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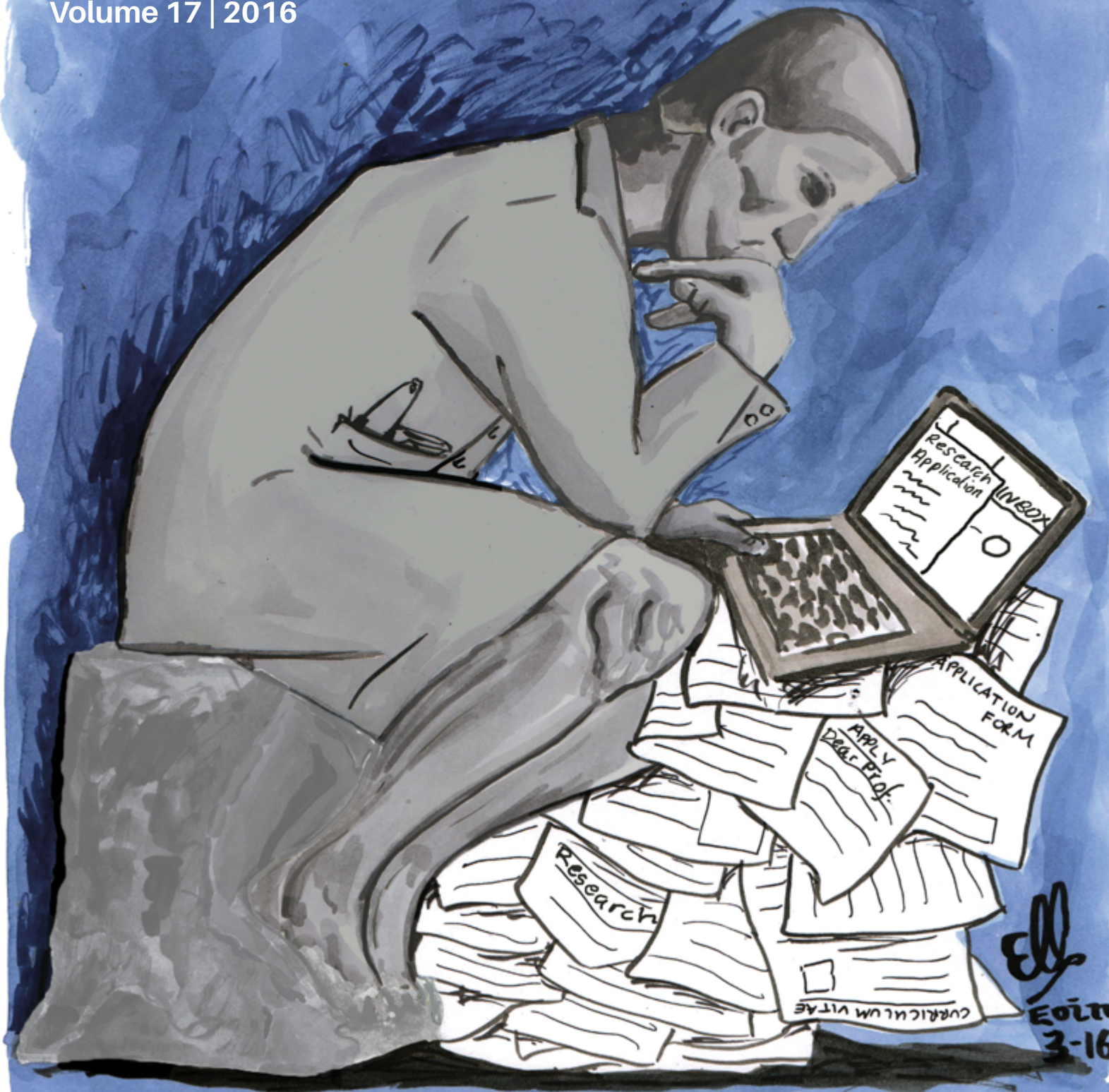

RESCULPTING THE APPROACH TO RESEARCH ELECTIVES

The Trinity Student Medical Journal (TSMJ) is intended to provide an inclusive vehicle for students to communicate current medical research, opinions and thoughts to other students, faculty members and faculty of affiliated institutions. We publish articles relating to many aspects of medicine including scientific research and clinical experience. Articles are accepted from students in medicine and other related fields, as it is our view that medicine is the meeting point of many disciplines. The aim of the Journal is to provide a medium that is responsive to the rapidly changing face of contemporary medicine and is able to grow and expand as rapidly as the subject.

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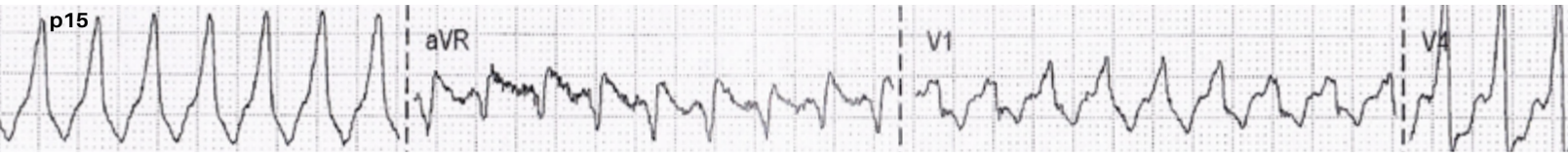

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Make the most of that line on your CV

Medical student research output has increased quite dramatically in recent decades. Research projects are progressively being integrated into medical school curricula and students' drive to engage is becoming stronger as opportunities become more accessible. With a bit of effort, undergraduates might expect to get at least one publication by the time they qualify.

Often, the rationale behind us pursuing research is to decorate our curriculum vitae. Indeed, it can feel like there is a lot of pressure to do so. Although we will surely gain skills and experiences that will stand well to us from such an approach, pursuing research with the sole aim of gaining a publication can cause one to overlook why publications receive points on specialty applications in the first place. With slightly more consideration to what we want to do and why we want to do it, we can derive more from what is, undeniably, a limited opportunity requiring a great deal of personal initiative.

It is really important to carefully consider what is likely to be gained from a potential project in terms of skills and experiences and how these can translate to one's career progression. It may be that a student wishes to gain more experience in research methods or that they might like to develop their writing or presentation skills. Whatever the aim, different formats of research, including original research, literature reviews and case reports, will offer unique advantages. Similarly, the decision between joining a research team and leading a small project can influence the impact of the research, the student's responsibilities on the project and the length of time the research will take. The process of applying for research electives and scholarships presented in this edition's cover article is one systematic way of considering the issues.

Equally important as considering the technicalities of a project, is to maintain sight of the fact that research at medical school is an opportunity to cultivate interests and potentially make a substantial contribution to medicine.

At the start of the summer of 1921, Charles Best, a second year medical student, won a coin toss that earned him a summer research project examining canine pancreatic extracts. This of course, was the project that culminated in the discovery of insulin and *almost* a Nobel Prize for this industrious student. In the 1950s, Thomas Fogarty, still at school, worked part-time as an operating theatre technician. There, he noted a high mortality rate following embolectomies which, at the time, were performed with a forceps. Subsequently, as a medical student, he began developing a device that would minimise the invasiveness of the procedure. Lo and behold, by the time he qualified in 1960 he had produced his embolectomy catheter, the first minimally invasive surgical device. Patented in 1969, it remains the most widely used device for embolectomies worldwide. These are just two examples of a long tradition of outstanding medical student research. There are also many individuals whose initial work at university led them on to immense achievements further down the line.

The moment of qualification from medical school is the moment the medical student can empty their pockets of their stethoscope and pocket-friendly handbooks. They can finally appreciate the magnitude of five years of knowledge acquisition and practice in the degree of indentation their stethoscope has left on their trousers. With knowledge and stethoscope having migrated upwards to be inside their head or around their neck respectively, the student can finally take upon themselves the long awaited responsibility for patient care that has taken half a decade to achieve. In the research world on the other hand, the contributions can commence from the very beginning and sometimes, even before that. It also goes without saying that the experience of doing research has great potential to inform and shape a student's career. So, in a period of one's life where a new pair of chinos may seem a luxury, let us try to be seen to be wearing our finest research caps so that we may make the most of the opportunities that come our way.

Mohamed Alsaffar, Editor, TSMJ

Since its establishment, the Trinity Student Medical Journal (TSMJ) has broken new ground year upon year. This edition, Volume 17, is the product of a newly adopted online-first publishing model that has enabled us to better showcase the exceptional standard of articles students are capable of producing. Online-first has also paved the way for our new features section, which aims to get to the very core of medical student issues. Of course, none of this would have been possible without the authors, who provided the excellent content for this edition, and the School of Medicine, Trinity College Dublin for their brilliant and continued support in the implementation of these developments.

TSMJ **Editorial Board, 2016**

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Applying for Research Electives

Conor Keogh
Peer Editor

Undertaking a summer research elective is a great way to assess whether academic research is something you would be interested in incorporating into your future training or career. It can also add something different to your CV when applying for more academically oriented specialisation training programmes. Despite this, very few people take advantage of the opportunities available to them and many that are interested in summer research simply don't know where to start looking.

This article will give a brief overview of where to start when considering a research elective, followed by first-hand accounts from students who have previously completed research electives.

*Further **student perspectives** and detailed information on the **major research funding programmes** can be found at our website:* **www.tsmj.ie/features/research-electives/**.

Identifying Opportunities

Broadly speaking, when planning a research elective you should consider the research group, the location as well as funding. Where you start should be dictated by the relative importance of these factors to you.

If there's a really specific area you want to work in, you're effectively governed by where groups working in that area are located. If you aren't already aware of them, Google search will usually identify places pretty quickly, as will researching the principal investigators (PIs) of publications written in the field. It's important though, to look at the group's publication lists to see if it is actually in line with your interests. However, if you really want/need to be somewhere specific then look at the relevant university's research page and try to find groups you're interested in at that institution. Prioritising location above all else is a dangerous approach though, as you're far more likely to end up with a topic that you aren't interested in. Then again it is still your summer, so whether you're happier in southern California doing work you hate or in northern Sweden doing something you love is a personal choice.

Funding is probably the single largest limiting factor in terms of organising a research elective. You probably shouldn't work for free - it's not very good for your bank account and knowing you're at least being paid makes it more bearable when an experiment goes on for way too long. There are a number of major undergraduate research programmes, and many of these have restrictions on where you can take the money - also an important consideration. If funding is a major concern for you, it may be worth limiting your search to groups you know you will be eligible for funding programmes with. Outside of these programmes, it is also important to investigate whether your university/department offers funding to students interested in research, or to simply ask a PI you have contacted about a project for assistance in securing funding.

Once you have identified research groups, the next major step is getting in contact with them. PIs in major institutions receive a large number of unsolicited emails every day and some simply can't take summer students regardless of how well worded your email is. So, if you want a response it is best to keep it short and to the point - briefly explain who you are and why you want to work with them and attach a more detailed CV and cover letter in case they are interested. This demonstrates respect for the PI's limited time and any principal investigators that can potentially accommodate you will respond to iron out the details.

Preparing Funding Applications

If you are planning to apply for funding from one of the scholarship programmes, it is important to make careful note of their deadlines. Outline this to all potential PIs as soon as you have confirmation that they can take on students - because you will need adequate time in advance of application deadlines, many of which are in early February, to develop a project proposal with your PI.

In addition, you will need letters of recommendation for many applications, and it is important to ensure that your referees have enough time to write and submit their letters in advance of any deadlines. Asking someone to write and submit a letter of recommendation by the end of the day is unlikely to result in a very favourable response. In terms of who to ask, this will depend on your previous experience - someone who has previously supervised you directly in an academic setting, such as a supervisor for a previous project, is ideal.

It's worth putting some serious time into your personal statements - many of the undergraduate funding programmes are very competitive, so it's important that you very clearly outline why you're applying and how this opportunity would benefit you - i.e. make it clear how this research elective fits into your overall career plan.

Given the time it takes to properly prepare an application and the early funding deadlines, it's necessary to start planning very early in the academic year if you want to be eligible for one of the funding opportunities. Generally speaking, it's never too early to register your interest with a potential research group.

Other Funding Sources

There are a numerous other funding sources for undergraduate research outside of the major programmes. In the event that there is a specific lab you want to work with which is not eligible for one of those sources, or if you were unsuccessful in getting funding from them, it is important to consider whether getting funding either from your university is possible or whether the PI of the lab can organise funding.

