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Editorial

Propaganda

Michael Trimble

As we approach the start of a new academic year, this issue sees two guest editorials outlining new developments in medical education within the Province. These look forward to the first intake of students at the new medical school at the University of Ulster and describe the ongoing process of curriculum review at Queen's University. Appropriately, as the editorial board is seeking to raise the profile of the journal among medical students, there are two papers written by students. As the pandemic continues to cast its shadow over the coming Winter there are also several clinical papers relating to Covid.

In the popular press, Covid continues to feature. Sometimes it is hard to see the wood for the trees. As I write, there are conflicting pieces in news media about the need to vaccinate teenagers against the coronavirus. Headlines seem to vary from the factual "Scientists not backing jabs for 12 to 15-year-olds" to the emotive "My parents won't let me get the Covid vaccine" – both appearing on the same screen. [1] The latter piece may be seen to fit in with the view that we are being manipulated. As has been reported, even "members of the Scientific Pandemic Influenza Group on Behaviour (SPI-B) expressed regret about the tactics… about the role of psychology in the Government's Covid-19 response." [2] Along with the now infamous quote that they advised government that "the perceived level of personal threat" from Covid-19 should be increased because "a substantial number of people still do not feel sufficiently personally threatened". [3] Is this government propaganda?

In previous editorials, I have alluded to the writings of Aldous Huxley and Jacques Ellul. Both men understood and warned against the use of propaganda as a means of control of the population by those in power. For Huxley this is a requirement in a society which he terms "over-organised". [4] For Ellul, propaganda is both a necessary consequence of the expansion of technology or *technique* and at the same time dependent on the technologies which allow mass communication. [5] What Huxley describes as propaganda is what most understand by the word. It is an appeal to the masses – either rationally, in terms of enlightened self-interest or non-rationally, using "passion, blind impulses, cravings or fears." [6] Huxley feels that "unlike the masses, intellectuals have a taste for rationality and an interest in facts. Their critical habit of mind makes them resistant to the kind of propaganda that works so well on the majority." [7] Readers of this publication may be tempted to feel somewhat smug at this point and congratulate themselves on being immune to such crass means of manipulation. Ellul however is not so optimistic about our state. The individual "must make his own judgements. He is thrown entirely on his own resources; he can find criteria only in himself."[8] Education is no defence. As Konrad Kellan summarises, the intellectual is most vulnerable to propaganda as they absorb the most information, have a compelling need to have an opinion on issues of the day, and feel themselves capable of making their own judgements. [9]

Ellul also points out the misapprehension that propaganda necessarily contains lies. On the contrary, it may be wholly truthful but fail to mention other inconvenient facts.[10] How the facts are presented also makes a great difference. Is the current crisis in health care because GPs and emergency departments "fail to meet targets" or because demand outstrips the available resource? Propaganda may also misuse statistics to make a point, the use of graphs with poorly labelled axes and differing scales being an example. [11]

Our presuppositions, our worldview, the "lens" through which we interpret information, also plays a part. In this issue, we reproduce the text of Professor Barry Kelly's 2019 Annual Oration at the Royal Victoria Hospital. Professor Kelly recounts the intellectual debates surrounding what we know as the "Big Bang Theory" of the origins of the universe. Initial opposition to the idea came from those within the scientific community who held to a steady-state view of the cosmos. They felt the proposal that the universe had a definite beginning gave too much ground to the Biblical creation story.[12] Now, even though the "Big Bang" is the accepted paradigm, there is still little allowance for the divine in the scientific worldview.[13] In a similar way, our worldview will determine whether we view the discovery of maternal mitochondrial DNA originating from a common ancestor[14] as pointing us to Donald Johanson's *Australopithecus afarensis,* "Lucy" [15] or the Bible's Eve. [16]

As readers approach a text with biases, authors too have their agenda. Historian Richard Evans gives us some helpful advice for approaching written material. We need to consider the limits of the author's objectivity. [17] Whenever we read a text, we must ask the questions: who is the author, and what are their motives for writing? We should apply this to what we listen to as well.

In a classical education, the first courses of study were in logic, rhetoric, and grammar. Only once these had been mastered could students progress to the more advanced subjects of arithmetic, geometry, music, and astronomy. The initial three subjects were termed the Trivium and were felt to be so basic that they gave us the modern word *trivial.* Perhaps it would help if we were all to have a good grounding in grammar, that we would understand the precise use (and potential misuse) of language; rhetoric, that we understood the power and techniques of persuasion; and logic, that we knew the mechanics of thought and analysis. And so, may I conclude by urging you to consider subtleties of propaganda, to reflect on the value of critical thinking, and to take time to be trivial.

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Guest Editorial

The birth of the School of Medicine at Ulster University

Louise Dubras

Accepted August 2021

In the late summer of 2021, some 16 months into a global pandemic which has reshaped the profile of disease worldwide, shown us the immense value of all healthcare professions, and highlighted yet again the appalling inequality in healthcare provision around the world[1] both in terms of disease burden and mortality, and availability of vaccination, I write this editorial: as a General Practitioner and Medical Educator on the threshold of opening the doors on a new medical school. When I started on my personal journey to bring this medical school into being, I chose to focus on the social contract held by a University with the community within which it is sited, and the wide value a School of Medicine can bring to a region. The Covid-19 pandemic has presented us all significant challenges personally and professionally, but it has the benefit of offering an additional lens through which to examine the journey. I therefore now add the wider dimension of "transformative learning" in all its aspects as outlined by Frenk and colleagues in their influential paper published in the Lancet in 2010, "Health Professionals for a New Century: Transforming education to strengthen health systems in an interdependent world" [2]

If ever we have seen evidence of an interdependent world it has been as the Covid-19 pandemic has unfolded ; so it seems timely to pay attention to this publication and I would encourage all readers to explore it, either to read for the first time, or to re-read as I have done in preparing this piece.

Whilst it is not good practice to lift large elements of others' work into one's own, I provide a quote here as a means of framing what I will write about:

> "Health is all about people. Beyond the glittering surface of modern technology, the core space of every health system is occupied by the unique encounter between one set of people who need services and another who have been entrusted to deliver them. This trust is earned through a special blend of technical competence and service orientation, steered by ethical commitment and social accountability, which forms the essence of professional work. Developing such a blend requires a lengthy period of education and a substantial investment by student and society. Through a chain of events flowing from effective learning to high-quality services to improved health, professional education at its best makes an essential contribution to the wellbeing of individuals, families and communities". [2]

I will indulge one other intellectual diversion here in reference to the title of my piece: that is to reference Michel Foucault. Foucault has long been a philosopher who I have found stimulating and challenging in equal measures (at times mostly challenging if I am to be honest). In "the Birth of the Clinic" Foucault challenged the way in which doctors think about the body and illness and the dominant paradigm of the Teaching Hospital where clinical medicine was viewed from a positivist perspective, maintaining the Cartesian dualism of mind and body. [3] A 2014 editorial by a colleague, Professor Jennifer Johnston, in which she invited readers to be inspired by Foucault to think differently , challenge a dominant discourse and "taken for granted" assumptions may also help to frame my reflections; [4] and for a further overview into the relevance of Foucault as a challenge to us as doctors and educators in "thinking, saying and being", I would encourage readers to seek the words of Brian Hodges and colleagues from 2014. [5]

June 1st 2018: I felt like a new starter at School. I had arrived at Ulster University as Foundation Dean of a Medical School whose birth had been affected by slow and complex decision making due to the unique political sensitivities in Northern Ireland. That there was a need for Northern Ireland to grow its medical workforce was undeniable.[6] Yet despite the obvious need, with the absence of a devolved assembly until January 2020, it was not possible for the University to progress the development of the School. I was nonetheless able to contribute to the care of patients working a day a week as a GP in the city of Derry-Londonderry, starting the lengthy process of meeting a wide range of stakeholders necessary to enable us to reach a point at which we could open the doors to the MBBS programme.

With a long history of commitment to Widening Access to Higher Education, alongside its stated commitment as a Civic University, Ulster University had determined that its MBBS programme would be Graduate Entry, purchasing a curriculum from St George's University of London, selected because it had a high percentage of GP based education (addressing the "By Choice not by Chance" challenge set by Val Wass in her report for Health Education England in 2016) ; and because the University of Limerick had already implemented the same curriculum some years beforehand.

Let me introduce our MBBS programme to you: this is a Graduate Entry 4 year Medical Programme. Applicants require a minimum of a 2.1 degree in any subject as the academic condition of acceptance to study, together with satisfactory performance in the Graduate Medical School Admissions Test (GAMSAT) which assesses, amongst other things, candidates' reasoning in the physical and biological sciences. Once the academic hurdle has been passed and candidates have achieved a satisfactory score in the GAMSAT they are invited for interview. Ulster University is using Multiple Mini Interviews although these were conducted virtually for 2021 entry.[7]

The four-year Ulster Graduate Entry medical degree is quite different to a traditional 5-year degree: students work hard over long university terms. There are no opportunities for intercalation because students already have a degree at the point of entry. Our students undertake Problem Based learning in their first two years.[8] Anatomy learning will not be cadaveric. The first clinical placements will be in General Practice in year 1, and GP placements will feature in each year of the programme. Much however is similar to a 5 year degree, most notably that the learning outcomes are the same, and of course when our graduates take their Finals examination in 2025 they will take the GMCs Medical Licensing Assessment before entering the UK Foundation programme.

