganglia in motor control. Thirdly, a study on rodent optogenetics showed selective activation of hyperdirect (cortico-STN) neurons to alleviate PD symptoms. (34) This contradicts an STN-DBS mechanism of disrupting hyperdirect pathway information flow. Furthermore, observations of post-inhibitory rebounds after stimulation cannot be accounted for by disruption as the tissue is polarised. Instead a delay and subsequent neurotransmitter release would be expected.

Conclusion

The STN and GPi are approved targets effective in alleviating debilitating PD symptoms. For those suffering from tremor dominant PD, additional benefit may be found from VIM-DBS. Though parameters vary by the structure targeted, effective

DBS ranges are 130-200Hz frequency, 60-100μs pulse width, and 1-5.5V constant voltage. Monopolar DBS requires a lower level of stimulation and hence offers more optimal battery life. However, bipolar and multipolar approaches are favourable for those with side effects from stimulation. GPe, SNr, and combined DBS may offer alternative future strategies.

DBS has been shown to induce both inhibitory and excitatory effects. A disruption view of DBS action may explain a synergy between these observations. However, this may also be explained by Moran et al.'s hypothesis of simultaneous somatic inhibition and axonal stimulation. Although, a disruption mechanism would account for the benefit of DBS in treating hyperkinetic disorders.

Generally, the firing rate PD model seems to best explain the inhibitory effects of DBS. While both inhibitory and excitatory hypotheses of DBS action fall in line with oscillatory firing patterns. The disruption hypothesis supports both of these models as well as Nambu et al.'s work on 'dynamic activity'.

As there is no unanimously agreed representation of basal ganglia connections, there remains no absolute model for PD aetiology, and consequently a lack of consensus on DBS action. There is no question that DBS has proven an effective approach to PD therapy and has paved the way for examining basal ganglia action. However, further investigation into the relationship between cortico-baso-thalamic connections and PD is required to gain a better view on the mechanism of DBS and refine its application in PD treatment.

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Education

Basal Cell Carcinoma with intravascular invasion

EDUCATION

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Summary:

We report the case of a 59-year-old Caucasian male with a primary infiltrative BCC with vascular invasion on the right temple. An excision biopsy was taken and histology confirmed BCC, 2.5mm thick, invading into the reticular dermis. The patient underwent a scar excision which demonstrated no further malignancy. The patient showed no clinical signs of recurrence 2 years after diagnosis.

Relevance:

Basal cell carcinoma (BCC) is the most common human malignancy and its incidence is increasing. Less than 1% of BCCs metastasize and very few cases of intravascular invasion by a primary BCC have been reported. This report discusses the clinical features of a BCC, the population at risk and summarises all known cases of BCC with vascular invasion in the literature.

Take Home Messages:

Due to the rarity of basal cell carcinoma with vascular invasion, there is a poor understanding of the disease process and the metastatic potential, resulting in uncertainty for clinician and patient regarding appropriate management.

Introduction

Basal cell carcinoma (BCC) is the most common malignancy in humans and its incidence is increasing worldwide. (1) Risk factors include exposure to sunlight, a lower Fitzpatrick skin phototype, genetic factors and burn scars. (2,3) The Fitzpatrick scale is a classification system that ranks the amount of melanin in a person's skin. Both the colour of skin, and how it reacts to ultraviolet light are taken into consideration:

1. Skin type I never tans and always burns. Skin is pale white, eyes are blue or green and hair is red or blond.

2. Skin type II tans poorly and burns easily. Skin and eyes are fair.

3. Skin type III tans after initially burning. Skin is a darker white.

4. Skin type IV tans easily and burns minimally. Skin is light brown.

5. Skin type V tans darkly and rarely burns. Skin is brown.

6. Skin type VI always tans darkly and never burns. Skin is dark brown or black. (4)

These risk factors explain how BCCs are most frequently found on the head and neck of white males in their fifth to sixth decade. (2) Despite the high prevalence, less than 1% of cases metastasize. (2,5–9) Of the few that do, the spread of metastases is thought to be via a lymphatic and haematological route. Very few cases of intravascular invasion by a primary BCC have been reported. (5–8,10) We report the rare case of a 59 year old Caucasian male with a primary infiltrative BCC on his right temple with vascular invasion.