Many universities have specific funds for aiding students interested in research. For example, the Trinity College School of Medicine offer the Henry Cooke Drury Student Research Fellowship, which students organising a research project can apply for by submitting a project proposal and a rough breakdown of the amount required. Funds such as these offer flexibility in terms of where the project is carried out and many have significantly later application deadlines (the Henry Cooke Drury Student Research Fellowship applications close in mid to late April). This offers additional time to develop a project proposal for students deciding late in the year to carry out a research elective.

Finally, if it is not possible to acquire funding through any of the sources mentioned above, it is worth asking the PI you are planning to work with for assistance - they will likely be aware of where any previous students have acquired funding, and in some cases may even be able to acquire funding for your project through one of their own sources.

Research Electives: Personal Perspectives

Ralph Hurley O'Dwyer
- Henry Cooke Drury Student Research Fellowship

In summer 2014, I spent three months undertaking research in the field of neurogastroenterology at the Mayo Clinic in Rochester, Minnesota. As I am very interested in the links between the gut and the nervous system - particularly considering the high prevalence of disorders such as IBS and their poor management clinically - in October of 3rd year, I decided to try organise a research elective in the area. Having read about the neurogastroenterology research centre at the Mayo Clinic, I chanced my arm and sent an email to Dr. Michael Camilleri, head of the department and current President of the American Gastroenterological Association, expressing my interest in his research. To my surprise, Dr. Camilleri replied and arranged for me to go and spend the summer working for him.

Undertaking research at the Mayo Clinic was an incredible opportunity. I was immensely lucky to receive outstanding support and encouragement from Dr. Camilleri, Dr. Acosta, my other supervisor, as well as the other staff. Working there gave me an insight into clinical research and its direct impact for the benefit of patients when I was given the opportunity to attend Dr. Camilleri's consultations. It was amazing to see Dr. Camilleri implement his own research and discoveries to better treat his patients, many of whom had suffered for decades from their symptoms. I also saw what is involved in clinical trials and I witnessed the development of ideas - once exchanged at lunchtime - into studies and journal articles.

I was well supported throughout my stay in Rochester and even managed to publish a paper on adult megacolon with my supervisors shortly afterwards. I managed to present the research at Digestive Disease Week in Washington DC in May 2015.

It is important to state that I never would have been able to undertake this elective without financial support from Trinity College Dublin in the form of the Henry Cooke Drury Research Fellowship. I'm very grateful for the chance this fund gave me and would highly encourage anybody interested in research to apply.

Undertaking this elective has been of huge benefit and has opened up many doors, most of which I never knew even existed. My advice to those interested in research would be to chance your arm and to write to people whose research you are truly fascinated by. Quite often, you will be unlucky. But if you persist and show your interest, you never know where it might lead to!

Conor Keogh
- *Amgen Scholars, Europe*

I spent a significant portion of my summer working in the Institute for Biomedical Engineering, ETH Zurich, Switzerland. I decided early in third year that I wanted to do a research elective, largely because I have an interest in research and wanted to get some experience to evaluate whether or not the realities of academic work were some something I was actually willing to deal with long-term.

I started out by wasting time with unfocused searching for opportunities I might be interested in; eventually, however, I became efficient at finding labs in my field of interest, and from there I started sending unsolicited emails to principal investigators, which included a short statement outlining who I was (medical student interested in research), what I hoped for (to work with their group) and why, along with a CV and more detailed cover letter attached in case they didn't just instantly delete my email. I was actually met with a surprising amount of positivity, with most of the initial people I contacted replying to me - generally with positive responses. That said, I'm still pretty convinced no one ever actually looked at my CV and cover letter.

The next step was trying to secure funding so I could actually afford to leave Dublin. I had initially limited my search to the UK and Ireland, intending to apply for a Wellcome Trust summer scholarship, but through a search for other options I came across the Amgen Scholars programme, which I ended up applying to after some "logistical restructuring" (budget cuts) resulted in the project team I had initially committed to no longer being able to supervise students. After quickly going through all the labs in the host institutions, I pretty rapidly found one that was very well aligned with my interests, and applied directly to that lab. I was fortunate enough to be accepted, and ended up spending quite a bit of time there.

Going over, I very much expected the experience to be grim, spending most of the day working in a lab with little to no social contact. This was not the case. I got on very well with my lab, and since the Amgen Scholars programme is cohort-based (i.e. there was a group of us working in Zurich at the same time), I consistently had people to be a tourist with. The Amgen Foundation puts a strong emphasis on the social side of the programme, as it is good for their public image, so we had funding to go on numerous trips on the weekends, etc. and to see more of Switzerland than the inside of its technical institutes.

In the end, I was very glad I went ahead with a research elective. I got everything I had hoped to get out of it academically, as I experienced hands-on research in a world-leading institution in an area I'm interested in, while also living in a great city and actually having the time and money to enjoy myself. I'll openly admit that going in I was hesitant to give over my summer to research when I could have been on a beach in Thailand, but, I definitely don't regret it.

*More **student perspectives** as well as details of the **major undergraduate research programmes** can be found at our website:* **www.tsmj.ie/features/research-electives/**.

Concealed Accessory Pathway in Late Presentation Wolff-Parkinson-White Syndrome

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Background

During normal electrical conduction of the heart, an electrical impulse begins at the sino-atrial (SA) node and spreads across the right and left atria before passing through the atrioventricular (AV) node. It then passes down to the ventricles via the right and left bundle branches (of His) and finally the Purkinje fibres.

This pattern of electrical conductance creates the familiar tracing on an electrocardiogram (ECG) of a P-wave (representative of atrial depolarisation), followed by a flat section, the P-R interval; representing a delay as the electrical activity passes through the AV node, followed by a QRS wave representing ventricular depolarisation.

The P-R interval is normally 0.12 to 0.20 seconds in duration and the QRS complex is normally less than 0.12 seconds (Figure 1). This is important to note as in Wolff-Parkinson-White (WPW) syndrome, characteristic ECG changes may show a shortened P-R interval and widened QRS complex. These ECG changes may or may not be present at baseline.

In 1930, Louis Wolff, John Parkinson, and Paul Dudley White published an article in the American Heart Journal describing 11 patients with functional bundle branch block, a short P-R interval and arrhythmias (Wolff et al., 1930). To date, the authors now lend their names to a syndrome that encompasses ECG changes revealing of an accessory pathway (AP) of conduction within the heart and tachycardia. If the specific ECG changes associated with an AP occur without tachycardia, this is termed WPW "pattern".

In approximately 0.1% to 0.3% of the population (Ehtisham et al., 2005; Rodday et al., 2012), myocardial fibres connect the atria to the ipsilateral ventricles across the mitral or tricuspid annuli (Wolff et al., 1930).

This acts as a concealed AP for conduction that bypasses the AV node (Figure 2A). Unlike the normal AV nodal function, conduction is not delayed when traveling down these accessory pathways and thus pre-excitation or premature partial-depolarisation of the ventricles occurs, thereby, reducing the P-R interval. This produces the characteristic slurred and slow rising initial up-stroke of the QRS complex, or delta wave, immediately after the termination of the p-wave (Figures 1 & 3).

As described in our case, ECG changes may only occur when the AP becomes electrically active during tachycardia.

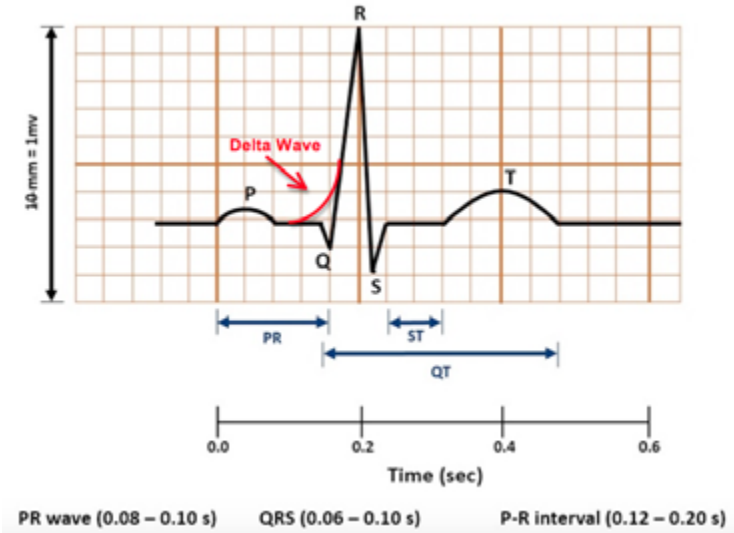

Figure 1. Normal Electrocardiogram (ECG) tracing and Delta wave.

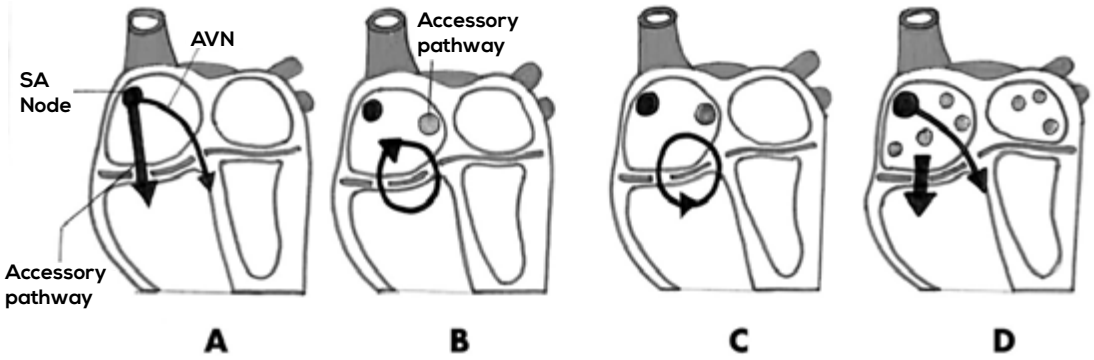

Figure 2. (A) A physiological mechanism of conduction in WPW with accessory pathway conduction (atrioventricular) resulting in the delta wave. (B) Orthodromic conduction in WPW syndrome occurring down AVN and retrogradely up accessory pathway. (C) Antidromic conduction where accessory pathway conducts anterogradely (atrioventricular) and the impulse returns to the atria via the AVN. (D) mechanism of AF in WPW syndrome.

Therefore there are no ECG changes at baseline and this can be described as a concealed AP (Kulig et al., 2010). If ECG changes are present at baseline this is described as a manifest pathway. These APs (Figure 2) may permit atrioventricular re-entrant tachycardia (AVRT), whereby electrical conduction travels as a circuit from the atrium to the ventricles and back to the atrium resulting in repeated AV nodal stimulation, inducing tachycardia. This accounts for 95% of re-entrant tachycardias in WPW patients (Blomström-Lundqvist et al., 2003).

Most commonly, the electrical impulse travels to the ventricles via the AV node and back to the atria via the AP in a retrograde manner. This is classified as orthodromic reciprocating tachycardia, and no delta wave is seen on ECG investigation (Figure 2B).

If the electrical impulse anterogradely travels to the ventricles via the AP and returns via the AV node, this is classified as antidromic reciprocating tachycardia (Figure 2C). This occurs in only 5-10% of cases (Blomström-Lundqvist et al., 2003). Lastly, the AP may lead to atrial fibrillation (Figure 2D). These arrhythmia experienced in WPW patients are potentially fatal and a summary of risk factors, signs and symptoms, ECG findings, and investigations can be found in Table 1.

Case Presentation

Here we describe a case of a concealed accessory pathway in a 64 year old lady who presented to cardiology in 2015 with acute chest pain, palpitations and shortness of breath on a background of heavy smoking (10 pack years), high cholesterol, type 2 diabetes mellitus and aortic regurgitation.

On admission, the patient was apyrexial with a blood pressure of 118/67, a pulse rate of 100/min and respiration rate of 15. The initial symptom of chest pain occurred at 11am in the morning following mild to moderate exertion whilst painting indoors on a ladder. The pain was continuous, dull and described as a central tightness across the chest radiating to the left neck and shoulder. Her subjective pain score was 8/10. The pain worsened on inspiration and there were no alleviating factors. Other presenting symptoms were pre-syncope, weakness, and numbness on the left side of the tongue.

The patient had slowly walked for nearly an hour to her General Practitioner who called an ambulance and administered sublingual glyceryl trinitrate without symptomatic relief. Of note, the patient's previous medical history revealed two previous admissions to A&E for chest pain in 2006/2007 which had been excluded as cardiac in origin by the cardiology team following negative blood tests, a normal 24 hour Holter ECG, and two non-revealing stress tests achieving 96% of her target heart rate.