The University had embarked on the process of GMC accreditation for a new MBBS programme in 2016, progressing through initial expression of interest, through financial audits, to full submission of a comprehensive range of documents for Stage 3 of the process. This mammoth task was where the GMC sought evidence that the University could support a medical degree programme at every level, from library and computing, to student support, staff expertise, experience in assessment, systems for quality assurance, and appropriate governance. [9]

Following scrutiny of Stage 3 documentation, and the provision of follow up documentation which formed Stage 4, I was keen to progress as far as we could despite the political situation; so we progressed to a GMC visit to Ulster University's Magee campus in July 2019. We all have moments in our working lives where we take a brave decision that stands us in good stead for the future, and the GMC visit at that point proved to be one such decision. We had a positive assessment from the GMC, having met key members of the University whose roles were to support the MBBS programme, as well as key local stakeholders. Whilst we did not at that stage have a medical school building to show the GMC team, they were able to see our campus facilities as well as meet the team in person.

Thereafter the GMC process was paused from September 2019 until May 2020 when a political announcement of our places was made, after which we were able to resume the accreditation process to the point of a Stage 6 decision in July 2020, enabling the University to start to recruit students for 2021 entry.

We are expecting 70 medical students to join us on August 23rd 2021, so by the time you read this editorial they will be with us, already embarked on their journeys to become doctors.

How will they compare to medical students you might have taught in the past? What journey will they undertake?

Students will be older as they enter the programme, and with prior degrees in a range of subjects they are likely to see life from a different perspective to that of school leavers. Their lines of enquiry on their journey towards their MBBS degree are likely to be different. Readers who are clinical teachers will notice a difference. They will however also notice similarities to the many students with whom they have previously interacted. Ulster University's MBBS students will take the same Medical Licensing Assessment in the summer of 2025 as students graduating from Queen's University Belfast, and more widely throughout the UK. They will be "Foundation programme ready" and will complement and enhance your workplaces from 2025 onwards.

Before concluding however, I wish to return to Foucault, and introduce another concept, that of "Disruptive Innovation", introduced in the business world in 1995. In business terms, "disruption" occurs when a small company can successfully challenge an established incumbent business; and it could be argued that in establishing a Graduate Entry Medical programme where none previously existed in Northern Ireland, Ulster University has provided disruption and innovation. [10] I propose though, that in establishing the School not at a hospital, but on a University campus, within a community, the innovation is less about the nature of the degree itself, but more about the nature of the population we serve, the commitment to challenge the dominant paradigm of medicine as a hospital- based speciality, and reframe it in the Community, with patients and general practice at its heart, helping to pick up the gauntlet laid down by Wass in 2016, enabling students to see General Practice and community based medicine as an attractive career choice, challenge the hidden curriculum and stigma associated with General Practice. As a GP leader, I intend that General Practice and hospital medicine have equal value in our MBBS programme. It is my intention to reframe some of the power relationships in medical education and refocus some of the discourse around what "counts".

I would like to conclude by saying that to arrive in Northern Ireland, work in the North West alongside remarkable colleagues within the University, in clinical settings, and at Queen's University Belfast has been a remarkable privilege. Daily I observe work of the highest quality, aimed to enable us all to deliver on what is, I think,

the most important theme, the Social Accountability of Medical Schools, defined by the WHO as "the obligation of medical schools to direct education, research and service activities towards addressing the priority needs of the community, region or nation that they are mandated to serve. The priority health concerns are to be identified jointly by governments, healthcare organisations , health professionals and the public". [11]

The birth of the School of Medicine at Ulster University- for all its philosophical underpinnings, has demonstrated practical joint working by government, university, health professionals and wider stakeholders in an unprecedented way, and I look forward to the next stage in our development to demonstrate the value of that shared commitment.

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Guest Editorial

C25 in QUB: a transformed curriculum for a transformed healthcare system

Neil Kennedy, Pascal McKeown

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Queen's University Belfast (QUB) has completed a curriculum review resulting in the most significant revision of the undergraduate medical programme since 1996. The result is 'C25' named to reflect the year (2025) when the first students from this programme will graduate. In this article, we will briefly answer *why* and *how* the review was completed, focussing on the *new components* of C25 and the evidence-base that underpins them.

Why undertake a curriculum review?

From its origins in 1835, the QUB medical school has sought to shape and reshape its curriculum to be relevant to the practice of medicine both locally and internationally[1]. As society and its needs change, so must medical curricula change to be fit for purpose in both the short and medium term [2]. Nationally, the latest version of *Outcomes for Graduates* [3] published in 2018 recognises the need for doctors to provide integrated care for growing numbers of patients with multiple morbidities in home and community settings, applying their knowledge of behavioural and public health science to individual patients. Locally, *Systems not Structures (2016)* [4] envisages new models of healthcare delivery, a blurring of the primary and secondary care divide, with a focus on quality improvement, preventative medicine and population health. In addition, the medical profession is faced with exponentially increasing amounts of knowledge; the digital transformation has resulted in 'democratisation' of that knowledge, and changed the way that students acquire it [5]. Aware of these trends, the QUB curriculum was comprehensively reviewed to prepare our future graduates with the professional values, behaviours, knowledge and skills required to meet the challenges of healthcare provision in the 21st century.

How was the review completed?

Over 18 months, an extensive stakeholder listening exercise was conducted involving students, recent graduates, medical educators from all disciplines, clinicians in primary and secondary care and public health, members of the public, Department of Health, Northern Ireland Medical & Dental Training Agency (NIMDTA) and colleagues from nursing and pharmacy. Early clinical contact, cadaveric dissection, the final year assistantship and the range of Student Selected Components were highlighted as existing curricular elements to be retained. We were also told there were things to improve; we needed to integrate teaching of biomedical and public health science with clinical science, both within and between years of the course; we needed to provide more time in primary care and reduce 'silos' of learning and increase active learning opportunities during the first two years. Following review of best practice in other UK medical schools, and with the valued assistance of external facilitator Professor Val Wass, a new curriculum was planned – a transformed curriculum fit for a transformed healthcare system.

What are the components of C25?

C25 comprises three phases (Table 1) – Foundations of Practice (years 1 and 2), Immersion in Practice (years 3 and 4) and Preparation for Practice (year 5). The need for better integration of learning underpins each of the major curricular developments which the remainder of this article will expand upon: helical themes, case-based learning, longitudinal clerkships, more time in primary care, and progress testing.

Helical Themes

Cross-cutting or 'vertical' themes are a feature of 'spiral' curricula, serving to integrate and ensure content delivery of concepts such as public health, professional behaviour and ethics within every module and discipline[6, 7]. In C25, these themes are:

- **G** lobal and population health
- **C** linical science and practice
- **A** chieving good medical practice
- **T** eamwork for safe care

The 'GCAT' themes are named after nucleotide bases and represented pictorially as helical, serving to emphasise that they represent the 'DNA' of the curriculum and medical practice. Each theme consists of six sub-themes (Table 2).

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Table 1: Curricular phases and delivery in C25

Phase (Years of Study)	Curriculum Delivery
Foundations of Practice (1&2)	• Integrated, systems-based teaching of biomedical, behavioural, public health and social science • Case-based learning • Early clinical contact in clinical skills centre and primary care • Cadaveric dissection
Immersion in Practice (3&4)	• Workplace-based learning • Longitudinal Integrated Clerkships (LIC): o Year 3 – centred on secondary care. o Year 4 – integrated primary and secondary care rotations across the life cycle of child health, women's health, ageing and mental health. • Quality improvement project in year 4 • Case-based learning
Preparation for Practice (5)	Clinical elective Consolidation of learning through rotations in primary care, acute care, and chronic care Final year assistantship in primary and secondary care

Table 2: Helical themes and sub-themes in C25

Helical Theme	Sub-themes
	**G** Public and Population Health Global Health Cultural Competence, equality and diversity Interface between care settings Social determinants of health Social accountability and sustainable healthcare
	C Clinical reasoning Clinical skills Consultation and communication skills Clinical research and scholarship Prescribing Biomedical and behavioural science
	A Professional behaviour Ethics and law Raising concerns, safeguarding and duty of candour Self-directed and lifelong learning Self-care, wellbeing and resilience Teaching
	T Leadership and followership Teamwork and interprofessional education Communication and negotiation skills Quality improvement Dealing with risk and uncertainty Healthcare systems

Designated academic leads have been appointed for each theme to ensure integration and representation in curriculum content (for example, case-based learning) and assessment (in OSCEs and progress test) throughout the course.

Case-based learning

Case-based learning (CBL) is defined as "preparing students for clinical practice, through the use of authentic clinical cases. It links theory to practice, through the application of knowledge to the cases, using inquiry-based learning methods."[8] Curricular material (such as biomedical, social, public health and clinical sciences) is integrated within 'real-life' clinical scenarios which are studied independently or in groups. CBL is a more guided form of inquiry than PBL (problem-based learning), fostering deeper learning whilst preventing pursuit of unfocussed or unnecessary outcomes.[9]

CBL delivery varies [9]; in C25 CBL is the skeleton anchoring all the other learning material throughout years 1 and 2 of the course. At the beginning of a 2-week-long cycle, groups of 9 or 10 students are presented with a clinical scenario which is aligned with defined learning outcomes. Video clips, animations, dialogue between family members and results of investigations all provide authenticity. Students work together to clarify the issues raised, identify gaps in learning and write learning objectives. A trained, non-expert facilitator who has a list of essential, desirable and less-desirable outcomes, guides discussion to avoid students missing the point or going off on a tangent. Students then work independently on the outcomes, producing shared learning notes which are presented at the second meeting several days later. Further information is provided and the process repeated. Students meet again towards the end of the 2 weeks. Other lecture, tutorial, practical and skills-based teaching throughout the cycle align with the essential case outcomes.