Case Report

A 59 year old gentleman was referred to Dermatology with a 1.5x1.5cm pearly papule on his right temple, present for approximately two years duration. Clinically, the lesion was thought to be a basal cell carcinoma. The patient has skin type 2 and with the exception of his father having prostate cancer, no family history of malignancy of any kind. Relevant past medical history included numerous benign skin lesions such as a trichofolliculoma on his right forehead. He had eczema affecting his face as a child, but not into adulthood. Social history included high sunlight exposure, as he has been working outside as a manual labourer for the past 13 years. An excision biopsy of the presenting lesion was taken. The histology confirmed a basal cell carcinoma infiltrating the local vasculature (figure 1), 2.5mm thick, invading into the reticular dermis. CD31 immunostain (figure 2) and BerEP4 immunostain (figure 3) confirmed basal cell carcinoma within the vascular channels. There was positive expression of BerEP4, EMA, MNF116 and CK7. There was no expression of CK20 or TTF-1. This immunoprofile makes the lesion extremely unlikely to be an incidental metastatic malignancy. In addition, there was no clinical evidence of a second primary. The patient underwent a wider scar excision, which demonstrated no further malignancy. At follow up after 2 years, there was no evidence of recurrence of the BCC on the right temple and there was no lymphadenopathy or hepatosplenomegaly. The patient was subsequently discharged from dermatology.

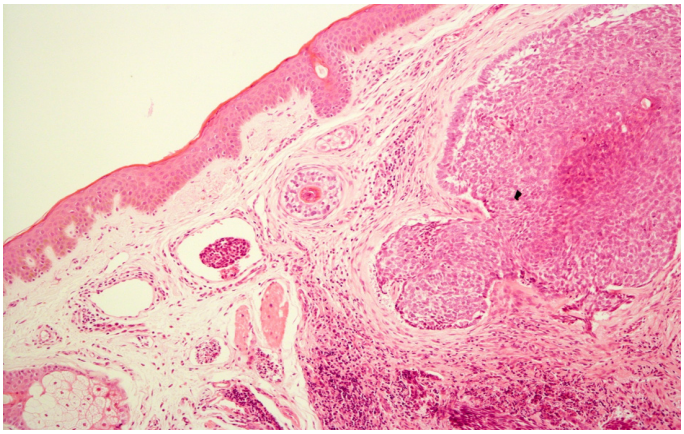

Figure 1: H&E X20 magnification, showing basal cell carcinoma within vessel. 1) Island of BCC within the dermis. 2) Vascular space. 3) Intravascular BCC.

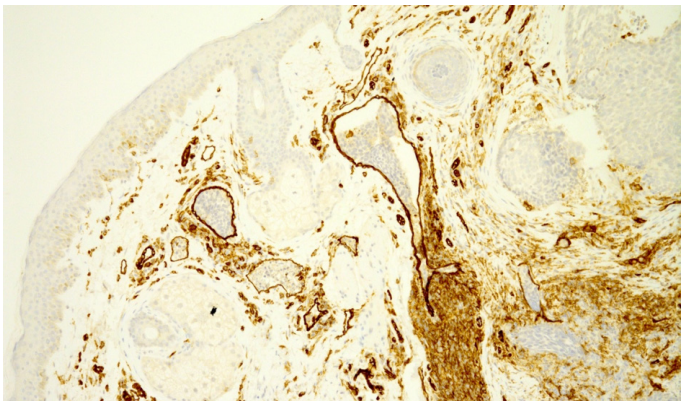

Figure 2: CD31 immunostain highlighting the walls of the vascular channels (arrowed) containing basal cell carcinoma 903x677mm (72 x 72 DPI). Note that the tumour does not stain with this antibody.