Table 1. Summary of most common structural risk factors, signs and symptoms, ECG findings (not always present) and possible investigations in WPW syndrome

Risk Factor	Signs and symptoms	12 lead ECG findings indicative of WPW syndrome	Additional Investigations
Ebstein's Anomaly; The most commonly occurring congenital defect associated with WPW syndrome. It involves malformation of the tricuspid valve and may lead to cyanosis, dyspnoea, fatigue, arrhythmias, and congestive heart failure.	Palpitations Dizziness Dyspnoea Atrial Flutter Atrial Fibrillation Syncope or presyncope Tachycardia Sudden cardiac death	Shortened P-R interval of <0.12 s A prolonged QRS complex >0.11 s Delta Waves (bidirectional AP) No delta waves (retrograde AP)	Echocardiogram Treadmill test Pharmacological testing with procainamide or ajmaline may define duration of anterograde effective refractive period of the accessory pathway. Electrophysiological Study

ECG Findings

The appearance of the 12 lead ECG on admission revealed a wide QRS complex and regular monomorphic ventricular tachycardia (VT) (Figure 3). The patient was diagnosed by the clinician on-call as having monomorphic unstable VT and emergency direct current (DC) cardioversion was delivered as a synchronised shock. The patient was then converted to sinus rhythm (Figure 4). A differential diagnosis for wide complex tachyarrhythmias is given in Table 2 and in this clinical situation, the Brugada Criteria (Figure 5) provides a flow chart to the clinician that may be used to ascertain whether or not the tachyarrhythmia is ventricular or supraventricular in origin.

Investigations

Throughout the patient's admission, blood tests were non-revealing for any indication of ischaemia or other pathology. A coronary angiogram was performed to rule out coronary artery disease. As represented in Figures 6 and 7, very mild arterial disease within the right and left coronary arteries was found, mainly at the bifurcations and not in keeping with the signs and symptoms experienced by the patient. Both the coronary angiogram and transthoracic echocardiogram did not reveal any structural abnormalities. Following coronary angiography, delta wave ECG changes were detected, allowing for

Table 2. Differential Diagnosis of Wide Complex Tachyarrhythmias

Supraventricular Tachycardia With Bundle Branch Block	Bundle branch block can occur with any supraventricular arrhythmia
Supraventricular Tachycardia With Atrioventricular Conduction Over an Accessory Pathway	May occur during atrial flutter, atrial fibrillation, atrioventricular nodal reciprocating tachycardia (AVNRT), atrioventricular reciprocating tachycardia (AVRT), and atrial tachycardia
Ventricular Tachycardia	May be diagnosed using Brugada Criteria

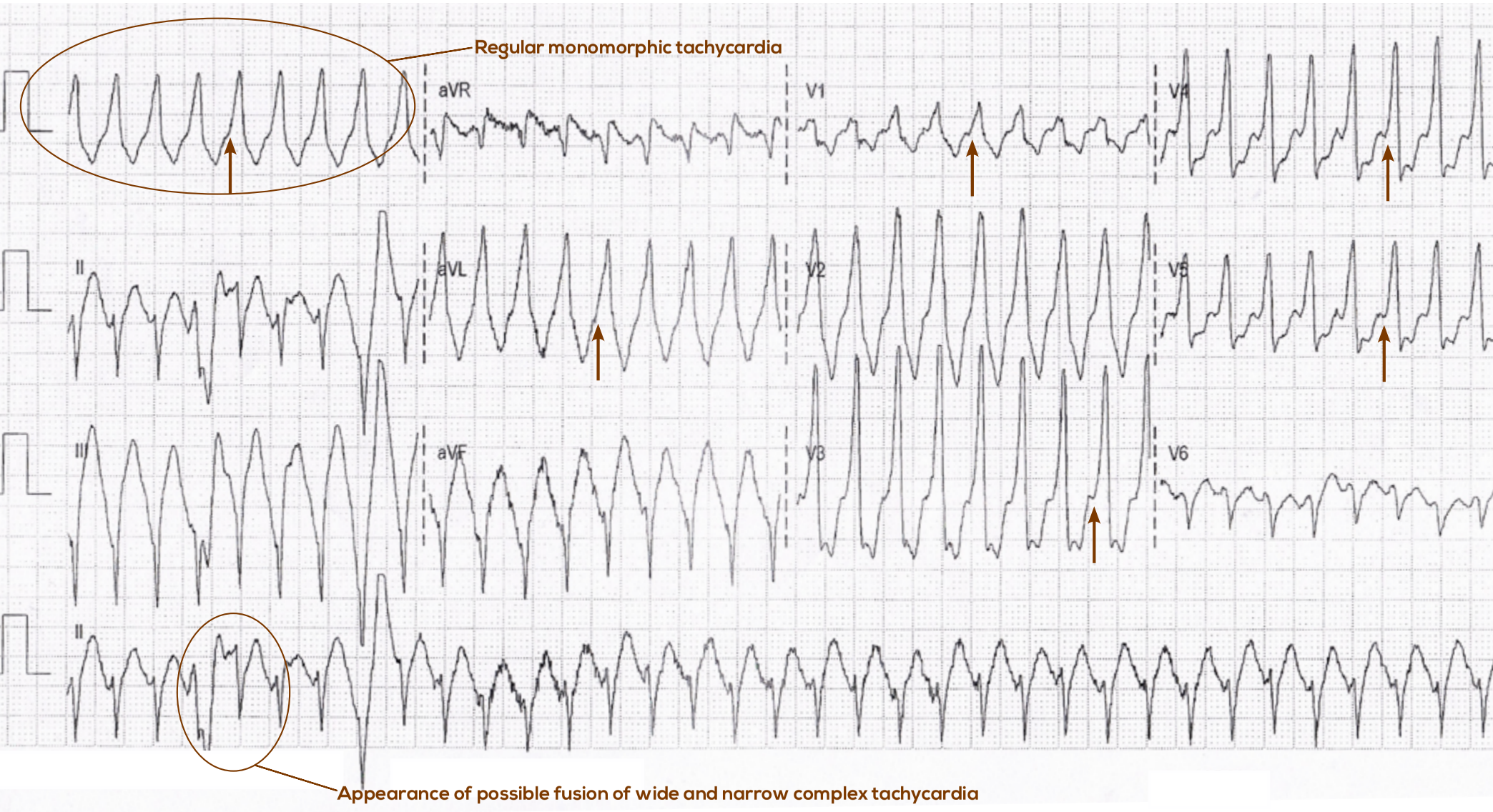

Figure 3. ECG on admission: Wide complex regular tachyarrhythmia showing delta waves (arrows) and right bundle branch block pattern.

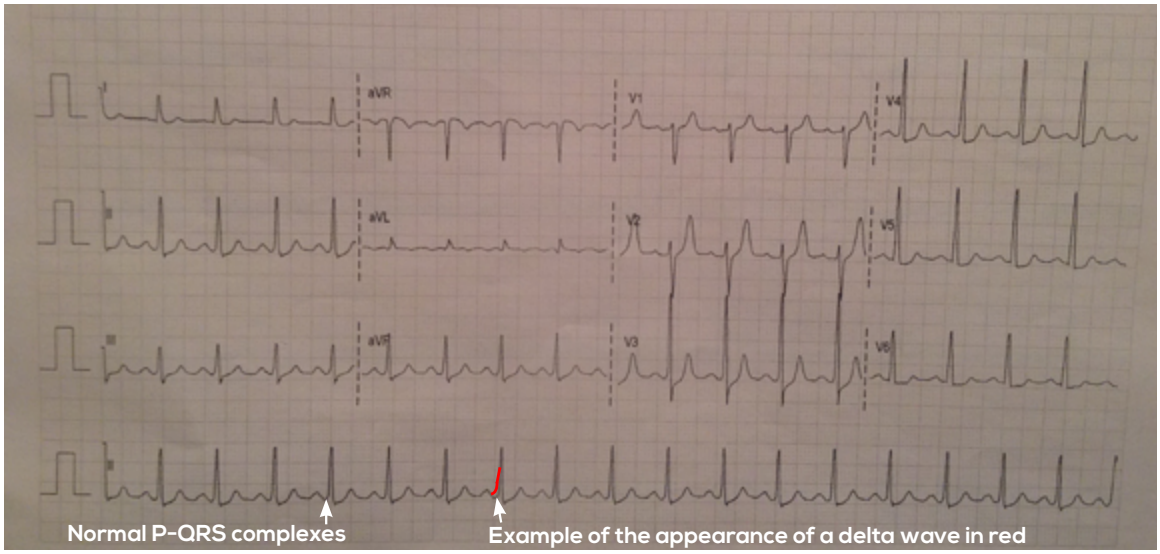

Figure 4. ECG following direct current cardioversion (DCC). Delta waves are not present on the post-DCC ECG which is highly suggestive of a concealed accessory pathway.

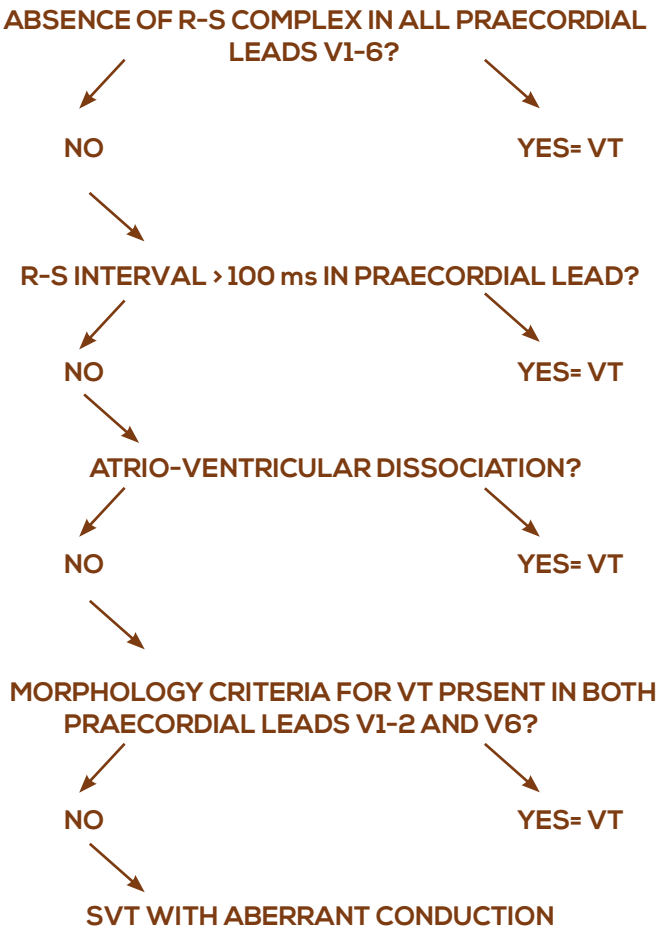

Figure 5. Based on Brugada Criteria (1991). Clinical guideline for a definitive diagnosis of wide complex tachyarrhythmias. In particular this flowchart aids in the differentiation between ventricular and supraventricular tachyarrhythmias.

definitive diagnosis of WPW syndrome. The patient was subsequently sent for electrophysiology in a separate procedure that was successful in locating and ablating a left sided accessory pathway.