There is good evidence [8, 9] that CBL is enjoyed by both learners, who believe it fosters deeper learning, and teachers who appreciate active student engagement. CBL promotes integration of knowledge. Amongst undergraduates, assessment results are similar to those of students taught in traditional, lecture-based courses, although knowledge retention amongst weaker students is improved. Interventions using CBL to deliver continuing professional development have demonstrated improvements in patient care [9, 10]. Some studies report student concerns about not covering the core learning outcomes adequately for assessment [8]. In C25, this is addressed by clear facilitator notes, and a final wrap-up lecture by the case-writer to the entire cohort.

Longitudinal integrated clerkships (LICs)

In C25, a series of short discipline-specific rotations in years 3 and 4 of the course are replaced with LICs. LICs emphasise continuity in workplace-based learning; continuity in time (LICs are longer than traditional placements), location (students move around less), supervision (students get to know their supervisor) and care (students follow patients through their admission). Participation in day-to-day clinical activities is fostered. Students are taught and achieve learning outcomes across multiple disciplines simultaneously[11-13].

In year 3 (beginning 2022), students will complete two, 14 week-long LICs in both a district and tertiary hospital. They are allocated to base wards in medical and surgical disciplines. Although students are allocated to different wards, they have to achieve the same generic learning outcomes, participating in a coordinated programme of online-learning, and completing a range of clinical task (supervised histories and examinations, clinics and theatre attendances). An average of 1 session per week is spent in primary care, focusing on patient journeys between primary and secondary care.

In year 4 (beginning 2023), students will complete integrated primary and secondary care placements across the life cycle of child health, women's health, cancer, ageing and mental health.

An extensive literature exists to support the effectiveness of LICs [11-13]. In comparison to students in traditional block rotations, students in LICs have better communication skills and understanding of the biopsychosocial needs of patient. They participate more in care, feel more confident in doing so, and develop a stronger professional identity. Through continuity of supervision, they receive more feedback matched to their developing skills.

Student assessment performance is reported as identical to, or better than traditional rotations [11, 13]. Partly this is due to the well-known positive benefits of 'spaced learning' and 'interleaving'. Students in a range of disciplines, including medicine, retain and apply knowledge better if a topic is taught alongside other topics, and revisited several times [14]. LICs counteract the pattern of 'learn, assess, forget' associated with medical student learning in block rotations.

It is important to note that students frequently experience a degree of disorientation when first exposed to LICs; student and supervisor preparation is critical to success [11, 13].

More time in primary care

The most compelling reason for increasing placement time in general practice is that it is where 90% of clinical encounters between doctors and patients occur. Therefore training in authentic medical practice requires that students spend substantial time in primary care [3, 15].

In C25, students will spend 25% of clinical placement time in primary care, weighted towards the senior years of the course, achieving the target set by the Royal College of General Practice [16].

Compared with experience in secondary care placements, students in primary care report a range of benefits including (a) seeing a greater number and range of patients (b) enhanced understanding of patients' experiences and

feeling of empathy towards them (c) improved confidence in managing complexity and uncertainty (d) excellent opportunities to practise history, examination, and clinical reasoning skills in a range of disciplines, and receiving individualised feedback about them [15, 17]. Primary care placements provide the opportunity to integrate learning, a major aim of C25.

Building placement capacity requires time, funding, and most importantly a change in attitude towards the importance of the task amongst both primary and secondary care doctors [15-17]. QUB is extremely grateful to colleagues in Northern Ireland who are rising to this challenge.

Progress Testing

Progress testing (PT) is longitudinal assessment of students' knowledge, pitched at final year level, with tests repeated several times per year for each year of the course. Results are accumulated over the year to make progression decisions [18]. Assessment 'growth charts' can be produced, providing excellent feedback to individual students, cohorts and teachers [19].

In C25, PT comprises the main element of written summative assessment. Students will sit one formative test in year 1, and a series of summative tests in years 2-4. Written finals, the Acquired Knowledge Test (AKT) element of the GMC Medical Licensing Assessment, are held a year before graduation. All students in each year take the same test at the same time. The tests will be tagged and weighted to AKT domains. Approximately 20% of the questions will cover biomedical and public health science.

There is evidence that PT integrates learning, reduces exam stress, encourages deeper and consistent learning, primes students for future learning and focuses teaching for lecturers [18, 19]. The domain-focused feedback generated by each test has been shown to improve performance in licensing examinations [18].

Generating high-quality questions is facilitated by collaborative arrangements with other medical schools [20]. QUB has entered a consortium with this purpose with several other UK universities.

CONCLUSION

C25 represents a step-change in curriculum delivery in QUB. We thank all colleagues who have helped us get this far, and welcome future involvement in the delivery of this innovative, relevant and integrated curriculum.

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Medical Education

QUB Students: Changing the Climate of Planetary Health Education

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What does climate change have to do with being a doctor or medical student in Northern Ireland? Why should you care about climate change? Advocating for global change to halt the climate crisis and to protect our environment is not just for the Greta Thunberg's and David Attenborough's of the world - healthcare professionals can also help lead the charge. The World Health Organisation has called climate change "the greatest threat to global health in the 21st century" [(1)]. The health of humanity is dependent on our environment which is changing rapidly and in disastrous ways; from rising global temperatures, increased frequency of abnormal weather patterns and natural disasters, urbanisation and destruction of vital environments for agriculture, and pollution levels, the environment has huge impacts and devastating effects on individual and population health. So, how can healthcare professionals in Northern Ireland make a difference and help combat climate change?

Over the past year, five students from Queen's University Belfast (QUB) contributed to an international report called the Planetary Health Report Card (PHRC). The PHRC is a student-driven, metric-based initiative to inspire planetary health and sustainable healthcare education engagement in medical schools [(2)]. Each participating school wrote and published school-specific individual reports alongside a larger comparative report on World Earth Day, the 22nd of April 2021. Alongside individual school reports, the comparative report was derived to help identify areas of strength and provide recommendations to all participants on improving engagement and education. This report was prepared by student teams with faculty input from sixty-two medical schools from across the USA, UK, Ireland and Canada, including QUB, and was supported by: Medical Students for a Sustainable Future; Planetary Health Alliance; Practice Greenhealth; Healthcare Without Harm; Students for Global Health; Global Consortium on Climate and Health Education; and Human Health & Climate Change Club at the University of California, San Francisco.

The PHRC was designed to operate as a needs assessment tool to identify planetary health strengths and opportunities for growth within and between medical schools. The PHRC consisted of discrete metrics in five main category areas: planetary health curriculum; interdisciplinary research in health and environment; university support for student planetary health initiatives; community outreach (centred on environmental health impacts); and medical school campus sustainability. For each metric, individual scores were provided, alongside a detailed explanation of collated evidence and suggested recommendations for improvement. Generation of both a QUB-specific report and the comparative report has helped facilitate dialogue within the School of Medicine, Dentistry & Biomedical Science (SMDBS), its aligned research institutes, other schools within the university and the Student's Union; promoting cross-institutional sharing of best practice and showcasing innovative forms of planetary health engagement. The report will also be used to help track progress over the coming years as the medical school provides greater resources, promotes research and facilitates discussion between staff and students to help advance the global planetary health movement.

The core team at QUB was first established when team leader Victoria England, a member of QUB's Students for Global Health society, was asked to spearhead the initiative. Victoria is currently completing an intercalated master's degree in Clinical Health Psychology and recruited the remaining members of the team: Amanda Madera (BSc Biology, MPH Global Health), Hannah McPhee (BSc Biomedical Science, Year 2 Medicine), Rhiannon Wells (MSc Global Health, Year 4 Medicine) and Riley Westwood (Year 1 Medicine). Between them, the group have experience of living, working and volunteering in differing healthcare systems and health environments, including Northern Ireland, Germany, the Falkland Islands, India and East Africa. The student team engaged actively with faculty within the SMDBS, establishing regular review meetings for support, updates and information sharing, and along with the students, the staff have been committed and enthusiastic about addressing health inequalities, providing planetary health education, and tackling the climate crisis.

Compared to other participating UK Medical Schools, QUB was ranked within the top 10 for their overall grade, scoring well in most categories of the report, as can be seen in ***Figure 1.*** Whilst this is a very encouraging result, it is

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important to remember that this report card is not a league table, but a needs assessment tool aiming to motivate and facilitate improvement.