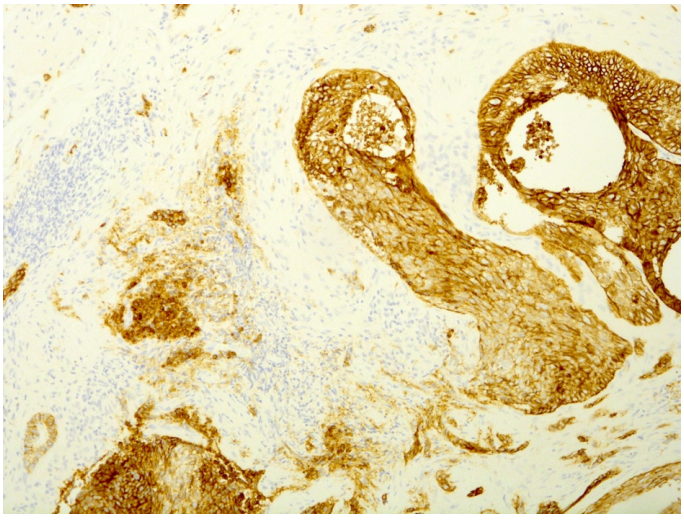

Figure 3: BerEP4 immunostain confirming basal cell carcinoma within vessels (arrowed) 677x903mm (72 x 72 DPI). The BerEP4 antibody stains the tumour brown but does not react within the vessels.

Discussion

The main clinical features of a basal cell carcinoma include:

- A slow-growing, raised, solid skin lesion (plaque or nodule)
- Similar colour to normal skin, or pinkish due to increased blood supply
- Size varies from millimetres to centimetres in diameter
- The lesion may bleed or ulcerate (11)

As there are no clinical features that can differentiate a BCC with vascular invasion from an un-invasive lesion, biopsy and subsequent histology are of great importance. Until recently, there has been little literature on the vascular invasion of BCC. In 1984, Von Domarus and Stephens published a report of five metastatic BCC case studies. Two of these cases had histology suspicious of vascular invasion. (9) In 2012, Machan et al., document the first recorded case of primary cutaneous BCC with histopathologically documented venous invasion. They presented the case of a 51-year-old male with a lesion on his upper chest. Histology showed an infiltrative and micronodular BCC, which widely invaded the reticular dermis. It was also identified within a muscular venule. Intravascular tumour was confirmed with dual immunohistochemistry. Further excision of the scar showed no further disease. (5) Three more case reports of BCC with vascular invasion were published in 2016: a 96-year-old female with intravascular BCC on the right posterior helix; (6) a 75-year-old male with a lesion on his left nasal sidewall; (7) an 81-year-old female with an enlarging lesion on the right nasal tip. (8) The first two cases underwent Mohs micrographic surgery, the third was surgically excised with clinical margins of 3 mm. (6–8) Another case was reported in late 2018: a 61-year-old male with a lesion on the vertex of his scalp showed both intravascular and perineural invasion during Mohs micrographic surgery. Despite post-operative radiotherapy, the patient presented with skin graft breakdown 4.5 years after surgery and biopsy showed recurrent BCC in the bone marrow. (10) Excluding this last case, the longest follow up period reported is only four months, therefore long-term recurrences or metastases cannot reliably be commented on. (5–8) Table 1 provides a summary of all known cases of primary BCC with intravascular invasion.

In view of the rarity of vascular invasion of BCCs, there are no guidelines to dictate appropriate adjuvant treatment or prognosis. The British Association of Dermatologists (Britain) and the National Comprehensive Cancer Network (USA) recommend adjuvant radiotherapy for "high-risk BCCs", but are no more specific regarding intravascular invasion. (3,12) Without available guidelines, the decision to treat is left to clinical judgement and the local multi-disciplinary team. Although the cases summarised appear to have minimal vascular invasion and no cases of metastases since 1984, the rarity of this condition results in a poor understanding of the disease process, its potential to metastasize and therefore the appropriate treatment plan.