Discussion

WPW patients may be asymptomatic or they may experience palpitations, chest pain, syncope, headache, dizziness, nausea, dyspnoea, impaired vision, arrhythmias or even sudden cardiac death in less than 0.1% of cases (Kulig et al., 2010). In a recent 8-year prospective study of 2,169 WPW syndrome patients in Italy, a greater proportion of asymptomatic patients

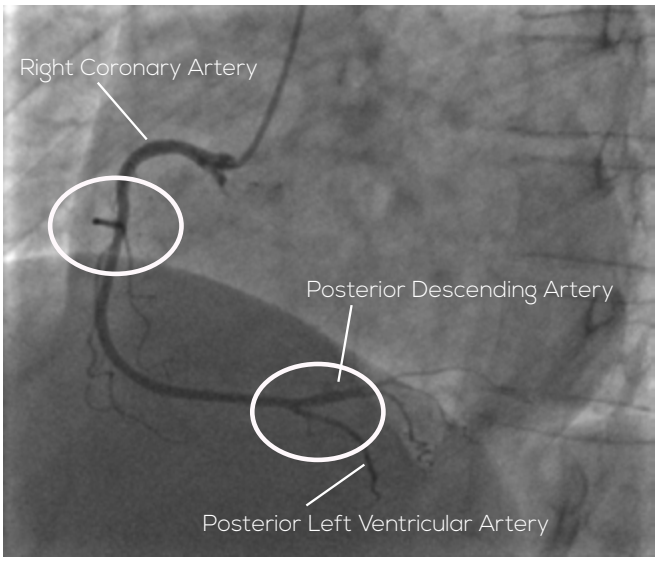

Figure 6. Angiogram of right coronary arteries from patient. Circles indicate areas of mild disease (continuity is slightly irregular in the areas of the bifurcations, as circled, but there is no obvious occlusion or stenosis).

experienced malignant arrhythmias (MA) and ventricular fibrillation (VF) than symptomatic patients. However, this was pertained to be due to symptomatic patients receiving ablation, leading to better long term outcomes. None of the 1168 patients who underwent ablation suffered MA or VF post-operatively compared to 93 of the 1001 non-ablated patients (Pappone et al., 2014). Fortunately, our patient eventually presented with symptoms and ECG changes in keeping with the WPW syndrome diagnosis, which allowed her previously concealed AP to be located and ablated.

In a larger 15 year prospective cohort study of 22,500 healthy aviation personnel undergoing systematic ECG screening, the WPW pattern was seen in 0.25% of subjects, and only 1.8% of those had documented arrhythmia diagnostic of WPW syndrome (Davidoff et al., 1981). For the general population, the risk is considered to be small and screening for WPW syndrome is not recommended at present. However all patients found to have WPW syndrome should be fully evaluated due to the risk of lethal arrhythmias (Blomström-Lundqvist et al., 2003).

Interesting aspects of this case include the concealment of her ECG findings as baseline and the age of the patient at presentation. Concealed APs may occur in approximately one third of accessory pathway tachycardias and are an important prognostic feature, as accurate diagnosis and ablation should lead to a permanent cure of tachycardia and prevents potentially lethal future arrhythmias (Ross and Uther, 1984). Patients with WPW syndrome may present at any age; however, it more commonly occurs in young people and decreases with age due to loss of pre-excitation (Jung et al., 2011). Our patient was 64 years old when she presented with detectable evidence of cardiac arrhythmia and positive ECG findings. It is therefore important to consider WPW syndrome as a differential diagnosis for cardiac arrhythmias with tachycardia irrespective of age or previously normal ECGs.

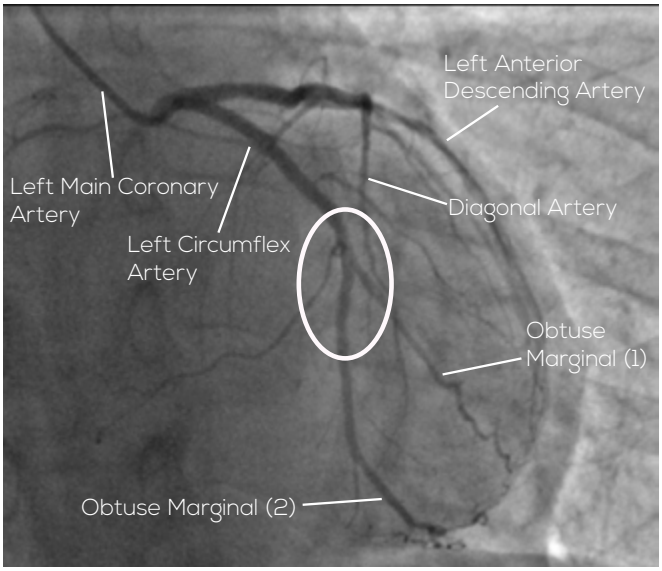

Figure 7. Angiogram of left coronary arteries from patient. Circles indicate areas of mild disease (continuity is slightly irregular in the areas of the bifurcations, as circled, but there is no obvious occlusion or stenosis).

Additionally, the patient presented acutely unwell with ECG findings of complex ventricular tachycardia. The treating clinician suspected the possibility of a fusion of wide and narrow complex tachycardia (Figure 3) and provisionally made a diagnosis of ventricular tachycardia. In actual fact, this was a p-wave followed by a wide complex QRS-complex wave, indicating supraventricular tachycardia. This was only confirmed post coronary angiogram having made a definitive diagnosis of WPW syndrome based on the ECG findings taken throughout the procedure.

The history of this patient was an important clue in helping ascertain a correct diagnosis. A patient with ventricular tachycardia is likely to be extremely unstable and unlikely to walk to her local GP over the course of an hour. However, at the time of presentation the patient was acutely unwell and did not reveal these details until after DC cardioversion.

Certain guidelines (Frankel et al., 2015) will advocate the use of IV adenosine before DC cardioversion in the management of our case. Adenosine is an antiarrhythmic with a half-life of less than 10 seconds and its effects are therefore self-limiting. It is, however, contraindicated in WPW with atrial fibrillation due to the risk of precipitating ventricular flutter and increasing the likelihood of sudden cardiac death. In these cases, ibutilide, procainamide, or flecainide are the preferred drug choices as they are capable of slowing conduction along the AP (Blomström-Lundqvist et al., 2003). Adenosine used in the presence of unstable ventricular tachycardia may lead to further deterioration and is therefore contraindicated.

As the clinician on call had made the provisional diagnosis of VT during initial presentation, this case highlights the importance of treating the case as ventricular tachycardia until proven otherwise.

Conclusion

This case describes an atypical acute presentation of a concealed AP in a female patient with WPW syndrome, presenting unusually late in life. The ECG appearance was that of a wide QRS complex, regular monomorphic VT, and new delta-waves presenting during an acute episode of tachycardia and post coronary angiogram. This case highlights the need to be vigilant in history taking, ECG analysis, and formulating a differential diagnosis in order to provide the best treatment for our patients.

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Promoting Resilience in Medical Students: A New Approach to Medical School Mental Illness

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Staff Writer

A Bleak Perspective

The mental health of medical students is a subject which has received copious attention in the past three decades. The perspective is usually bleak. As is the case for mental health in general, the focus has been on the negative aspects of students' psychological health – on vulnerability, or risk, rather than resilience. Indeed, trainee physicians appear to be uniquely vulnerable, with rates of depression among medical students as high as three times that of the rest of the population. Shockingly, almost a quarter of medical students in the United States suffer from some form of mental illness. The reasons for this increased vulnerability are numerous - among them the sleep deprivation and stress that many within this field consider par for the course. While the consequences of mental illness amongst future physicians, including worse patient care and more medical errors, are disturbing, this population has especially low rates of help-seeking. As such, it is imperative that medical schools emphasize the development of positive mental health early during training. A number of institutions have already begun trial programs to do just that, with significant success.

Mental Illness among Medical Students

As I've alluded to above, rates of depression and other mental illnesses appear to be significantly increased in medical students. Trainee physicians have much higher levels of distress, anxiety and depression than the population in general. Not only are medical students more depressed, they are also at a higher risk of suicide; the proportion of depressed medical students who experience suicidal thoughts is much higher than even those with severe depression. Medical students also score higher than population norms on general psychological distress tests. It is often said that those who pursue a career in the medical field are inherently more susceptible to mental illness, given the high entry requirements, which means they need to be high achieving and academically inclined. Some have even suggested that doctors' personality traits increase their vulnerability. Physicians tend to be more obsessional, experience more doubt and have an out-of-proportion sense of personal responsibility. This so-called "compulsive triad", while undoubtedly lending itself to conscientious patient care, could make medical students more likely to suffer from high levels of stress, increasing their risk of mental illness. This debate between social selection and social causation remains controversial but, in any case, it seems likely that medical education contributes significantly to psychological distress.

Under-treatment of Mental Illness and its Consequences

Alongside the high levels of mental illness in trainee doctors are parallel levels of under-treatment. There are a number of reasons for this. The most common reason is a perceived lack of time, followed by a lack of confidentiality, a fear of not being understood, as well as apprehension regarding the stigma surrounding mental illness. Students also express concern that seeking psychiatric help may tarnish their academic records. Indeed, medical students appear to have poor attitudes towards their own general health, with only approximately a third seeking regular healthcare. We cannot forget that medical students are mere years away from becoming practising physicians, and consequently their

health (or lack of) has a direct impact on patient safety. It is well known that doctors with poor mental health are more likely to commit medical errors and provide a lower standard of patient care. On the other hand, stable, resilient and healthy physicians are better able to provide their patients with better care, comfort and hope. Physicians who take good care of their own health are also more likely to discuss health promotion with their patients. Essentially, doctors who invest time and energy in their own well-being are better equipped to take responsibility for the well-being of others.

Changing the Focus from Risk to Resilience

Given the serious issue with medical students experiencing psychiatric distress for which they may not seek treatment, there is a serious need to approach the problem from a different angle. Many suggest adjusting the focus from treatment to prevention and from vulnerability and risk, to resilience. While it would be erroneous to suggest that depression (or indeed any mental illness) can be completely prevented by improving coping skills, coping strategies are undoubtedly a modifiable risk factor for depression. Indeed, psychoeducational "resilience" interventions may increase the ability of students to cope and also reduce the symptoms of mental illness. Some have gone as far as to suggest that interventions providing medical students with coping skills early during training is a matter of both patient and physician safety: "In a university medical degree course in which students are taught about managing the health of others, there is an imperative to provide them with effective, evidence-based ways to manage their own stress." wrote the authors of a key study on the effectiveness of mindfulness practice for medical students. Arming medical students with the skills to safe-guard their own mental wellbeing throughout medical training and beyond is important not only in terms of improving physician mental health but also in terms of improving professionalism, physician fulfilment and patient care. There is a growing consensus that student doctors who take part in stress-management programs experience benefits that range from decreased depression and anxiety and enhanced empathy to improved immunologic function. In a population who are clearly more susceptible to developing psychiatric illness, we need to attempt to modify the risk where possible. Intervening before illness occurs and cultivating resilience in medical students has benefits not only for the students themselves but also for their future patients.

The First Steps in the Right Direction

Although there is much work to do in terms of investigating the impact of resilience interventions on medical student mental health, so far there have been some promising steps in the right direction. The majority of programmes instigated to improve medical student resilience are based around mindfulness practice. Importantly, there is robust evidence implicating mindfulness as a means to improve anxiety and mood. In essence, students are taught evidence-based methods of stress reduction, an important coping skill, and one that will hopefully serve them well when facing the challenges of medical education. Despite the disparate methods of teaching and program organisation, mindfulness-based stress reduction courses for medical students seem to be effective. These courses, ranging from 4 to 10 weeks, reduce student depression and anxiety while increasing positive mood states and empathy. They also reduce stress and negative emotions in general and enhance mindfulness and self-compassion. The latter are important factors in terms of physician self-care, which, as we have noted, has a direct impact on professionalism and empathy. Mindfulness is not the only form of wellness intervention that may be used. Medical students who attend relaxation skills courses focusing on progressive muscle relaxation and autogenic training - a technique involving the use of visualisations to induce relaxation - seem to be less affected by burnout as well as anxiety. There is growing evidence that simple, implementable stress-reduction interventions may be effective in making medical students more resilient, and, in the process, decreasing their rates of mental illness. The imperative now is to build on the work that has been done and to incorporate it into medical school curricula in a standardised manner.

Conclusion

To conclude, medical school is a time of great upheaval and stress during which many students encounter issues with their mental health. In addition, too few are inclined to seek help. To combat this problem, many experts suggest a change in focus to building positive mental health and resilience earlier in training. Studies in this field have generated strong results so far which are indicative of the potential efficacy of these type of programs. They highlight the importance of an early focus on positive mental health, as opposed to waiting for symptoms to emerge before confronting it - a strategy which could alter the grim narrative of mental health in medical school. Above all, these studies represent an imperative to expand on the work that has already been done: these programs all work - but which work best? And how can we standardise this practice? Should such courses be mandatory or optional? When, during medical school, should they be provided? These questions, and more, will need to be answered before we see real change.

An Oncologist's Dilemma: How to Effectively Eliminate CNS Cancers in Children with Radiation Therapy Whilst Preserving Cognitive Function?