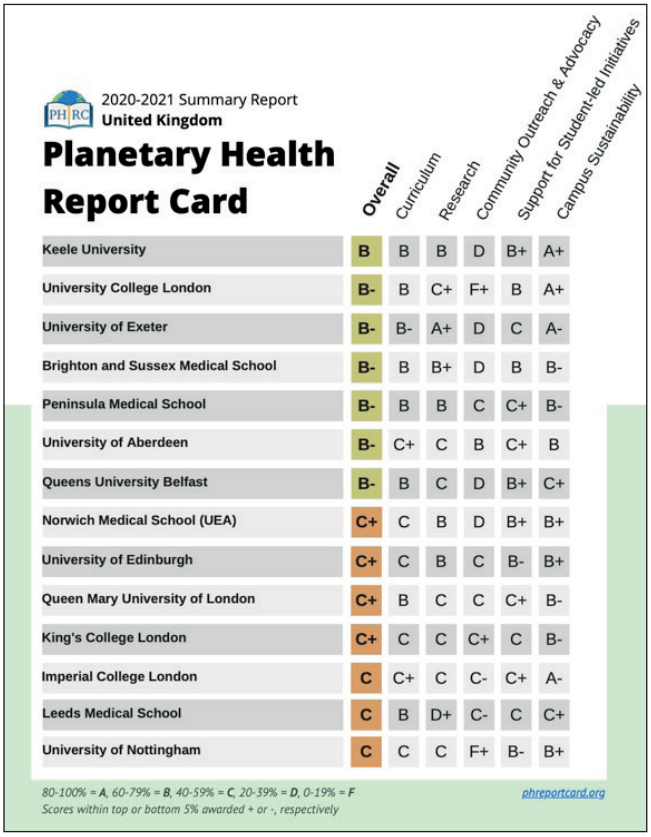

Figure 1: *Extract from Planetary Health Report Card Summary Ranking of UK Medical Schools. Overall, Queen's University Belfast scored a B-, a very encouraging grade at the beginning of this assessment of the university's dedication to planetary health education and activism. Image taken from (2).*

SUMMARY OF FINDINGS

Curriculum

Planetary health and sustainable healthcare education are evident in the core curriculum - particularly following the introduction of the new medical C25 curriculum in 2020 - and various elective courses. One of the themes of the C25 curriculum, titled 'Global and Population Health' has enabled the longitudinal integration of planetary health subtopics into the core curriculum. This is integrated at a practical level, for example: discussions about a vegan diet due to concerns about the agricultural impact on the environment are included in a case concerning a patient with anaemia. In the comparative PHRC, QUB was highlighted as a good example within the metric of Curriculum due to the presence of this core longitudinal theme and its subtheme entitled "Social Accountability and Sustainable Healthcare" - these subthemes aim to highlight to students that, regardless of their stage of training, they must address the priority of health concerns that mandate wherever they serve. It also highlights some of the concerns they will face, including the impact of the healthcare system on climate change and the government's commitment to a Net-Zero NHS by 2050. The availability of numerous Student Selected Components (SSCs) also led QUB to be highlighted as an exemplar in the Curriculum metric. SSCs included are "Healthcare Needs Smaller Feet – Sustainable Healthcare: Theory into Practice", "SusQI" and "Global Health: Concepts, Trends and Priorities", all of which involve discussions on sustainability within clinical practice and climate change. The new curriculum was only implemented within the last year (2020-21) and whilst making great strides in planetary health education, there is room for improvement, and in the coming years, planetary health will continue to develop as an integral part of the curriculum.

Interdisciplinary Research

Currently, planetary health research is not a primary research focus within the medical school, and the university lacks an institute solely dedicated to planetary health research. Although there are no researchers with a primary focus on planetary health within the SMDBS, many researchers at Queen's are working on this, and the establishment of the Centre of Sustainability, Equality and Climate Change proves that planetary health research is becoming an area of expertise and importance within the wider university. Establishment of this centre offers many opportunities for interdisciplinary research and climate action in the coming years. The success of the conference entitled "Healthy People on a Healthy Planet", which involved several staff members from the school and others at QUB has further highlighted the need for environmentalism within medicine and should encourage similar events to take place in the future.

Community Outreach and Advocacy

Many vital partnerships exist between QUB and the community, such as the Widening Participation Partnership, but few exist with the SMDBS itself, leading to a low score in this metric (***Figure 1***). Numerous community-facing events have been held including a collaboration between Northern Ireland Science Festival in which staff members from the School of Biological Sciences have presented research recognising the global and local impacts of climate change and ideas on how to mitigate these. Numerous working groups within the university strive towards better climate action, such as the QUB Students' Union (QUBSU) Climate Action Group, which communicate regularly with interested students and staff. Following the wider university's example, the medical school should continue to establish its community partnerships and hold events related to planetary health and sustainable healthcare.

Support for Student-led Planetary Health Initiatives

QUB provides great support for student-led initiatives and scored very highly in this metric compared to other medical schools (Figure 1), but there is plenty of opportunity for greater involvement and funding for planetary health

Summary of 13 Recommendations from PHRC	
Utilising Existing Resources	Appreciate the work that has already been done in advancing planetary health across the world and draw upon resources from other institutions and organisations when developing learning objectives or generating new resources
Learning Objectives	Formalise curricular content on both planetary health and sustainable healthcare with students by developing testable learning objectives; the curricular content should emphasise skill-building as well as clinical knowledge
Curricular Thread	Planetary health and education for sustainable healthcare is relevant to every organ system, and spaced repetition is more effective for learning; therefore these should be a cross curricular theme integrated into existing lectures, small groups, and projects whenever possible, rather than a standalone lecture; faculty members should be empowered, educated and incentivised to integrate the topics into their existing content
Electives and Student Selected Components	In addition to the core curricular content on planetary health and environmental health required for all students, provide opportunities for deeper exploration for interested students, such as electives, community engagement opportunities, and optional reading
Communication in Clinical Scenarios	Research shows that community members rely on their primary care doctor for information on climate change, however most medical students feel unprepared to answer patient questions on climate change; therefore medical schools should include clinical curriculum on taking an environmental history and communicating information on planetary health to patients
Planetary Health in the Global Context	The ecological crisis is a global issue and given the interconnected nature of human health globally, medical students should understand the health impacts of climate change throughout the world, its disproportionate effects on low- resource nations, and impacts on global stability through mechanisms such as food security; in teaching about planetary health and climate change, curriculum should acknowledge how indigenous groups who have long lived in harmony with the planet are disproportionately affected by climate change and many climate solutions require partnerships with indigenous populations
Equity Focus	Ensure that planetary health and environmental health curricular content and auxiliary opportunities centre the disproportionate impact of all health effects on vulnerable populations, such as communities of colour, low- income communities, indigenous populations, and older adults
Support Students	Create funded opportunities for students to engage with planetary health, environmental health, and sustainability, such as sustainability grants, research fellowships, student groups, and community-based projects; support student advocacy efforts and take action in response to student input
Mentorship	Facilitate accessible mentorship of students with an interest in planetary health
Community Engagement	Partner with community organisations, develop community- facing courses on planetary health, and include planetary health in patient educational materials and marketing
Research	Encourage interdisciplinary research on planetary health and environmental health topics by facilitating research networks, awarding funding, hosting conferences, and recruiting researchers actively exploring these subjects
Interdisciplinary Centre	Institutions should create interdisciplinary centres with education, research, policy, and community engagement pillars that focus on the intersections between climate change, the environment, and health, bridging traditional divides among disciplines to ensure collective vision, problem-solving and action
Sustainability	Divest from fossil fuels, set carbon neutrality goals, and create an environmentally sustainable learning and working environment by setting guidelines for supply procurement, lab spaces, events, and buildings

***Figure 2**: Summary of the 13 recommendations identified by PHRC based on the information provided by the participating medical schools and their individual report cards. These recommendations provide a foundation for medical schools to build upon to further improve planetary health education, research and engagement.*

initiatives. For example, the SMDBS has a well-established and popular funded summer studentship scheme which would be an ideal opportunity for interested students to get involved in research related to either global or planetary health or investigating ways to improve sustainability within healthcare. The Student's Union also provides great support for such initiatives, by funding societies like Students for Global Health, and are partnered with other groups such as Green at Queen's, so students with an interest in this topic have various extracurricular activities to choose from during their time at university.

Campus Sustainability

Sustainability is an ever-developing area within the university, with the development of numerous sustainability practices on campus, including the establishment of an Office of Sustainability, implementation of sustainable building practices, availability of a range of environmentally friendly transportation options, catering-specific sustainability criteria and a widely used recycling programmes. However, there are still several important steps that QUB needs to take to improve sustainability, including setting and achieving a goal of carbon neutrality, divesting from fossil fuels and increasing utilisation of renewable energy sources.

Alongside the individual goals established by each participating medical school, the PHRC identified 13 key recommendations across all participating institutions, as can be seen in ***Figure 2***. These recommendations aim to inspire expansion of medical school's planetary health curriculum, research efforts and engagement with local communities most affected by climate change and environmental injustice. Based on the recommendations outlined by the PHRC, and analysis of Queen's report card, an action plan was created by the Queen's PHRC team and SMDBS faculty.