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Report	Age / sex	Clinical Features	Location	Histology	Treatment	Follow up
Machan et al., 2012 (5)	51 ♂	0.9X0.4 cm pearly papule	Upper chest	Infiltrative, micronodular BCC; identified within muscular venule and confirmed with immunohistochemistry.	Excision biopsy followed by further surgical excision of scar.	Clinical follow up every three months. No adverse features detected. Time period unknown.
Shea, Weinberger and Cook, 2016 (6)	96 ♀	1.6X1.0 cm pearly, ulcerated nodule	Right posterior helix	BCC with irregular islands of basaloid cells; CD31 immunohistochemistry confirmed intravascular invasion.	Mohs micrographic surgery.	No follow up due to age of patient.
Milam, Bogart and Manolson, 2016 (7)	75 ♂	2.0X1.1 cm erythematous plaque	Left nasal sidewall	Nodular and morpheic; vascular invasion confirmed by CD31 immunohistochemistry.	Mohs micrographic surgery.	Frequent clinical follow up. No adverse features detected. Time period unknown.
Lonie, Niumsawatt and Castley, 2016 (8)	81 ♀	0.8X0.8cm enlarging lesion	Right nasal tip	Invasive sclerosing BCC; intraluminal invasion confirmed with immunohistochemistry.	Excision biopsy followed by adjuvant radiotherapy.	Clinical follow up. No sign of recurrence at four months.
Mazloom, Rich and Grider et al., 2018 (10)	61 ♂	5cm scar	Vertex of scalp	Infiltrative BCC with both intravascular and perineural invasion.	Mohs micrographic surgery followed by adjuvant radiotherapy.	PET CT scan negative at one year. Local recurrence at 4.5 years.
Jones, Patel, Mudaliar et al., 2019	59 ♂	1.5X1.5cm pearly papule	Right temple	Infiltrative BCC. CD31 immunohistochemistry confirmed invasion into local vasculature.	Excision biopsy followed by further surgical excision of scar.	Frequent clinical follow up. No adverse features at 2 years.

Table 1: A summary of all known cases of BCC with intravascular invasion.

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Reflections

Flour fortification with folic acid to reduce risk of Spina Bifida

EDUCATION

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Summary:

Spina bifida is the most common neural tube defect (NTD) and is caused by an interaction of genetic and environmental factors. The congenital condition results from the failure of closure of the caudal neural tube and can led to a variety of complications. Current prevention and management interventions include taking folic acid supplements and undergoing operation before or after birth. The compulsory fortification of flour with folic acid has been successful in countries such as the USA, where studies have found that the prevalence of spina bifida declined by 31% since fortification was introduced. Despite the evidence to support the legislation, there are many concerns regarding folic acid fortification. These include certain ethical considerations regarding the feelings of those already living with NTDs as well as a potentially increased risk of cancer due to excess folic acid in the diet.

Relevance:

The British Government has recently announced plans to discuss the mandatory fortification of flour with folic acid. This is in response to the establishment of a causal link between NTDs such as spina bifida and low folic acid levels in mothers during the embryonic stage of pregnancy. Evidence suggests that a diet containing folic acid reduces the risk of spina bifida in offspring by up to 70%.

Take Home Messages:

Further research is needed to explore the long-term effects of increased folic acid in the diet; however, it appears as though the evidence for the mandatory fortification of flour with regards to a significant reduction in the risk of developing NTDs such as spina bifida outweigh potential risks.

In November 2018, the British Government announced plans to consult on the mandatory fortification of flour with folic acid in a bid to reduce the incidence of neural tube defects (NTDs). The causal link between NTDs (such as spina bifida and anencephaly) and low folic acid levels in pregnant women was established in 1991 through trials conducted by the U.S. Department of Health and Human Services. (1) 26 years of subsequent pressure from independent scientists, charities and the Scientific Advisory Committee on Nutrition forced the government to discuss the introduction of this new regulation. The fortification of flour with folic acid is generally thought to be beneficial by the medical community, including The Royal College of Obstetricians and Gynaecologists. (2)

Between 1991 to 2012, the prevalence of pregnancy complicated by NTDs in the UK was 1.28 (95% CI 1.24 to 1.31) per 1000 total births, whereas NTD live births was only 0.20 per 1000 live births. However, there is evidence to suggest that had fortification been implemented at the level adopted by other countries (such as the USA) between 1998 to 2012, there would have been an estimated 21% reduction in the prevalence of NTDs in the UK. (3) Despite the evidence in favour of fortification, potential concerns have been raised, which has delayed the process of implementing the public health measure. This paper aims to provide a background on spina bifida before discussing the advantages and disadvantages of fortifying flour with folic acid.

NTDs are a spectrum of disorders characterised by the abnormal development of the brain or spinal cord. Spina bifida is the most common NTD. The term spina bifida is derived from Latin for 'split spine' and the earliest known cases were two mummified newborns found in King Tutankhamen's tomb. (4) Spina bifida is a multifactorial condition, caused by both genetic and environmental factors. (5) One of the genes most commonly associated with spina bifida is the MTHFR gene, which codes for an enzyme involved in processing folic acid, which is needed convert homocysteine to methionine. (6) It is thought that the failure to convert homocysteine leads to NTDs. Other risk factors include maternal diabetes, obesity (7) and exposure to teratogenic medications, such as the antiepileptic sodium valproate. (8)

Spina bifida results from the failure of closure of the caudal neural tube. In normal embryology, neural tube closure occurs from the 23rd (rostrally) to the 27th (caudally) day after fertilization. (9) However, in spina bifida the vertebrae and membranes surrounding the spinal cord at the lumbosacral region fail to fuse.