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Abstract

Cranial irradiation is commonly adopted in the treatment of central nervous system (CNS) tumours, even in younger cancer patients, despite its severe early and late side effects. One of the major consequences of using radiation therapy in the CNS is the inevitable occurrence of normal tissue toxicity and resultant morbidities including cognitive dysfunction, learning impairments and a lower quality of life. These symptoms are in part due to an arrest in the production or survival of neural precursor cells in particular proliferative regions of the brain including the hippocampus. As the population of childhood survivors of CNS or metastatic malignancy grows, more attention must be paid to the debilitating cognitive co-morbidities resulting from radiation therapy in particular. Protective prophylactic pharmacological agents and precise 'hippocampal-sparing' radiation techniques should be considered during treatment, while drug or behavioral interventions may be indicated during a patient's long term follow up period. This brief review overviews radiation therapy uses and mechanisms, investigates some of the currently known cellular and molecular events that lead to functional decline post-irradiation, examines the scarce therapies available to childhood CNS cancer survivors for their long-term cognitive morbidities to date and identifies possible therapeutic niches that could be targeted either during or post-radiation therapy to attenuate its long term consequences in the human brain.

Introduction

Tumours of the central nervous system (CNS) represent the most common solid neoplasms of childhood and overall are one of the more prevalent childhood malignancies (38 cases per million per year in Ireland) (NCRI, 2014) and are second only to the paediatric leukaemias (Pollack and Jakacki, 2011). Survival rates for childhood cancer in developed countries have improved considerably over the last few decades (5-year survival rate of ~70% amongst childhood CNS cancer patients in Ireland (NCRI, 2014)), owing to highly specific diagnostic procedures and the implementation and improvement of multi-modal treatment strategies (Kaatsch, 2010). It follows that a growing number of people are living with the effects of their anti-cancer treatment and thus survivorship is an extremely important topic, but one that may have been overlooked in the past (Jena and Coles, 2015). Unfortunately, CNS cancer survivors tend to be at an increased risk for developing chronic health conditions with the severity of these conditions often depending on the mode of treatment adopted to cure their cancers (Oeffinger et al., 2006). Radiotherapy (RT) alone or in combination with surgery and/or chemotherapy is a common therapeutic strategy for children with CNS tumours treated in Ireland (NCRI, 2014) and elsewhere (Pollack and Jakacki, 2011). Cranial radiotherapy, despite often acting as a curative agent in CNS cancer, has been associated with the development of late neurocognitive sequelae – namely cognitive dysfunction - often characterized by impaired short term memory formation - in both adults (Dias et al., 2014) and children (Dietrich et al., 2008; Ellenberg et al., 2009; Mulhern et al., 2004). Often untreated, these deficits severely detract from the quality of life of childhood cancer survivors and have been correlated with lower academic and socioeconomic achievement (Ellenberg et al., 2009). In fact it has been estimated that of all patients receiving cranial RT at an age less than 7 years, nearly 100% require special education. After 7 years of age ~50% require special education while some degree of memory dysfunction is thought to occur in the majority of children treated in this manner (Monje, 2008).

Local changes in neurogenesis have been characterized in the adult and child response to ionizing radiation (Raber et al., 2004). It is believed that cranial irradiation's off-target effects include the reduction in the neural precursor cell (NPC) pool of the memory formation and consolidation areas of the brain - i.e. in the hippocampus (Dietrich et al., 2008; Madsen et al., 2003; Monje et al., 2002; Monje et al., 2007). Damage manifests in the form of neural precursor apoptosis, glial cell perturbations and micro-vascular disturbance (Belkaet al., 2001) and these effects are thought to underlie the problems associated with cognition in the childhood cancer survivor population.

Few therapies are available to alleviate late neurocognitive effects post-RT and few prophylactic or mitigating strategies exist to preserve neurocognitive function before RT takes place. Thus, it appears that new treatments are urgently needed for this growing patient population. Both preventative and alleviating therapies should be designed with NPC molecular and cellular mechanisms in mind.

Meanwhile the clinician is faced with the dilemma of whether or not to apply increased doses of radiation therapy to the childhood brain for curative or relapse preventative reasons - all the while, not knowing how severe neurocognitive sequelae will be in each patient and how they will treat them post RT. In some cases higher doses of RT may be associated with both better cure rates and greater morbidity. In contrast, protocols aiming to minimize toxicity may increase the risk of relapse, disease progression, metastasis, or death (Askins and Moore, 2008).

Below RT is discussed in terms of its indication, mechanism of action and its most serious late side effects in childhood CNS cancer patients. Survivors' long-term cognitive morbidities are identified and explained biologically followed by a brief review of current treatments and possible therapeutic niches that could be targeted to attenuate the long-term consequences of brain irradiation and arm clinicians with a greater battery of tools to manage their patients effectively.

RT Indications, Mechanisms and Side Effects

Radiation therapy (RT) is an effective treatment for CNS neoplasms. The benefit of cranial irradiation in a clinical setting largely resides in its ability to effectively target microscopic and/or gross intracranial pathologies (Gondi et al., 2010). The main goal when treating malignancies with radiation therapy is to deprive tumor cells of their reproductive potential. Ionizing radiation causes direct and indirect DNA damage that ultimately facilitates death or quiescence of tumour cells by apoptosis, mitotic catastrophe or cellular senescence. Rapidly proliferating cells tend to be particularly sensitive to the effects of irradiation, which allows RT to non-specifically and successfully eliminate tumour cells (Eriksson and Stigbrand, 2010). However, damage to normal, surrounding tissue constitutes a major problem, and radiation therapy is associated with early and late adverse side effects, particularly in pediatric patients. CNS malignancies carry the greatest long-term side-effects of any tumor site (Heath et al., 2012).

One major late side effect of cranial RT, that may manifest months to years after treatment, is neurocognitive decline. Children tend to show a greater degree of debilitating injury and neurocognitive deficits post-RT than adults. This is not surprising given the inherent vulnerability of the developing brain, its higher content of rapidly proliferating neural precursor cells (NPCs) (Fukuda et al., 2005) and its ongoing high levels of neurogenesis and synaptogenesis (Dietrich et al., 2008; Gibson and Monje, 2012; Monje et al., 2002). The intensity of neurocognitive symptoms seems to be negatively correlated with the age of the patient at the time of treatment and positively correlated with increasing dosage of RT delivered (Lawrence et al., 2010). The functional neurocognitive domains that are affected the most by cancer treatments are attention, executive functioning, processing speed, working memory, and ability to learn, which in turn adversely affect the academic performance of pediatric cancer patients and childhood cancer survivors (Askins and Moore, 2008; Mulhern et al., 2004). Given the significant burden of post-RT morbidities, one might question the need to use radiotherapy at all. However the usefulness of radiotherapy should not be overlooked as it is one of the most effective non-surgical treatments of primary brain tumors and metastases.

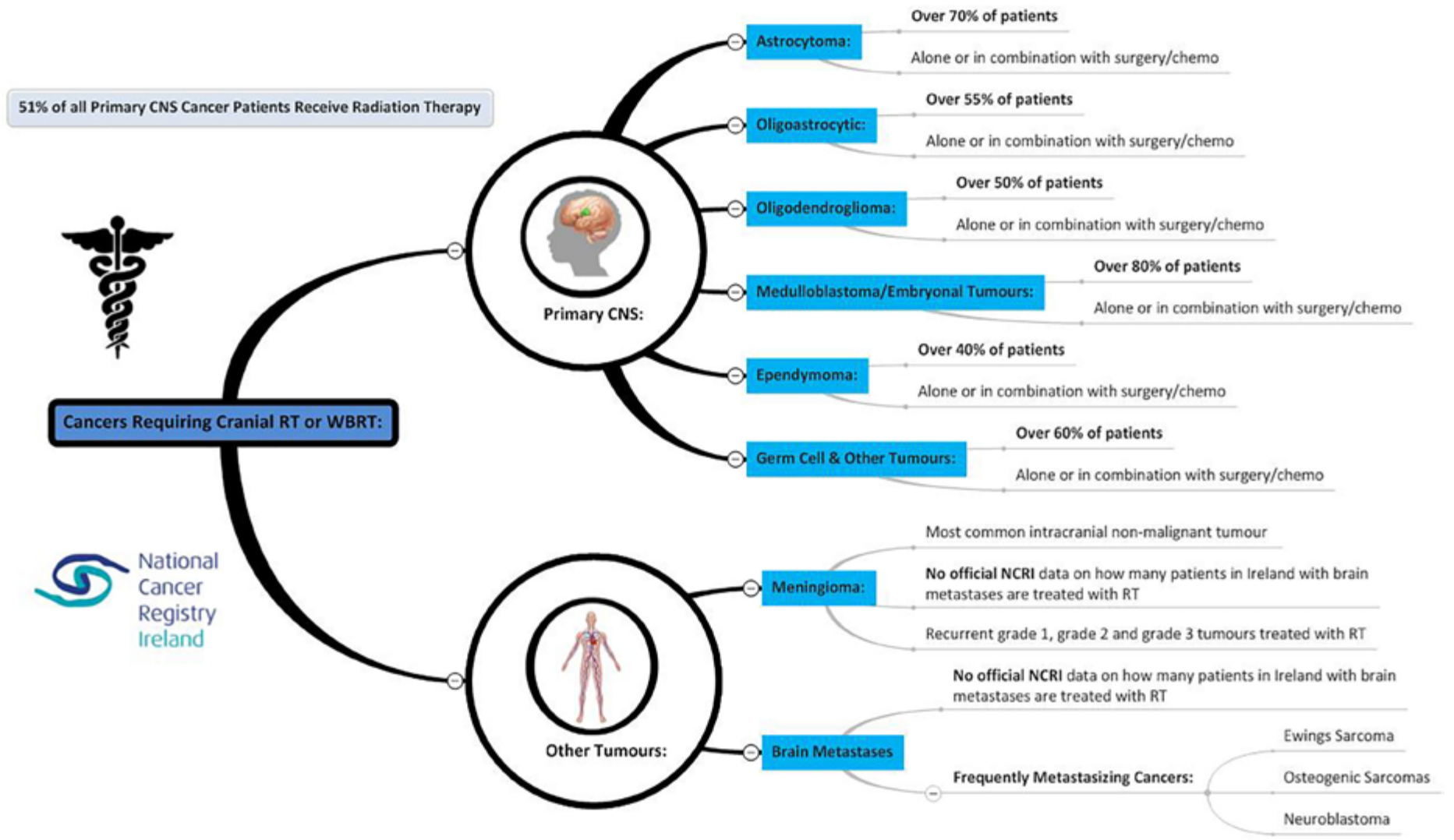

Figure 1. Schematic of CNS cancers requiring cranial irradiation (% of patients per year in Ireland).