This action plan identified short-term and long-term goals for both the medical school and wider university to work towards, and encompassed the key recommendations made by the PHRC (***Figure 2***). For example, to address the recommendation entitled curricular thread, which aims to integrate planetary health and sustainable health education into learning as a cross-curricular theme, the school aims to create a toolkit to help learning facilitators explore and evaluate the importance of the "Global" theme within case studies, and many simple suggestions to incorporate planetary health topics into the current curricular content were made. Many resources exist at Queen's highlighting the university's dedication to climate action, although this information is difficult to find, and the development of a planetary health and sustainability website (currently in progress) will provide transparency to the university's commitment to climate action and help develop further resources. Other proposed goals outlined in the action plan included the creation of a sustainability handbook or induction for all new students to help explain what planetary health is and why it is important to consider within healthcare; and to increase community outreach, the group hopes to collaborate with organisations such as the Northern Ireland Science Festival and the Northern Ireland Confederation for Health and Social Care (NICON). The creation of this report card has been a huge success within the SMDBS, with the findings discussed at the School Management Board Meeting and the Faculty Executive Board Meeting of the Faculty of Medicine, Health & Life Sciences, and has encouraged other schools to share best practice goals and get involved in the initiative. The SMDBS has since signed 'Health Declares: Climate and Ecological Emergency', declaring a climate emergency and committing the school to advocate to protect planetary and human health [3]. The student team has engaged with other key stakeholders within Queen's, including the Faculty Engagement Manager, QUB Estates Manager for Environment, the Student's Union and QUBSU Climate Action and Sustainability Group, beginning the process of building and strengthening interdepartmental groups dedicated to climate action, planetary health education and engagement. Going forward into the next academic year, 2021-22, the QUB student team is seeking to welcome more members to build upon the work done so far.

The PHRC is not a standalone metric to compare how well QUB is ranked compared to other universities in terms of its planetary health actions, but instead is a mediating platform to allow the students the opportunity to instigate positive change within the medical school and wider medical community to help change and shape our current healthcare system into a more sustainable one. This project has only further highlighted the importance and dedication required by healthcare professionals to educate, encourage and create positive change in a time of climate crisis.

So, how can you get involved in environmentalism and sustainability? Start small, and momentum will build: begin conversations around the subject, and make small changes where you see them – in your department, in your peer group, and in your own life! No individual can solve the climate crisis, but together, by making small changes, we can make a huge impact.

The full PHRC summary report can be accessed at https://phreportcard.org alongside the QUB specific report.

Acknowledgements

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Grand Rounds

Pituitary metastasis: a clinical overview

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ABSTRACT

The pituitary gland is an unusual site for metastatic spread and has been associated with a poor prognosis. Clinical presentation is variable but can include visual field defects, cranial nerve palsies, anterior pituitary dysfunction and/or diabetes insipidus. Management options include surgery or radiotherapy, chemotherapy/immunotherapy or a conservative approach. The pituitary should not be overlooked as a site for metastasis in patients with known cancer and can be the first presentation of neoplastic disease in some patients. Given that patients are now living longer with cancer, clinicians should be alert to the varied presentation of pituitary metastasis. We provide a clinical overview of pituitary metastasis with the aid of illustrative clinical cases.

INTRODUCTION

The pituitary gland is a rare site for metastasis, and accounts for less than 1% of clinical intracranial secondary tumours in clinical practice[1]. Autopsy studies have demonstrated its prevalence between 1-4% in patients with advanced cancer, which suggests that these lesions may go unrecognised[2-3]. More recently there appears to be an increasing incidence of patients diagnosed with pituitary metastasis (PM) in part due to improvements in neuroimaging, laboratory testing and the fact that patients are now living longer with cancer[4-7]. This leads us to anticipate that the number of patients developing metastatic involvement of the pituitary gland will rise, creating a greater need for awareness of its presentation among clinicians. Clinical presentation of PM is variable but can include visual field defects, cranial nerve palsies, anterior pituitary dysfunction, diabetes insipidus and compression of adjacent structures[8-10]. Management options can include surgical decompression, radiotherapy, chemotherapy/immunotherapy or a conservative approach[11-13]. However, given that metastasis is commonly present in other sites when PM becomes clinically evident, prognosis is often poor. In addition, endocrine dysfunction arising from PM can complicate the clinical picture and has the potential to adversely affect clinical outcomes[14-16].

Case 1

A 19-year-old male presented with a one week history of headache, pyrexia and back pain. His medical history included asthma and polycystic kidney disease. Routine investigations revealed raised inflammatory markers, deranged liver function and hypercalcaemia. A CT-CAP scan showed extensive hepatosplenomegaly, multiple lytic skeletal lesions, para-aortic and porta-hepatic lymphadenopathy. Serum LDH was 4888 U/L (135-225). After transfer to the Regional Oncology Centre in Belfast, a bone marrow biopsy confirmed a diagnosis of diffuse large B-cell lymphoma. He underwent chemotherapy with one cycle of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) and two cycles of COPADM (cyclophosphamide, vincristine, prednisolone, doxorubicin and methotrexate) with partial disease response.

Four months later he represented with worsening headache and new left upper seventh cranial nerve palsy with CNS relapse confirmed on MRI and lumbar puncture. He underwent three cycles of R-IE (rituximab, ifosamide and etoposide). MRI brain at that time did not show any focal abnormality. One month later, his symptoms progressed to include nystagmus and ataxia, MRI brain (Figure 2 A+B) demonstrated a 14 x 12 mm mass involving the floor of the 3rd ventricle, hypothalamus, pituitary stalk and pituitary fossa. Pituitary function testing revealed secondary hypothyroidism (fT4 11pmol/l and TSH 0.03mU/l), hyperprolactinaemia (1004mU/l) and hypogonadism (testosterone < 0.2 nmol/l). He developed hyponatraemia (Serum Na 116 mmol/l) without overt polyuria or polydipsia. This was attributed to SIADH and confirmed on biochemical testing, and slowly resolved with the addition of slow sodium, furosemide and fluid restriction. Diabetes insipidus was not present. He was commenced on oral dexamethasone 750 mcg daily. No hormonal replacement was required. Given the extent of his disease with CNS involvement refractory to treatment he received input from palliative care and with cranial radiotherapy and comfort measures, he died 14 months after

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his initial presentation (3 months after PM was diagnosed).

Case 2

A 53-year-old man presented to his GP with a short history of hip pain and general malaise. Initial pelvic x-ray revealed multiple lytic lesions in both hips and proximal femora. Serum calcium was significantly elevated at 3.9 nmol/l (RR 2.20-2.60). Urinary Bence-Jones protein was positive. He was diagnosed with ISS stage III multiple myeloma with favourable cytogenetics. He was commenced on VTD chemotherapy (bortezomib, thalidomide and dexamethasone) combined with zoledronic acid with the intention to progress to autogenic stem cell transplant. However, despite treatment his kappa free light chains continued to rise and he was instead escalated to lenalidomide and cyclophosphamide with dexamethasone. Treatment was further complicated by a traumatic humeral fracture requiring surgical fixation and multiple chest infections which precluded him from transplant options despite successful harvest.

While on third line treatment with bortezomib and panobinostat he represented with left eye pain, ptosis and double vision. MRI scanning (Figure 1) revealed a large mass arising from within the clivus and extending anteriorly into the sphenoid sinus and superiorly into the pituitary fossa in keeping with a plasmocytoma, he was deemed not suitable for neurosurgical intervention. Endocrine investigations revealed hypogonadism, and the rest of the anterior pituitary function was normal. He had no clinical evidence of diabetes insipidus. Shortly afterward he developed a respiratory tract infection. Palliative care was initiated and he died 19 months after his initial presentation and one month after diagnosis of PM.

Case 3

A 41-year-old man presented with a four week history of polyuria (12 litres/24 hours), polydipsia (15 litres/day) and a right sided headache while attending a routine respiratory outpatient appointment for follow up of his asthma. He had a complex medical history including squamous cell carcinoma of the anus treated by excision and mapping biopsy, severe eczema, mitral regurgitation and severe non-atopic asthma requiring multiple ICU admissions and long-term steroids (leading to secondary myopathy and osteoporosis). Investigations revealed a normal serum sodium (141mmol/l) a low urine osmolality (153mOsm/kg) and urine sodium (<20mmol/l). He was admitted for investigation and treatment of clinical diabetes insipidus.

CT scanning of his chest, abdomen and pelvis revealed extensive mediastinal lymphadenopathy, hepatic, pulmonary and para-aortic node involvement. MRI brain revealed an abnormal soft tissue mass in the pituitary fossa (Figure 2 C+D), extending into the pituitary stalk which was thickened, with some slight expansion of the sella. The optic chiasm appeared unremarkable. Hormone profiling revealed panhypopituitarism with secondary hypogonadism (LH 0.4IU/l, testosterone <0.2nmol/l), hypothyroidism (TSH 0.14mU/l, free thyroxine 6.5pmol/l) and hypoadrenalism Cortisol was 154 nmol/l 30 minutes after synacthen (RR > 450). He was commenced on desmopressin and prednisolone.

The midline distribution and raised β-HCG (129.6U/l) suggested a testicular tumour: however testicular ultrasound was normal. Lymph node biopsy revealed a mucin secreting adenocarcinoma of unknown primary, most probably of the upper GI tract. He received palliative chemotherapy with carboplatin but this had to be withdrawn after a single cycle due to poor clinical condition. He developed respiratory failure from a combination of his asthma, pneumonia, tumour obstructed bronchi and lymphangitis carcinomatosis. He received palliative care and died less than one month after his initial presentation.