There are three classifications of spina bifida: occulta, meningocele and myelomeningocele. Spina bifida occulta, known as 'hidden' spina bifida, is the mildest and most common form. It is believed that up to 10% of the British population have spina bifida occulta. (10) Formal diagnosis is through plain film radiograph, though newborns often have a visible indication above the spinal defect such as an abnormal tuft of hair, dimpling or a birthmark. (11) There are no consequences of spina bifida occulta and so no treatment is required. In meningocele, the meninges herniate through the vertebral opening, forming a fluid-filled sac. This cyst does not contain the spinal cord, so nerve damage is unlikely but when it does occur, patients often experience bowel incontinence as the only resulting symptom. (12) The most severe form of spina bifida is myelomeningocele, in which both the meninges and spinal cord herniate through a gap in the vertebral arch. This results in a variety of complications such as lower limb motor and sensory dysfunction, urinary and bowel incontinence, orthopaedic deformities, hydrocephalus and Chiari II malformation (a downward displacement of cerebellar tonsils through the foramen magnum). (10, 12) Figure 1 summarises the three types of spina bifida.

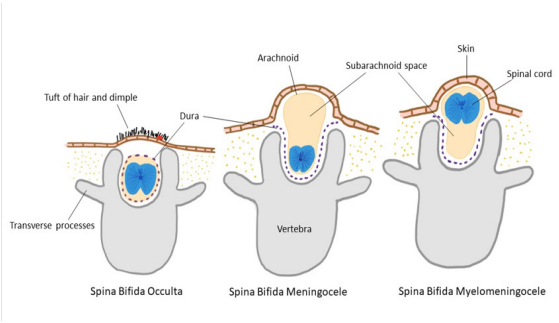

Figure 1: The three types of spina bifida

Spina bifida meningocele and myelomeningocele are surgically treated either by intrauterine repair surgery, or surgery within the first few days after birth. The herniated meningeal sac is excised and in myelomeningocele, the spinal cord is returned to the spinal canal, before the surrounding dura mater is closed over the defect. (13) Surgical correction is required to prevent neurological infections as well as injury to the exposed spinal cord and nerves.

Folic acid is required for haematopoiesis, DNA synthesis and neural development. (14) In a bid to reduce the risk of spina bifida, expectant mothers are currently advised to take folic acid supplements. Daily recommendations for folic acid are usually 200µg for anyone over the age of 11 years, but 300µg plus a 400µg supplement of folic acid during the first 12 weeks of pregnancy for expectant mothers. (15) Evidence suggests that taking these supplements reduces the risk of a mother giving birth to a child with spina bifida by up to 70%. (16)

Without supplementation, folic acid can only be obtained via the consumption of natural folic acid-containing foods (such as legumes, asparagus, eggs, potatoes, brussel sprouts and baked beans). (17) Large portions of these foods would be needed to reach a daily intake of 400µg, which is often too difficult for many women to achieve. Moreover, adequate folic acid levels are most important during the embryonic stage of pregnancy (as this is when the neural tube develops), which is also when many women do not yet know that they are pregnant. Fortification could boost folic acid levels during the first trimester of pregnancy in the bodies of those most at risk from deficiency and therefore at risk of having a child with a NTD. (18) Women at risk include those from lower socio-economic groups, younger mothers and those with unplanned pregnancies.