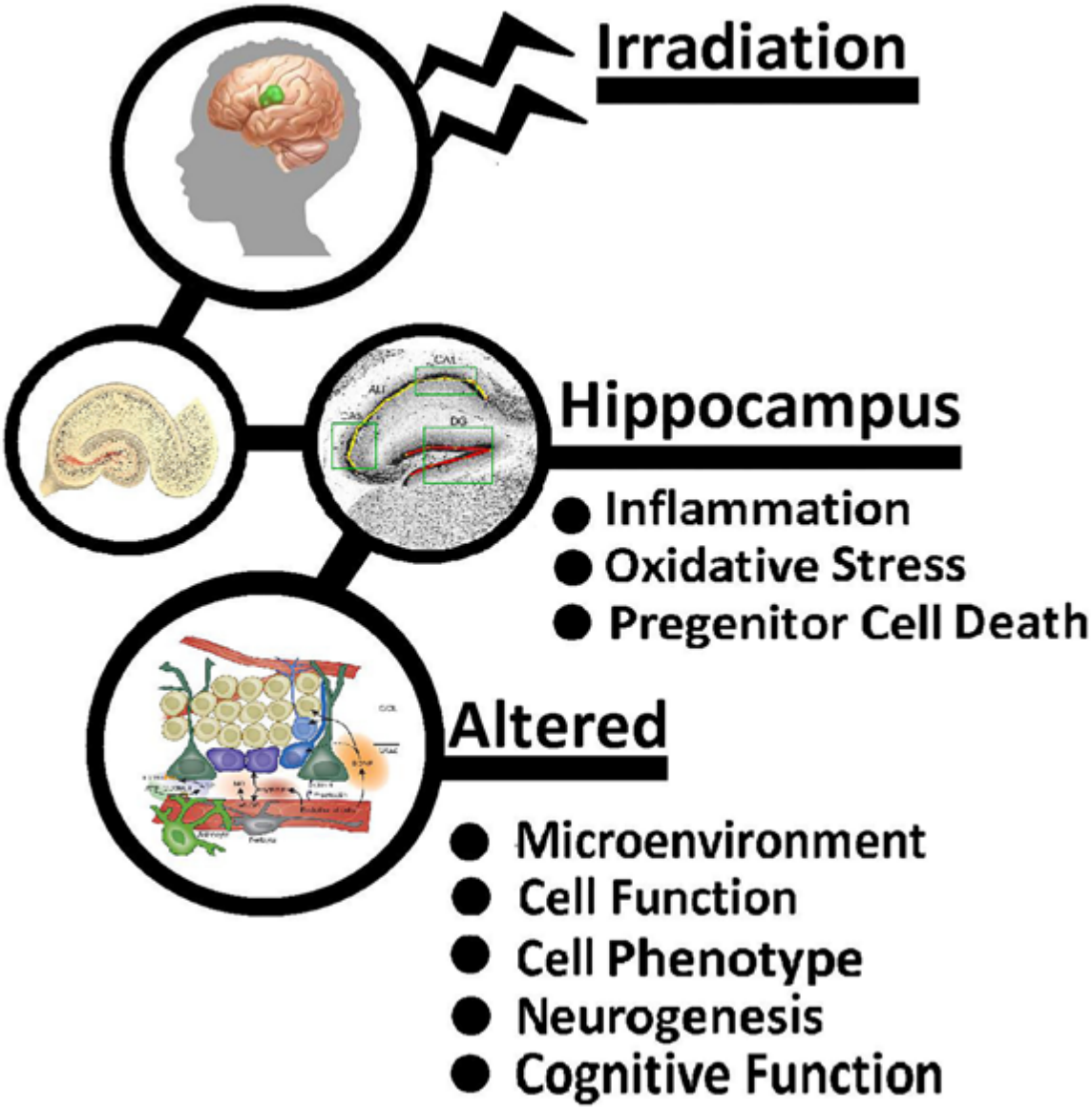

Figure 2. Schematic of radiation induced damage.

Cellular & Molecular Reasons for Neurocognitive Decline in Children

It was once thought that the neurocognitive decline that occurred in children post-RT was caused by direct damage to neuronal circuits. More recently, it was discovered that loss of cerebral white matter and near-complete ablation of the NPCs in proliferative regions of the brain are in fact causing at least some of the negative symptomology. White matter destruction is thought to partly account for changes in IQ score (Mulhern et al., 2004) while loss of NPCs in the hippocampus is thought to account for impaired memory formation in the irradiated infant brain (Gibson and Monje, 2012).

The latter observation has gained much attention in recent years and has become the subject of intense research due to its potential as a target for modulation. Much data has been gathered from rodent experiments (Kalm et al., 2013; Monje et al., 2002) and human studies (Monje et al., 2007). The formation of new memories has been associated with the lifelong mitotically active compartments of neural stem cells located in the sub-granular zone (SGZ) of the hippocampal dentate gyrus (DG)

Table 1. Current post-RT and pre-RT/preventative pharmacological strategies being studied worldwide	
Post-RT Interventions	**Preclinical/Clinical Stage? Effective?**
Donezapil	Studied in adults undergoing brain RT. Shows some improvement in cognitive function and mood (Shaw et al., 2006)
Methylphenidate	Prescribed to childhood cancer survivors with learning difficulties and shows some improved cognitive function (Meyers et al., 1998)
PPAR Agonists	Prevents cognitive impairment in irradiated rat model (Zhao et al., 2007)
Renin-Angiotensin System Blockers	ACE Inhibitors are being investigated in irradiated rat models. Data show reduced cognitive function change (Lee et al., 2012)
Pre-RT Preventative Strategies	**Preclinical/Clinical Stage? Effective?**
Memantine	NMDA antagonist used to prevent neuronal excitotoxicity. Reduces neuronal injury in rat models. Being investigated in a Phase III trial for adult whole brain RT and shows increased time to cognitive decline (Brown et al., 2013)
Indomethacin	Modulates inflammatory radiation response in rat model of neuroinflammation (Monje et al., 2003)
Lithium	Protects neuronal precursors in irradiated mouse model (Zanni et al., 2015)
Armodafinil	CNS stimulant that has been studied in adults receiving partial brain RT. Shown to reduce fatigue (Page et al., 2015)

and the subventricular zone (SVZ) in the lateral walls of the lateral ventricles (Eriksson et al., 1998). It has been shown in animal models that radiation induces apoptosis and loss of cells in the immature and juvenile rodent brain (Monje et al., 2002) and that the SVZ and SGZ are particularly susceptible to radiation-induced apoptosis. Decreases in cell proliferation and decreases in neuronal differentiation also occur in proliferative regions (Monje et al., 2002).

Recent studies have suggested that radiation not only directly induces cell death, but also affect the fate of the precursor cell pool by altering the local microenvironment. Radiation-induced inflammation was demonstrated to cause neural progenitors of the SGZ to differentiate into glial cells instead of neurons (Ekdahl et al, 2003; Monje et al., 2003). Hence, in addition to killing neuronal progenitors, radiation may direct the differentiation of remaining NPCs away from a neuronal lineage, resulting in further loss of neurons. Other micro-environmental determinants of neurogenesis include the presence of the trophic signals required for NPC proliferation, differentiation, survival, and the absence of inhibitory factors (Eriksson et al., 1998). In addition NPCs form a close anatomical relationship with the microvasculature in the neurogenic regions and this neurovascular relationship is believed to be crucial for nutritional and trophic support of newly formed neurons. Experimental models of irradiation injury often show that this niche also becomes perturbed post-therapy (Monje, 2008). In fact it has been noted that neurovascular damage sustained during the delivery of cranial RT in children may predispose these patients to further cerebrovascular issues such as stroke later in life (Roddy and Mueller, 2015).

An important negative regulator of the neurogenic microenvironment is microglial inflammation, particularly in disease states.

Pro-inflammatory cytokines secreted by activated microglial cells (which increase in number post-irradiation), including IL-6, IL-1-alpha and TNF-alpha, inhibit neurogenesis via a specific blockade in neuronal differentiation, as well as a nonspecific increase in precursor cell death (Monje et al., 2003).

Preventative Strategies & Therapies for Neurocognitive Decline in Children

There were no official clinical guidelines (NICE or otherwise) available for RT-induced neurocognitive sequelae management while this review was being composed. Hence the following is a collection of potential interventions that are being studied in clinical trials or in preclinical models.

Advances in RT Technology

Use of 3-D planning and intensity-modulated radiotherapy may help to prevent damage to critical neural structures (Belka et al., 2001). The use of fractionated cranial radiation therapy to deliver a greater number of small doses effectively (albeit incompletely) reduces toxicity to surrounding tissue. Stereotactic radiosurgery precisely targets a tumor by the use of very high-resolution neuro-imaging scans coupled with 3D computer-guided radiotherapy, so that the beam of ionizing radiation converges on the tumor while surrounding tissues receive only minimal exposure (Askins and Moore, 2008). Recent phase II clinical trials have shown promising results for the use of conformal hippocampal avoidance technology when delivering RT to the brain. Such hippocampus sparing attempts to avoid highly proliferative regions of the brain and directly targets tumours (Gondi et al., 2014; Gondi et al., 2010). The main disadvantage to this therapy is the suggested increased risk of incomplete ablation of cancer cells in certain regions. Another promising therapy - proton beam radiotherapy - involves almost all of the RT energy being focused onto the tumour, thereby sparing surrounding tissues of most toxic effects. This may not however be an appropriate treatment modality in all CNS cancers.

Pharmacological Interventions

Pharmacological interventions ideally should maximize brain function and minimize further damage. They can prophylactic, mitigating or treating in nature and are classified according to the time-points in which they are delivered (Moulder and Cohen, 2007). Most currently available pharmacological therapies are agents used to treat post-RT brain injury and include stimulants such as methylphenidate, acetylcholinesterase inhibitors like donezepil and the NMDA-receptor blocker memantine (Rooney & Laack, 2013). These drugs operate by altering neurotransmitter levels in the brain and are prescribed to alter cognitive function and attention post injury - with some effect. However they fail to address the apparent root of the problem - which a wealth of convincing data suggests is the neurogenic niche.

Take home points

- With improved childhood cancer diagnostic tools and therapies available, an increasing number of young patients are surviving CNS malignancies.
- Cranial irradiation is a mainstay of CNS anti-cancer therapy and often results in late and progressive neurocognitive dysfunction in both adult and younger patients being treated for primary CNS or metastatic cancers.
- Studies suggest that the underlying reason for the manifestation of late neurocognitive symptoms is a disturbance in the proliferative stem cell niches of the brain.
- Few (if any) effective therapies are available to treat the long-term neurocognitive side effects that result from the anti-cancer treatments patients receive.
- Preventative strategies for treatment induced cognitive decline including refined RT techniques and pharmacological interventions are being investigated but are yet to reach the clinic.
- To ultimately improve quality of life outcomes for patients, greater attention should be paid to cancer survivorship, in both the clinical and biomedical research settings.

Inflammation has been associated with reduced neurogenesis and administration of molecules that inhibit the production of pro-inflammatory cytokines by glia, such as microglia (e.g. minocycline), has attenuated this effect in animal models (Ekdahl et al., 2003). Other groups have shown that neuroinflammation alone inhibits neurogenesis and that inflammatory blockade with indomethacin, a common non-steroidal anti-inflammatory drug, augments neurogenesis after cranial irradiation (Monje et al., 2003). Given the breadth of evidence available to support the assumption that brain irradiation causes NPC loss due to the production and maintenance of a chronic inflammatory environment in the DG, it would stand to reason that local anti-inflammatory agents administered at different time points relative to radiation therapy should be investigated. Additional preclinical safety data are needed to ensure that calming the microglial response does not adversely affect tumor treatment efficacy.

Finally preclinical animal models support the use of lithium as a neuroprotective agent in the context of cranial irradiation. Lithium treatment protects irradiated hippocampal neurons from apoptosis and improves cognitive performance of irradiated mice. Lithium - more commonly associated with the treatment of psychiatric illnesses including bipolar disorder - has been shown in animal models to prevent neurocognitive deficits resulting from cranial irradiation (Yazlovitskaya et al., 2006; Zanni et al., 2015).

Stem Cell Transplantation

Animal brain irradiation experiments suggest that a depleted pool of DG neural precursor cells is the underlying reason for the development of neurocognitive difficulties over time - which then highlights the possibility of transplanting allogeneic neural stem cells into the injured brain to preserve function (Monje, 2008). Modulation of the recipient pro-inflammatory hippocampal microenvironment would have to occur before transplants to enhance transplanted precursor cell survival.

Behavioral Rehabilitation

Cognitive or behavioral remediation may provide benefit in attention, verbal memory, and mental fatigue. Programs consisting of developing new strategies to use intact cognitive pathways to perform impaired functions in new ways may improve the overall quality of life of patients in which all other available treatment modalities are contraindicated. Patients with the most severe impairments may not benefit from behavioural therapy due to cognitive deficits limiting the production of compensatory strategies (Askins and Moore, 2008).

A Need for Better Strategies

Finding a silver bullet strategy to target cognitive symptoms in the entire childhood CNS cancer survival population is highly unlikely. Differences between patients - with regard to tumour type, additional co-morbidities and concurrent therapies alongside RT - presents a highly heterogenous population to the biomedical scientist and to the oncologist. The biomedical scientist must thoroughly investigate as many neuroprotective avenues as possible and estimate clinical benefit. Meanwhile the clinician must decide what the optimal treatment is for childhood CNS cancer patients on a case-by-case basis. Personalised medicine - i.e. treatment tailored to an individual - is extremely fitting in this population. Ultimately it is down to the clinician's reasoning - based on the evidence placed in front of them in the form of a patient - to decide what strategy is required to maximize both survival and positive neurocognitive outcomes post-therapy. This places a lot of responsibility on the shoulders of the clinician and thus, requires the development of tools (mathematical models and advanced imaging techniques (Peiffer et al., 2013; Pospisil et al., 2015)) to predict the outcomes of each child's therapy and likelihood of cognitive decline. In order for oncologists to perform better and successfully treat cancer patients, they need more tools at their disposal.