Case 4

A 73-year-old lady presented with an acute loss of power in both her legs whilst a surgical inpatient for treatment of acute cholecystitis with the development of hyponatraemia (127 mmol/l). Her medical history included retrosternal goitre, heart failure and bilateral total hip replacements. On examination she had absent lower limb reflexes and was found to be in urinary retention. Sensation was intact over her legs and anus, however she was unable to feel the insertion of a urinary catheter. An urgent MRI scan of her spine revealed metastatic infiltration of vertebra T5-8 and L1 causing cord compression at the level of T5/6. On MRI brain imaging an infiltrating pituitary lesion (Figure 3) was centered in the sella. The soft tissue extended into the sphenoid sinuses, the cavernous sinuses and along the dorsum sellae over the posterior cisternal surface of the clivus. The pituitary gland was bulky within an expanded sella. She was commenced on dexamethasone and received emergency radiotherapy to which she responded well. CT CAP did not reveal a primary tumour. Endocrine investigations showed hyperprolactinaemia (1517mU/l) and primary hyperthyroidism (TSH 0.01mU/l and free thyroxine 39.6pmol/l) although the latter was related to her retrosternal goitre rather than any carcinoma. Measurements of serum osmolality (256mOsm/kg) and serum sodium (123mmol/l) were consistent with a diagnosis of SIADH. Her condition worsened with bronchopneumonia following transfer to the oncology centre and she died three weeks after her initial admission.

INCIDENCE

Pituitary metastasis occurs most often between the ages of 60 and 70 years and incidence is unaffected by gender[4]. PM is rare, accounting for only 0.4% of secondary intracranial tumours. It is estimated that of all trans-sphenoidal hypophysectomies performed for cancer only 1% are for metastatic lesions[17]. A recent analysis of patients with PM reported an incidence of 1.9%, which implies they are often under recognised or fail to present clinically[18].

IMAGING

Failure of clinical recognition may be explained by the fact

that most pituitary metastasis are asymptomatic. Many are noted incidentally on imaging studies performed for other clinical reasons. Differentiating PM from pituitary adenomas can be difficult. PM on pituitary MRI can appear as dumbbell shaped and can indent the diaphragm sellae. There can be sellar erosion without sellar enlargement and loss of the posterior pituitary bright spot[19]. As pituitary adenomas can present with increased metabolic uptake, functional imaging with PET-FDG is limited in distinguishing between adenomas and PM.

PATHOLOGY

More than half of all reported cases arise from the breast and lung. Other primary carcinomas known to metastasize to the pituitary in around 3-5% of cases include kidney, prostate and colon. Other rare causes include melanoma, thyroid, pancreas, haematological and from unknown primary cancers[20-22].

ENDOCRINE DYSFUNCTION

Cranial diabetes insipidus is the most common presenting complaint of pituitary metastasis and is present in around 50% of PM cases[11]. Other signs and symptoms include visual disturbance, cranial nerve palsies and headache. Anterior pituitary deficiency has been reported in around 25-45% of cases with central hypothyroidism and hypocortisolism frequently identified. As in our case series hyperprolactinaemia is also commonly found in around 2/3 of cases, presumably from pituitary stalk interruption[23-24]. Hyperfunction is more unusual but there are reports of acromegaly and Cushing's syndrome related to pituitary metastases from excessive GH and ACTH secretion respectively. SIADH is also a rare feature, estimated to occur in 1.5% of cases[19]. However in cases with apparent hyper function it can be difficult to exclude alternative causes, such as co-existing microscopic adenomas of the pituitary or ectopic secretion.

MECHANISMS OF METASTATIC SPREAD

Several mechanisms of metastatic spread to the pituitary have been proposed. Conventional haematogenous spread can occur in two ways, either through the hypophyseal arteries of the posterior lobe or the hypophyseal portal system of the anterior lobe. The second-degree nature of the portal system may confer a degree of protection to the adenohypophysis by siphoning malignant cells from the rest of the body's circulation. This explains why most metastases appear in the neurohypophysis. Only 15% of pituitary metastases involve the anterior lobe alone[25-26]. Alternatively, this could be due to the smaller volume of the posterior lobe, making it more vulnerable to disruption of function than a similarly sized lesion in the anterior lobe and thus more likely to be diagnosed by producing symptoms. Another mechanism is through circulating cerebrospinal fluid, which can act as a vector for malignant cells throughout the central nervous system[19]. This also contributes to the increased likelihood of posterior lobe involvement as it has more surface area in direct contact with the meninges. Finally, and less commonly, bony metastases to the base of the skull can erupt from the bone's surface to compress or invade the gland as seen in the MRI of case two.

MANAGEMENT

There is lack of consensus on how best to manage PM due to a paucity of data in addition limited survival of these patients leaves little time for meaningful research to take place and the inherent low incidence makes recruitment for sufficiently powered trials on outcomes difficult. The effects of chemotherapy are largely unknown. Surgical resection of pituitary metastasis has been shown to have beneficial effects through symptom relief but is not associated with increased survival[12]. Total resection via the trans-sphenoidal approach is technically challenging due to invasion of densely packed adjacent structures, such as the cavernous sinus, and due to high vascularization. Radiotherapy has been shown to have comparable symptomatic relief and may be better tolerated than surgery due to fewer complications and can be the more easily delivered option in the palliative setting[27].

PROGNOSIS

The prognosis of patients diagnosed with pituitary metastases is poor, as they invariably occur in the context of advanced disease. Estimated survival is between 6 and 22 months (median of 12.9 months) and no treatment has been shown to have a significant survival advantage[1,8]. Younger age, smaller volume lesion and time between initial disease diagnosis and pituitary metastasis presentation have been associated with longer survival[1].

SUMMARY

Pituitary metastases are rare and under recognised but not innocuous. While their impact on survival is devastating for a patient's prognosis there is significant scope for symptom relief in the inevitable palliative setting. Clinicians should have a low threshold of suspicion for pituitary involvement in malignant disease, particularly in patients presenting with features of diabetes insipidus.

Table 1 Patient characteristics at diagnosis

Case	Age at diagnosis	Gender	Primary disease	Survival*
1	18	Male	Large B-cell lymphoma	3
2	53	Male	Multiple myeloma	1
3	41	Male	Unknown primary	1
4	73	Female	Unknown primary	<1

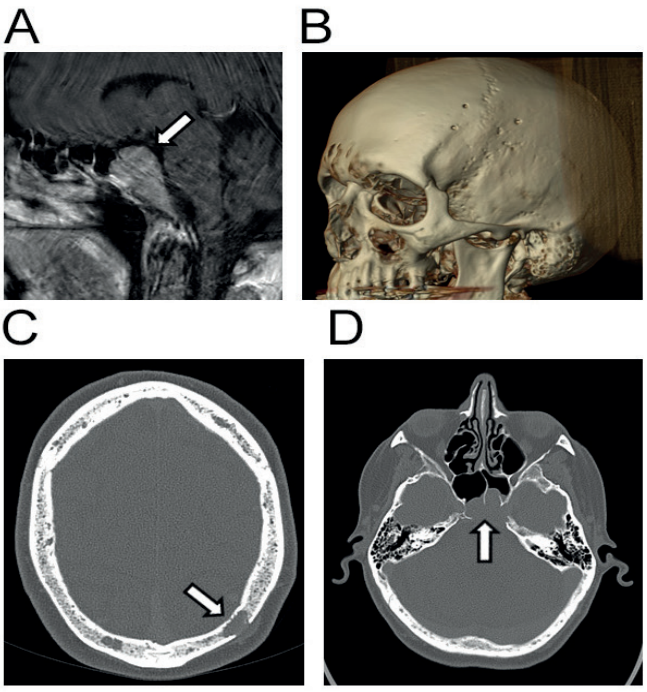
* Survival after diagnosis of PM (in months)

Table 2 Pituitary function at initial presentation

Hormone	Case 1	Case 2	Case 3	Case 4
ACTH	ND	↔	ND	↔
Cortisol	ND	↔	↓	ND
FSH	↓	↔	↓	↓
IGF-1	ND	↔	↔	↔
LH	ND	↔	↓	↓
Prolactin	↑	↑	↔	↑
Testosterone	↓	↓	↓	ND
Free Thyroxine	↓	↔	↓	↑
TSH	↓	↔	↓	↓

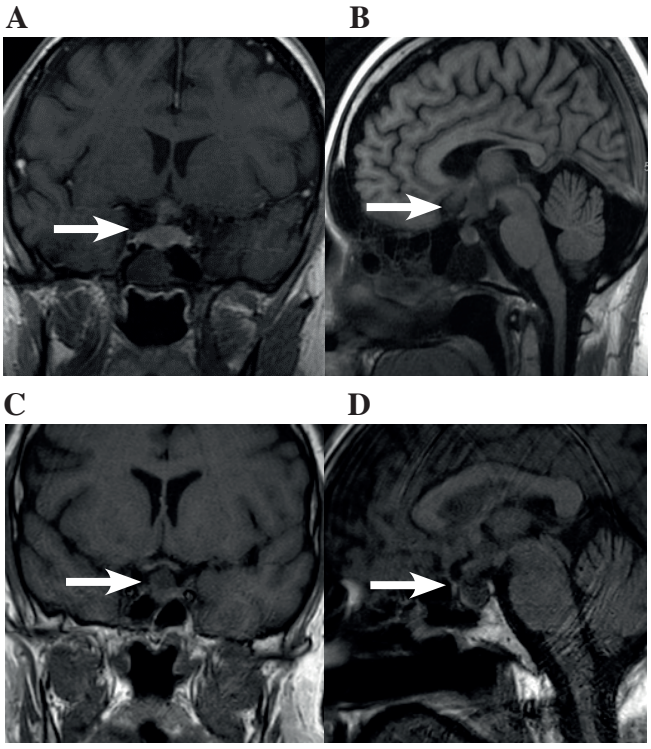
Anterior pituitary function measured at time of first recognition of pituitary involvement (↔, within normal range; ↑, beyond upper limit of normal; ↓, below lower limit of normal). ACTH, adrenocorticotrophic hormone; FSH, follicle stimulating hormone; IGF1, insulin-like growth factor; LH, luteinising hormone; TSH, thyroid stimulating hormone), ND-not done.