Food fortification has previously been implemented in the UK. Under the UK Bread and Flour Regulations 1998, industry is currently required to add iron, calcium, thiamine and niacin to all wheat flour and white bread in a bid to reduce deficiencies. (19) Moreover, the compulsory fortification of flour with folic acid has been successful in countries such as Chile and the Unites States. Since introduced in 1998, a US study reported that within two years, the prevalence of spina bifida declined by 31% and the incidence of anencephaly by 16%, exemplifying the benefits. (20)

To summarise, the main advantage of fortifying flour is that the move would reduce the prevalence of folic acid deficiency. This would therefore reduce the incidence of folic acid-dependent conditions such as NTDs. Despite this advantage, there are several concerns, which have contributed to the UK government's delay in employing the change. The fortification of flour is essentially a public health intervention, which means that its implementation is likely to achieve outcomes at a population level but is also likely to fail to meet the immediate needs of individuals. Not all women consume the same levels of folic acid, so fortification may not be fully effective and could even result in some consuming too much folic acid in their diets. Long term consequences of a high intake (>1000µg per day) manifest as abdominal cramps, diarrhoea, irritability, nausea and skin reactions. (21) One could argue that the government should focus on providing health advice and treatment tailored to individual needs to avoid such consequences whilst still preventing a woman's pregnancy being complicated by a NTD, rather than via a non-specific public health measure.

There are also ethical considerations that the government will have to address when trying to eradicate NTDs; patients who suffer a significant disability due to a NTD may feel ashamed and unwanted by society and would rather the government concentrate on managing the needs of existing people affected by NTDs more effectively. Since folic acid is only one of the contributing factors to the development of spina bifida, fortification will not completely eradicate the disease. (22) Therefore, one could argue that it could be more cost effective to spend on improving the current treatment accessed by those suffering with spina bifida, whilst also increasing awareness and reducing the discrimination faced by those living with NTDs, in order to improve the quality of their lives.

Another concern with such a large-scale public intervention is the lack of population-based evidence regarding the long-term effects of increased folic acid intake. The US was the first country to introduce mandatory folic acid fortification in 1998, (16) before which there are no national records lasting over 20 years about the impact of folic acid consumption on the population. Further research is needed to assess the long-term effects of folic acid. Furthermore, high folic acid diets are thought to be associated with an increased risk of cancer. A meta-analysis of 19 studies found an increased risk of cancer overall (RR 1.07, 95% CI 1.00 to 1.14) in subjects taking ≥0.4 mg folic acid supplements per day. The risk of prostate cancer was significantly raised (RR 1.24, 95% CI 1.03 to 1.49). (23) Since the daily folic acid recommendations for most of the public are 0.2mg per day, yet the study observed increased cancer incidence from double that amount, it is possible that there may be a link between cancer and high folic acid intake.

Finally, there are worries that a high intake of folic acid from fortified food could mask macrocytic anaemia which is an important diagnostic sign of vitamin B12 deficiency. (24) As well as haematopoiesis, B12 is essential in brain and nervous function, and therefore deficiency can lead to neurological disturbances such as Alzheimer's disease. (25)

Currently, the government have only announced their plans to begin formal talks for mandatory fortification of flour with folic acid. Discussions regarding how this will be implemented, when and how the move will be regulated are yet to take place but are soon expected due to pressure from several MPs, independent researchers and NHS advisory bodies. (26) Moreover, further research is needed to explore the long-term effects of increased folic acid in the diet, especially its potential link to cancer. However, for now, it appears that the evidence for the mandatory fortification of flour leading to a significant reduction in the risk of developing NTDs outweigh the potential risks. Therefore, medical students and clinicians alike should continue to educate and advise the public about folic acid's health benefits, especially for expectant mothers.

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Reflections

A patient's death and the medical student

REFLECTIONS

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Case presentation

The student

Miss X is an enthusiastic second-year graduate entry medical student who, during a student selected component (SSC) placement week, inadvertently observed the treatment of Y. Miss X was looking for the consultant she was shadowing for the evening. The doctor was in the Resus room with the Emergency Department (ED) team waiting for an air ambulance call. Not knowing what the call was going to bring, Miss X was told to 'blend into the wall' and that it was going to be an upsetting scene. Even though Miss X is 'only' a medical student, being told to blend in did not make her feel as part of the team, and therefore, tried her hardest to not be in the way and observe quietly from a corner of the room.

The patient

Y was a teenager who was flown into the emergency department after being found unresponsive following a suicide attempt. Pre-hospital emergency medicine (PEM) doctors had placed a cardiac compression machine on the teenager as soon as they got to the scene. Y was brought into Resus within an hour of being found. PEM doctors gave a briefing on the situation and it was decided, by stand-by ED doctors and nurses, to stop compressions and all attempts at resuscitation.