Conclusions

Preserving neurocognitive function and childhood cancer survivor quality of life is becoming an important target in clinical trials as well as in daily practice. For progress to be made in the treatment of survivor cognitive comorbidities, the anatomy and biology of the neurogenic niches of the brain must be considered in the use of RT as a treatment or in protecting against or treating an RT-mediated insult. Therapies that help to protect or restore function in the hippocampus are fundamentally important in modern medicine. If the severe late effects of radiotherapy can be reduced, the overall quality of life would be greatly improved for the increasing number of children who survive CNS cancer. Specific diagnostic,

predictive and therapeutic tools need to be added to the clinician's arsenal so that they can further refine the balance between improved patient survival and acceptable toxicity and thus, ensure that children not only survive CNS cancers but also have the opportunity to live a normal life and achieve age-matched goals post-therapy.

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Paediatrics Prize Winner: The Neonatal Microbiome

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"*The supreme act of war is to subdue thy enemy without fighting*" – Sun Tzu, The Art of War

Introduction

"The human microbiome" was termed in 2001 by Nobel Laureate Joshua Lederberg to encompass, "the ecological community of commensal, symbiotic and pathogenic microorganisms that literally share our body space." (Peterson et al. 2009; Sherman et al. 2013). In other words, "the sum of all microbial life in or on the human body" (Gritz and Bhandari, 2015). Afterwards, Lederberg, Relman and Falcow envisioned a, "second human genome project" - The Human Microbiome (HM) Project (Sherman et al., 2013). Thus, in the last 15 years, the world of medicine has witnessed a revolution in how we view our symbiotic relationship with our microbiome. With evidence emerging from the project regarding the implications of bacteria, viruses, fungi and parasites in obesity, allergic and autoimmune diseases, diabetes (Sherman et al., 2013), cancer, mood disorders and even therapeutic faecal microbiota transplantation (FMT) the question of whether they are friend or foe arises. In adulthood, the human body is colonized by more than 10 times as many bacteria as human cells (Peterson et al., 2009). If we are covered in the region of ten to one hundred trillion microbes (Peterson et al., 2009), this begs the philosophical question, are we even human? In the neonatal period of modern medicine, Hippocrates is credited with saying, "all diseases begin in the gut". New evidence over-turns the paradigm that the foetus is in a sterile environment as the placental microbiome has been identified, which may colonise the foetus in small numbers (Wassenaar and Panigrahi, 2014). What we will learn from this essay is the elegance of the gut microbiome of the neonate, its journey from utero to early infancy. In particular, we will acknowledge its role in disease and how to prevent such states.

Methodology: The Arms Race

Metagenomics is a rapidly evolving field of medicine born from the Human Genome Project (HGP), describing the study of the structure and function of the "microbiome", the term being coined by Handelsman et al.. Remember, that in the human, the microbiome consists of a myriad of genomes of bacteria, archaea, viruses, fungi and protists. It took 13 years to complete the HGP in 2003 and the HM consists of 150 times more genes (Cong et al., 2015). In just over a century, we've moved from Koch and colleagues' methods of culture and isolation to culture-independent Next Generation Sequencing (NGS) (Sherman et al., 2013). In 1985, polymerase chain reaction (PCR) cloning of precise genes, such as the 16S ribosomal RNA subunit, has made waves in whole genome analysis that allow us to study phylogenetics and taxonomy (Gritz and Bhandari, 2015; Till et al., 2015; Dunlop et al., 2015). It is postulated that up to 50% of the species of the HM cannot be cultured (Dunlop et al., 2015). Therefore, it is a necessity that shotgun metagenomics and amplicon sequencing (a combination of NGS and PCR), are employed in analyzing the HM (Aho et al., 2015). DNA based techniques have been proven to be needed in this field when Venter et al. studied the microbiome of the Sargasso sea (Aho et al., 2015; Venter et al., 2004). In 2004, they demonstrated the superiority of shotgun metagenomics compared to PCR rRNA studies due to its quantitative identification of the species diversity (Venter et al., 2004). Amplicon sequencing is described as a genetic region, common to the members of interest, being amplified using universal primers (Aho et al., 2015). 16S rRNA amplicon sequencing is limited to prokaryotes. With a combined approach, with these tools of sequencing and workflow, we can begin to sketch the phylogentic tree that is the HM. New technologies include the 454/Roche and Illumina/Solexa sequencing. These greatly reduce the cost and manpower analyzing whole genomes (Thomas et al., 2012). Each of these technologies boasts advantages as regards their low error rates, length of reads and insert sizes. Extensive reviews describing these are available. In the future, it is

hoped that de Bruijn-type assemblers, specifically "metagenomic assemblers" will be developed for scientific use (Thomas et al., 2012). A drawback of all these technologies, however, is that they are still in their infancy and so reference libraries do not exist for comparative analysis.

A more pressing limitation is sample collection. Till et al. calls us to question whether faecal sampling is an accurate representation of the intestinal microbiome and whether the transient luminal bowel in its diseased state is synonymous with the mucosal microbiome (Till et al., 2015). Are we required to take direct endoscopic samples from various areas of the bowel to get a more precise representation of the gut microbiome? Sample sizes and stratification into sub-cohorts may hinder progress in this field for some time.

Finally, it is important to remember there are a number of ethical issues in the study of neonates in intervening or not intervening.

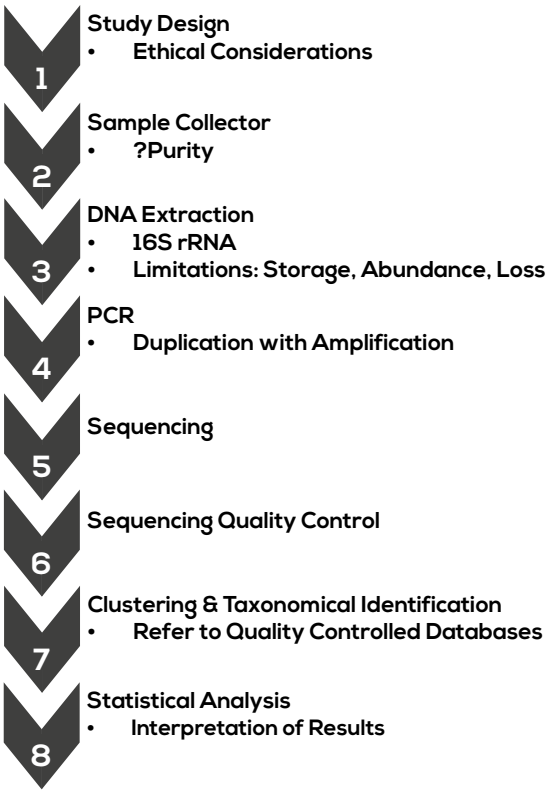

Figure 1. Potential workflow for a Microbiome Study. Adapted from Aho et al., 2015.

The Neonatal Microbiome

"*Il faut cultiver notre jardin*" (We must cultivate our garden) – Voltaire

A neonate's microbiome is influenced by a host of different factors. Genetic factors, the maternal microbiome, mode of delivery, diet, environmental factors and a dynamic interplay between the developing immune and metabolic systems all play a part (Figure 3). The neonate's microbiome launches into action in the first year of life, resembling a mature "adult-like" microbiome from 1-4 years to population equilibrium (Stewart et al., 2015; La Rosa et al., 2014). The average adult has a more individualized microbiome than genome as it harbours a mere 15% of the growing number of intestinal bacterial species already documented (Gritz and Bhandari, 2015; Madan et al., 2012). What this means is that there is huge diversity between the microbiota that colonize you and your neighbour. In neonates and infants, it plays a quintessential and dynamic part in prevention of pathogen invasion, and immune and metabolic programming.

Prenatal Microbiome

Despite popular opinion that the uterus and foetus are in a sterile environment and that our first encounter with the microbe corps is at birth, recent studies disprove this with the identification of the placental microbiome (Wassenaar and Panigrahi, 2014; Satokari et al., 2009). We have seen in many disease states (and indeed normal states), that commensal bacteria translocate to various locations such as the mesenteric lymph nodes, portal venous system and beyond (Satokari et al., 2009; Berg and Garlington, 1979; MacFie, 2004; Romano-Keeler and Weitkamp, 2014). In 2014, in a study by Aagard et al. involving 320 women, it was reported that "a unique placental microbiome niche, composed of nonpathogenic commensal microbiota from the Firmicutes, Tenericutes, Proteobacteria, Bacteroidetes, and Fusobacteria phyla," was found amongst study participants (Aagaard et al., 2014). This "garden" was similar to the oral microbiome (Aagaard et al., 2014). Investigators were unconvinced that these were the fruits of contamination (Wassenaar and Panigrahi, 2014). Instead it was suggested that Fusobacteria nucleatum may permit haematogenous transmission by increasing permeability with FadA binding vascular endothelial cadherin

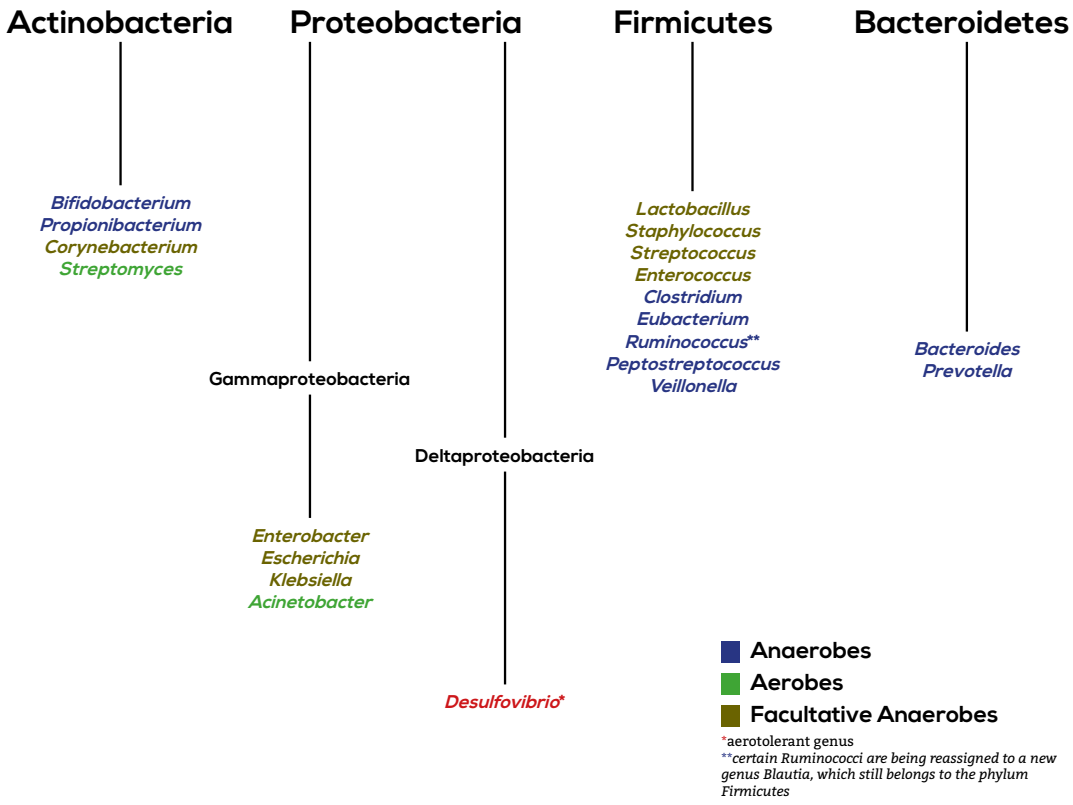

Figure 2. Common microbes in the Neonate. Adapted from Gritz and Bhandari, 2015.

at placentation (Wassenaar and Panigrahi, 2014). This potentially allows troops of microbes to cross the border to the amnion. However, this has not been demonstrated in a lab. Is the Placental Microbiome a friend or a foe? Or a symbiotic evolutionary natural occurrence that allows the fetal "gut barrier" and immune and alimentary immune system to develop? The precise timing of fetal or neonatal intestinal colonization is not known or proven (Romano-Keeler and Weitkamp, 2014). Infection and spontaneous preterm labour are almost synonymous with cause and effect with the origin thought to be from a vaginal or urinary tract infection (Goldenberg et al., 2000). Despite this, Goldenberg et al. showed in preterm labour with intact membranes, bacteria can still be cultured in a sterile procedure from chorioamniotic tissue (Goldenberg et al., 2000). Thus, in terms of the maternal-fetal microbiome the species, population and density of bacteria in the placenta directly play a part for pregnancy outcomes and fetal health (Romano-Keeler and Weitkamp, 2014; Epstein et al., 2000). In the first trimester, CD4+ and CD8+ cells can be identified (Spencer et al., 1986). Throughout fetal life we see Peyer's patches, Paneth cells and goblet cells developing from 9-17 weeks gestation (Brugman et al., 2015). T-regulatory cells develop in the second trimester possibly suggesting the idea that peripheral tolerance and exposure to microbial antigens occurs in utero (Brugman et al., 2015) and the maternal microbiome is the source of the fetal microbiome (Collado et al., 2012).