Figure 1



Imaging related to case 2. Sagittal MRI image demonstrating presence of myelomatous mass invading anteriorly from clivus of skull (A). Reconstruction of CT imaging demonstrating multiple lytic lesions of cranial vault characteristic of multiple myeloma (B). Same lytic lesions demonstrated transversely (C). Transverse view of clivus mass invading and compressing the pituitary gland (D).

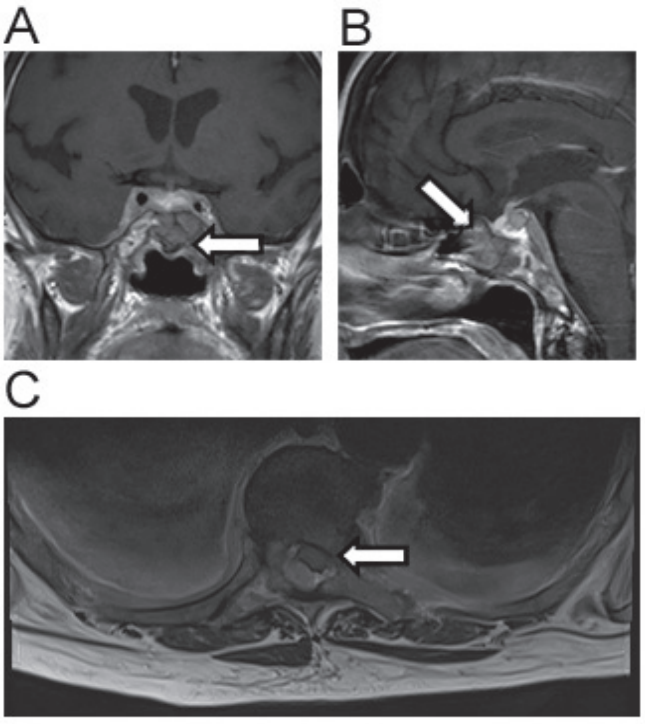
Figure 2



Imaging related to case 1 (A+B) and case 3 (C+D)

(A) Coronal and (B) sagittal MRI confirming malignant infiltration of the hypothalamus, pituitary stalk and pituitary fossa. (C) Coronal and (D) sagittal view demonstrating abnormal soft tissue mass in the pituitary fossa involving the pituitary gland and extending into the pituitary stalk

Figure 3



Imaging related to case 4. Coronal MRI image demonstrating compression of pituitary gland by cancer of unknown primary (A). Sagittal view of same lesion (B). Spinal cord compression by a posteriorly situated mass at the level T5/6 (C).

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Clinical Paper

SUPPORT FOR GENERAL PRACTITONERS DURING COVID-19

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ABSTRACT

Background: Evidence of initiatives to support General Practitioners (GPs) during the Covid-19 pandemic is scant.

Aim: To understand the impact of a novel method of providing support in the early stages of the pandemic.

Design and setting: A mixed-methods study of GPs working in a socially deprived area of Belfast.

Method: A survey was distributed to GPs who had attended a series of educational meetings at the beginning of the COVID-19 pandemic. The survey incorporated the Warwick Edinburgh Mental Wellbeing Scale and questions about the virtual meetings. Follow-up interviews were undertaken with five GPs to further explore their lived experiences and their perceptions of the virtual support forum.

Results: The Covid-19 pandemic resulted in a measurable diminution of emotional well-being in GPs in North and West Belfast. Attendees rated a series of virtual meetings highly and described the following themes (*and subthemes*): a sudden traumatic change (*emotional response, fight or flight, painful reminders of the status of general practice in the NHS);* a coming together *(stepping up to take responsibility, sharing of information, feeling of affirmation)*; reflections on what worked (*calming facilitation, careful selection of speakers, creating the right atmosphere, ownership and autonomy)* and building future direction (*defining future direction, capitalising on lesson learned).*

Conclusion: The virtual meetings harnessed the instinct to come together witnessed at the beginning of the pandemic, and as well as sharing valuable information, also provided emotional support along with a sense of comradeship, ownership and autonomy.

Keywords: General practice, COVID-19, pandemic, peer support, emotional support.

How this fits in: GPs did not feel included or supported at the outset of the pandemic. Coming together with fellow professionals was a welcome source of support. Professional support can be delivered using a virtual platform. Continued professional development is more acceptable than explicit emotional support, but when done well can bolster resilience and emotional well-being.

INTRODUCTION

The COVID-19 pandemic has presented the National Health Service (NHS) with a set of unprecedented challenges. Efforts to understand its impact, both on service provision and on individual clinicians, has often focused on frontline staff based in hospital [1]. However, the effects are widespread and have been felt across the NHS [2]. Some have expressed concern about insufficient attention on supporting primary healthcare professionals, particularly General Practitioners (GPs) [3]. At the same time, there has been a public discourse questioning the degree to which General Practice is open to the public, which has resulted in negative comments directed towards GPs and their teams [4].

Against this backdrop, GP Practices across the country have sought ways to support their teams to confront these extraordinary demands. However little guidance was forthcoming about exactly what type of support was required, particularly in the early stages of the pandemic. Key leaders (CL, DC & PL) of one Belfast GP Federation initiated a series of meetings (referred hereafter as 'Covid-Zoom meetings') to share education and best practice with their members. The meetings were extended to a neighbouring Federation after the first few. North and West Belfast Federations are comprised of 39 Practices of varying size, and serving a population of just over 200,000 people. Speakers from a variety of professions were invited to share their knowledge and experience of Covid-19. As the series progressed, it became apparent to the organizers, largely through informal comments, that the meetings were unexpectedly providing emotional support to many of the attendees. It is on this observation that this study

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was conceived.

This study aims to capture the impact of COVID-19 on a group of GPs and to explore the reasons the Covid-Zoom meetings were regarded so favourably. It is hoped that by so doing, themes might be identified to allow others to gain from our insights. The project aimed to address the following questions:

What was the professional and emotional impact of COVID-19 on a group of GPs?

Did a virtual forum provide meaningful support during a time of pandemic crisis?

What was learned that might inform post COVID-19 planning?

METHOD

Study setting

This study involved General Practitioners from North and West Belfast who attended at least one of 45 hour-long Covid-Zoom meetings undertaken from March to July 2020 each of which were facilitated by PL and DC. Most of the meetings were attended by between 50 and 70 GPs.

Study sample and recruitment

Participants were identified from a register of the email addresses of 74 GPs who had attended at least one Covid-Zoom meeting. A study information sheet was e-mailed to each GP including a hyperlink to an online survey. Individuals who were interested in participating in phase two of the study were invited to identify themselves to the survey lead (RK).

Design and analysis

A two-phase mixed-methods research study was developed.

Phase one: In early July 2020, all GPs involved in the Covid-Zoom meetings (n=74) were e-mailed a link to an anonymous online survey (via 'Qualtrics'). This survey took approximately ten minutes to complete and remained available for six weeks. The survey gathered demographic and professional information including age, gender, COVID-19 risk status, years of experience as a GP and Practice size. The survey incorporated the Warwick Edinburgh Mental Wellbeing Scale (WEMWBS) [5] which is a validated psychometric measure used to assess psychological well-being both in the general population [5,6] and in specific occupational groups [7,8]. Questions also quantified participants' attendance and perceived value from the Covid-Zoom meetings. Quantitative data was entered into SPSS Version 26 for statistical analysis. These findings were analysed using descriptive statistics and an independent sample T-test.

Phase two: Survey participants were invited to take part in a semi-structured interview; four volunteered do so. It was hoped to hold a focus group but at the time of data capture (a time when teams were more sparse due to staff trying to take overdue leave), it was impossible to find a time that suited everyone. One interview was conducted with two participants together and two interviews were conducted individually. Interviews took place in August and September 2020. In accordance with ethics requirements, and to afford participants with the assurance of anonymity to speak freely, only the survey lead (RK) and the interviewer (MD) knew the identity of each participant. Each interview was audio-recorded, transcribed verbatim and transcriptions were anonymised. The interviews lasted between 23 and 43 minutes and each was undertaken virtually using MS teams. The design of the semi-structured interview schedule (see Table 1) was informed both by the aims of the study and by the phase 1 survey findings. Questions focused on participants' personal and professional experiences of COVID-19, perceptions of the Covid-Zoom meetings and ideas that might inform future provision of professional and emotional support in General Practice.