The dilemma

When Y was brought in, the first thing Miss X noticed were the teenager's colourless feet. It was obvious not much else could be done for Y so compressions were not attempted, and death was called. The teenager's mother walked into the room and was in complete shock when told that Y was dead. At this point, Miss X, still trying to 'blend into the wall' felt she was in a surreal world. This was Miss X's first

exposure to a patient's death and she did not know what to feel or how to react. Miss X felt 'nothing' during and after the episode. She was not overwhelmed and/or upset by the fact that a teenager had died by suicide. Instead, Miss X felt troubled that she had no reaction to the situation and questioned whether this seemingly lack of empathy would make her a bad doctor in future.

Discussion

Miss X's dilemma presents two points for discussion: the impact of a patient's death on a medical student, and the role of empathy in such situation.

The impact of a patient's death on a medical student

Consultants, junior doctors and nurses offered Miss X support several times, but she did not feel like she needed it. However, this was Miss X's first experience of a patient's death and her reaction, or lack thereof, could have been shock.

Not many studies have been published on the psychological impact of a sudden or unexplained patient's death on doctors and medical students, but the results of those that have, warrant further investigation. It has been previously suggested that an emergency care doctor's view on death is subjective and dependent not only on their perceptions and actions, but also on the moment of life course of the patient, with the death of younger patients having the most psychological impact. (1) The same study concluded that patient deaths can be more or less difficult to overcome depending on the doctor's, as well as, the patient's situation. (1) In terms of healthcare students, a study has shown that those studying nursing demonstrate a greater emotional involvement with patient deaths than medical and physiotherapy students. (2) Interestingly, it has been demonstrated that emotional reactions to death differ depending on the setting, with sadness and grief being the main emotions in an inpatient setting, compared to surprise and shock in ED, (3) correlating with Miss X's experience. Furthermore, patient deaths seem to have a higher emotional impact in females than males. (4) However, this does not correlate to Miss X's experience, demonstrating that the effect of a patient's death on a doctor/medical student is subjective.

The role of empathy on a patient's death

Prior to, during and after medical school, students are constantly reminded of the importance of empathy. Putting themselves in the patients and their families' shoes is meant to make better doctors and help provide more patient-centred care. (5) However, one cannot help but wonder if this strong emphasis on empathy is making students question their capabilities as future doctors. Can we really be empathetic with every patient and their family?

The ED consultant reassured Miss X that 'not feeling anything' was OK, and that everyone deals with patient deaths in different ways, particularly when they are young patients. Doctors 'grow a thick skin' since they are exposed to death regularly, otherwise it would be impossible to mentally cope with the profession, which, as a result, could come across as not being empathetic enough. Although no research to date has been done on the psychology of 'feeling nothing' when related to a death, one small study demonstrated that qualified doctors with more than 3 years of experience expect death to happen on a daily basis at work and therefore find it 'normal'. (6) Furthermore, another study demonstrated that medical students had strong feelings towards death whilst on university placement. (3) Both studies illustrate how feelings and attitudes towards death change with age and experience in the medical profession. In this case of Miss X, it may have been that, although a student, Miss X had a strong scientific background and participated in various human cadaveric dissections, and therefore this life experience had already given her some resilience.

Recommendations

At present, medical schools do not generally expose students to patients' deaths until the clinical years because this is when the majority of patient contact occurs. However, hospital based SSCs and GP placements also take place during non-clinical years, and, although minimal, patient contact is also present. Therefore, the author suggests that students are taught about this subject earlier in their degree. Introducing the subject of death to medical students could be achieved by, for example, asking qualified doctors, particularly juniors as students will be able to relate to them more, to comment on their experiences. Another approach could be to organise a palliative care placement in the first year of the medical course where the aim would be for students to interact with patients who are dying, their families and doctors involved in their care. By introducing the topic earlier, students will be more aware that they should seek help and support, helping them cope, in the long run, with the psychological impact of the death, no matter how big or small.

It is also recommended that students talk to their clinical seniors about their experiences and feelings towards different patient deaths, helping them further realise and understand that emotions towards a shared situation are subjective. Students should be encouraged to provide support to their peers when exposed to similar situations.

Finally, and most importantly, students should be reminded that 'not feeling anything' towards a patient's death does not mean that they lack empathy and will become bad doctors. Instead, it will help

them cope with the psychological impact of the profession.

May Y rest in peace.

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