Perinatal Microbiome

At birth, facultative anaerobes are first to colonize, followed by anaerobic Bifidobacterium, Bacteroides and Clostridium (Cong et al., 2015). The microflora in the neonate and even to adult life is influenced by its mode of delivery. Born via the vaginal canal, one is graced with maternal vaginal and perineal microbes, but if born by Caesarian

section (CS) or in hospital, one carries with them nosocomial microbes (Penders et al., 2006). In the KOALA Birth Cohort Study (Netherlands) involving 1032 infants, Penders et al. showed that the CS group had decreased populations of Bifidobacteria and Bacteroides (100 fold) with increased Clostridum difficile (100 fold) and Escherichia coli compared with the vaginally delivered at home group (Penders et al., 2006). Vaginally delivered infants will be colonized by the vaginal microbiome (Lactobacilli and Prevotella) while CS infants will culture Staphylococcus from the skin Propionibacterium and Corneybacterium (Madan et al., 2012). CS delivered infants with lower Bifidobacteria mount a stronger humoral response at 1 month and then have higher rates of allergy, auto-immune, metabolic disorders (diabetes and obsesity) and GI dysfunction in later life (Brugman et al., 2015; Borre et al., 2014).

Postnatal

Breast fed infants have a greater and more stable population of Bifidobacteria that is beneficial to immune development (Collado et al., 2012; Borre et al., 2014). Skin flora such as Staphylococcus, Corynebacterium, and Propionibacterium will also begin to colonize the neonate as it begins to suckle. The bounty of Staph. epidermidis and Staph. aureus in breast-fed neonates' faeces versus formula fed infants' indicates an adventitious advantage as they are involved in lactose and galactose metabolism through the D-tagatose-6-phosphate pathway and play a part in the metabolism of milk oligosaccharides (Rodríguez, 2014; Schleifer et al., 1978; Hunt et al., 2012). Solely formula fed infants were associated with higher incidence of E. coli, C. difficile, Bacteroides and Lactobacilli and earlier introduction of non-maternal products being linked with infections (Collado et al., 2012). The microbial conquest of the baby via breast feeding also has a dynamic and interlinked role with passive immunity. Prematurity, Hospital and NICU admission also saw a spike in Clostridium species count, especially with hospital stay (Collado et al., 2012; Hartz et al., 2015). Antibiotics are the weapons we use to prevent and treat infections, but caution must be taken when doing an "airstrike" on the microbiome to wipe out the pathogenic enemies. Commensal innocent casualties are seen with depleted Bifidobacteria and Bacteroides, which we've already noted to be important for microflora stability and immune development. (Collado et al. 2012).

Neonatal Disease States

Neonatology and microbiology are interlinked with the peri- and postnatal immature immune system and gut being exposed to an abundance of microbes. Necrotising enterocolitis (NEC), short bowel syndrome (SBS), Hirschsprung's disease associated enterocolitis (HAEC) and late onset sepsis (LOS) all have preceding microbiome changes - a dysbiosis, often resulting in catastrophic consequences for the fetus. A particular knowledge chasm leaves us questioning the pathogenesis of such diseases and how to prevent them.

NEC is still a prevalent disease seen by paediatric surgeons and the neonatal intensive care unit (NICU), yet outcomes remain dismal despite advancements in medicine. It is a syndrome delineated by abdominal distension, bilious aspirates, blood stools and intramural air (pneomatosis intestinalis) on abdominal X-ray (Lissauer et al., 2015). The severity of which is classified using the Bell's staging (Lin and Stoll, 2006). A most grave gastrointestinal disease of preterm infants, affects 2-10% of very low birthweight infants (<1500g) with a mortality of 25-30% (Till et al., 2015; Lissauer et al., 2015).

Risk factors for NEC include preterm birth, formula feeding, hypoxic-ischemic insult to the gut, flawed intestinal motility and disproportional microbial colonization (Till et al., 2015; Lissauer et al., 2015; McElroy et al., 2012). Studies show that NEC does not manifest in germ-free mice and so we can deduce that the microbiome plays a role in its aetiology (Musemeche et al., 1986; Jilling et al., 2006). This corraborates the statement from the 2006 NICHD workshop on NEC research, "NEC can be thought to arise from an uncontrolled exuberant inflammatory response to bacterial colonization that characterizes the intestine of premature infant" (Gritz and Bhandari, 2015). 90% of the infants with NEC are premature and have a premature "gut barrier" and immune system (Lin and Stoll, 2006). The mature gut epithelial barrier has tight junctional complexes that permit protective mechanisms such as secretary diarrhea (Lin and Stoll, 2006). When underdeveloped, pathogens and toxins such as LPS are left interacting with the premature mucousa (Neu, 2014). The interaction between Toll like receptor 4 and lipopolysaccharides from gram negatives (such as Proteobacteria e.g. Klebsiella, E. coli) allows translocation to take place and promotes the inflammatory cascade

Figure 3. Influences on the Neonatal Microbiome.

that we see in NEC (McElroy et al., 2012; Neu, 2014). Whether it is a "top-down" or "bottom-up" hypothesis that occurs in coagulation necrosis at the mucosa in NEC is yet to be elucidated but a combination of both is probable (McElroy et al., 2012). Morrow et al. demonstrated that a week and <72 hours preceding a NEC diagnosis, 11 patients (Total n=35 preterm infants, <29 weeks Gestational age and <1,200 g) had an overabundance of Proteobacteria (Enterobacter and Escherichia) and decreased Firmicutes (Enterococcus and Staphylococcus) and diversity (Morrow et al., 2013). Bacteroidetes and Actinobacteria were minimally detected (Morrow et al., 2013).

Short bowel syndrome is caused by a number of paediatric surgical conditions from NEC, congenital defects, volvulus or anything that may result in resection of the intestine (Till et al., 2015). Lactobacillus overgrowth and limited Clostriudium leptum, Clostridium coccoides and Bacteroidtes was found in a small study of these patients (Till et al., 2015). Lactobacillus, a facultative anaerobe, may be an advantageous adaption as it can ferment carbohydrates (Till et al., 2015). Dysbiosis seems to be related more to parenteral nutrition in SBS with Enggstran et al. finding an overgrowth of Enterobacteriaceae in these patients (Lilja et al., 2015). Small sample sizes of SBS patients with

dissimilar profiles results in difficulties in standardizing and treating these patients.

Congenital segmental absence of the enteral nervous system results in intestinal obstruction and is treated with surgical resection (Till et al., 2015). Yet, 40% of this cohort still suffers from HAEC. Clostridium difficile is postulated to play a role, along with Proteobacteria and Firmicutes (Till et al., 2015). Faecal bacterial diversity was much greater than fungal with an overabundance of Candida species and decreasesd Saccharomyces and Malassezia in a trial by Frykman et al. comparing of 9 children with HAEC and 9 without (Till et al., 2015; Frykman et al., 2015).

NEC, SBS and HAEC all have complex and dynamic pathogeneses between the microbiome and immune and vascular systems but a similar theme is emerging - an abundance of Proteobacteria is documented in all (Till et al., 2015).

Leverage & Negotiations

Leveraging the populace of the microbiome to work in our favour could prevent not only neonatal disease states but adult diseases. Probiotics, prebiotics and successful FMT are currently being investigated in adults and neonates to alter the disease states (Sanz, 2011; Ly et al., 2011; Indrio and Neu, 2011; Gibson et al., 2004; Donovan et al., 2012; Brandt, 2012). Gibson et al. defines probiotics as "microbial food supplements that beneficially affect the host by improving its intestinal microbial balance, have been used to change the composition of colonie microbiota" (Gibson et al., 2004). Prebiotics are "nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacterial species already resident in the colon, and thus attempt to improve host health" (Gibson et al., 2004). Meta-analyses of their implementation argue strongly in favour of their use in preventing dysbiotic related disease (Aceti et al., 2015), yet more studies need to be done to corroborate findings as regards specific probiotic strains, dosage, duration and target population. Bifidobacteria species has been seen to reduce the rates of NEC (Aceti et al., 2015). However in Extremely low birth weight infants (<1000g), these probiotic effects make no difference (Aceti et al., 2015). Natural probiotics as we have seen from breast milk have a lower risk of NEC compared with formula fed infants (Aceti et al., 2015). No adverse effects were reported but we need to clarify the effects of probiotics in specific groups. In the wake of the prevalence of allergy and autoimmunity in the developed world, employing the use of probiotics may curb this rate (Collado et al., 2012). Prebiotics in maternal milk such as oligosaccharides, glycoproteins, glycolipids, glycoaminoglycans have a "bifidoegnic effect" and encourage a genetically similar and balanced microbiome in the neonate (Sherman, 2010). The glycans additionally protect the gut from microbe binding, detoxify the gut, dampen inflammation and aid development of innate immunity (Sherman, 2010). FMT which has a 90%+ cure rate could also be employed for specific SBS patients with dysbiosis (Lilja et al., 2015). The incidence of severe side effects such as inoculation with a donor infection is low; however, prudent medical and ethical consideration of the children and their health status must be taken into account before this is attempted (Lilja et al., 2015).

Conclusion

The reason I wanted to study medicine was because one day my obnoxious 4-year-old self refused to eat Weetabix and yoghurt, a prebiotic, when my father was trying to nurse me back to health. Exasperated, he told me an elaborate story of the "baddies" that had made me sick. The yoghurt and the Weetabix were teaming with the good guys, James Bond-esque figures, who would seek out and destroy those who dared cause illness to me. Essentially, I was inspired to take arms in the microbiome war. When we think that we are possibly 1% genetically human, it's quite difficult to ignore our ecological environment. Future studies, this author would recommend, should look to establish the concrete relationships between the immunological system and the microbiome. Specific biomarkers of disease states, in particular in relation to NEC and sepsis in neonatology could be developed to detect and treat diseases early so as to prevent morbidity, mortality and parental psychological/emotional pain. 20% of NICU costs in the United States, (i.e. several billion dollars), are attributable to just NEC. A bit of probiotic spilt milk to prevent this is nothing to cry over. Preventative medicine and non-operative treatment of these dysbiotic diseases would revolutionize neonatology, paediatrics, and long-term outcomes.

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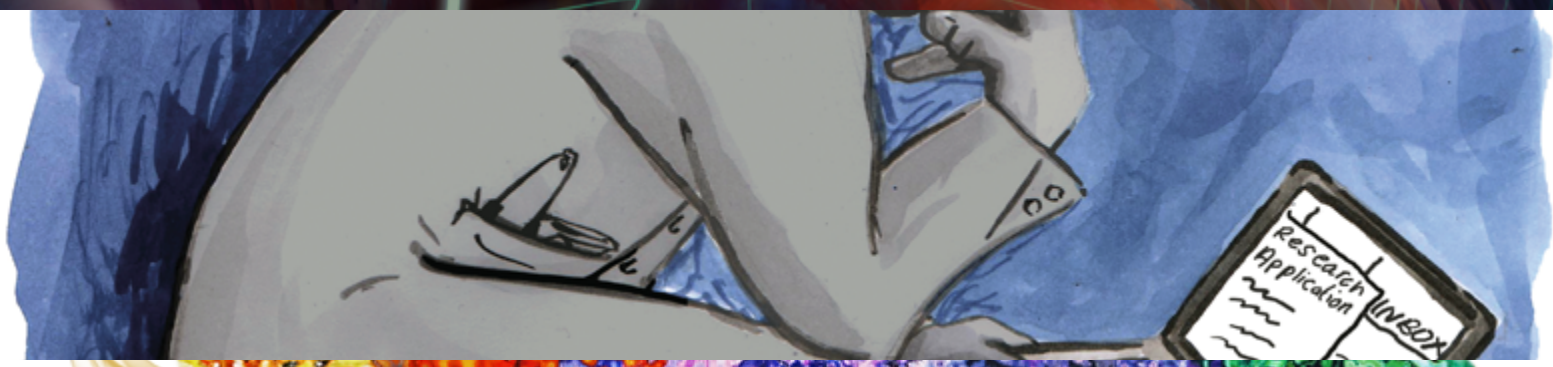

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