1. Please reflect on the biggest challenges you have experienced as a consequence of the COVID-19 pandemic.
    - What was the biggest professional challenge?
    - What has been the most significant emotional challenge?
2. Please reflect on your experience of attending the N&W Belfast GP Federation meetings.
    - How many meetings have you attended?
    - What have you enjoyed most?
    - How have the meetings helped you?
    - Have the meetings helped you to meet some of the professional challenges you have faced? If so, how?
    - Have the meetings helped you to cope with the emotional challenges you have faced? If so, how?
    - What has made the meetings work well?
    - Was there anything about the meeting that did not work so well?
3. Do you feel this format offers an opportunity to provide support to GPs and others in primary care in the future?

Thematic analysis [9], a flexible qualitative method without a specific theoretical foundation, was used to analyse the transcribed interviews. The research team were unable to meet in person and all communication was conducted virtually. RK, DC, GO'N and CL were trained in data coding and, along with MD, read and re-read each of the transcripts separately to become familiarised with the dataset (Step 1). A collective approach was undertaken to maximise breadth of coding. Each separately recorded their ideas and generated initial codes (step 2) which were then combined into draft

themes (step 3) by MD. This draft analysis was presented by MD to the research team via Whatsapp video, before being emailed to each of member of the analysis team in written form. Thereafter a virtual meeting was held with the wider research team to agree a preliminary set of themes and sub-themes (step 4).

MD then conducted a further interview. Following transcription and coding of this interview, it was agreed by the research team that no further themes were emerging and it was concluded that data sufficiency had been achieved and that no further refinements to the analysis would be required (step 5).

JD, PL and GO'N are practising GPs and have served as Federation co-chairs and DC is a GP and subdeanery lead of a pilot project in North Belfast. CL is a GP who now works full-time in medical education. MD is a Clinical Psychologist and NH is an academic GP. RK is a trainee clinical psychologist and led the phase 1 survey. MD and NH both have experience in Thematic Analysis and other qualitative research methodologies. Each member of the research team brought a different perspective to the study and endeavoured to consciously adopt a reflexive position in respect of his or her own beliefs, judgments and practices during and throughout the research process.

RESULTS

Phase one results: Thirty-nine GPs (response rate 52.7%) completed the online survey posted in July and August 2020.

The mean score on the WEMWBS was 48.0 (SD 7.65). A wider survey of GP wellbeing undertaken in Northern Ireland in 2017 reported a WEMWBS mean score of 50.2 (SD 8.0) [10]. An independent sample T-test compared the current mean WEMWBS score, with the 2017 survey and found the deterioration in mean score was statistically significant $t(258)=2.0316$; $p<0.05$. For comparison, a pre-pandemic survey of the general population survey in Northern Ireland reported a mean score of 50.8 (SD 9.0) [6]. The above comparisons suggest that mental wellbeing was significantly worse in a group of GPs surveyed during the pandemic when compared to a pre-pandemic survey.

The mean number of Covid-Zoom meetings attended was 14.7 (SD 7.50). The majority of respondents (84.6%) attended 10 or more meetings, and 28.2% attended 20 or more meetings. Participants rated the meetings highly with 94.9% agreeing that the meetings 'helpful' or 'very helpful'.

Table 1: Semi-structured interview guide.

		n	%
Gender	Female	27	69.2
	Male	12	30.8
Age	≤44	23	59.0
	45-54	11	28.2
	≥55	5	12.8
COVID-19 risk status	No risk	27	69.2
	Raised risk	9	23.1
	High risk	1	2.6
	Prefer not to say	2	5.1
Sessions worked per week	≤4	5	12.8
	5 - 9	29	74.4
	10	5	12.8
Years of experience	≤10	17	43.6
	11 - 20	15	38.5
	21 – 30	4	10.3
	> 30	3	7.7
Number of practice partners:	≤4	28	71.8
	≥ 5	11	28.2

Phase 2 results: The background of the 5 GPs who took part in the interviews is provided in Table 3.

Analysis revealed the following themes (in bold capitals) and subthemes (in bold).

EXPERIENCING SUDDEN, TRAUMATIC CHANGE

Participants vividly described their **emotional response** to the onset of the Covid-19 pandemic as being essentially one of fear. Much of the language and many of the metaphors evoked were reminiscent of trauma narratives.

[GP1]: I can certainly think back quite vividly, where it felt like we were waiting for a really large tsunami and not quite understanding what was coming behind it – probably all driven by the news and the way the news kind of magnifies the problem."

Table 3: Interviewee's Details

	Gender	Age	Covid risk	Years of experience
GP1	F	≤ 44	None	13
GP2 (locum)	F	≤ 44	None	11
GP3	F	≤ 44	Prefer not to say	14
GP4	F	45-54	Raised	27
GP5	F	≥ 55	None	22

[GP3]: "I was scared, there's no doubt, from a professional and personal point of view."

[GP4]: "I remember the first week or so of it very clearly. It's almost like it's in slow motion. You can remember, sort of, small details of it all. It seemed to happen very quickly. One minute, we were doing our normal job, well, I was doing my normal job. It was busy. You were trying to fit people in and bring patients down. Then, literally in the space of a few days, we went from that to the surgery being closed, the doors shut and nobody coming down. It was such a change within a week."

A sense of **fight-or-flight** and military language was often used.

[GP4]: "I remember standing in reception and getting that population text from Boris Johnson. It said, "Stay at home, do not go out." It was that sort of text. I remember thinking, "I wish! I just want to go home and stay at home like everybody else. I don't want to be here. I would love to be able to go and stay at home."

[GP2]: "Not only did I want to work, I wanted to be central to things. So, there was very much a feeling of wanting to be part of an army going to war."

Painful reminders of the status of general practice in the NHS exposed by the crisis were described.

[GP1]: "I don't want this to be about, "poor us" but I think there's something very sad about how lost we were within all of that. I think there's a massive lack of understanding of what we do."

[GP5]: *'In general practice, small teams working away, you can feel, perhaps-, I mean, there was certainly an opportunity to feel very isolated.'*

A COMING TOGETHER

Participants described how individual GPs, practices and teams joined-together in response to the crisis.

[GP3]: *"Every morning, it became the norm for us to just gather in the reception area, all staff. Doctors and receptionists, everybody, and we just had a chat for half an hour every single morning about how we felt, what could we possibly do."*

[GP4]: *"The health centre has several practices in it and initially we would have joined together."*

[GP5]: *'It was just that feeling of, yes, it's uncertain but people are starting to come together and you're part of a whole.'*

Stepping up to take responsibility for decisions about professional and personal challenges evoked a clear sense of professionalism.

[GP3]: "Generally, I think we knew what we had to do. I suppose we just did it. There was no advice from health Trusts or anybody like that. We just knew that we just had to do it ourselves."

[GP3]: "Right, we have to keep our staff and patients safe."

[GP4]:"At work, clinically the challenges were very real because it was a new illness. None of us really knew very much about it and obviously any guidance was probably not-, we're very used in medicine to everything being evidence-based. Nothing really was very evidence-based. It was all fairly anecdotal. So, the challenge clinically was to get on top of what was a new illness. There just seemed to be information overload and lots of guidelines coming out. It was a challenge to try and keep on top of it, to try and keep on top of all the emails."

[GP5]: "Had to make decisions, basically had to turn around the way we work completely."

Participants reflected on the helpfulness of the Covid-Zoom meetings and, in particular, the benefit of **sharing of information**.

[GP3]: "I think it was a lot of education at the beginning. The respiratory consultants, the A&E, the palliative. All the things that we had to have to be armed with knowledge."

[GP2]: "We came away armed with information. Most of the meetings, you came away armed with information or reassurance that what you were doing or what you were thinking of doing was going to be correct the following week."

The Covid-Zoom meeting also provided a **feeling of affirmation**, in that GPs were reassured that everyone was in the same boat and that everyone was feeling and thinking similarly.

[GP2]: "Total camaraderie."

[GP1]: "Common purpose, yeah. Also, something about an equaliser. That we're, kind of, all at the same thing."

[GP5]: 'Well, for me it was a relief because I'm the sort of person who likes to do the right thing. Yeah, so that was a relief. It was a relief that, yes, this is what others are doing because you learn from other people and how they're managing. "What are you doing?" "We're doing this, we're not doing this." That relief of not being a small island of a practice with 5,000 patients and four partners in the midst of this sea of uncertainty.'

[GP3]: *"It was very much sharing the fact that everybody's in the same boat and reassuring that every practice, more or less, had the same approach as well."*

[GP4]: *"You just saw your colleagues as a human, as a person, as opposed to just a name on a page or just another doctor. You kind of realise that they all have their different situations, concerns, worries, maybe health problems. You know, everybody had their own concerns at the time."*

REFLECTIONS ON WHAT WORKED

[GP2]: "Normally where I work they don't really come out of their rooms for lunch, or anything. They all went up for the meeting at 1:00pm. They found it so informative, so well run."

[GP4]: "Well, the overall feeling is that they were very positive, that they did help, that I enjoyed them, that I did gain relevant information from them.".

Participants reflected on the importance of **calming facilitation**

[GP2]: "The chair was very well-spoken and very well able to manage things, from the point of view of putting questions across to people, inclusive of people."

[GP3]: "[redacted], who was chairing the meeting, she was very calm throughout. I don't know if she felt calm but she appeared to be calm. I remember that."

Careful selection of speakers was also referred to and it was helpful to have both familiar local and prestigious national speakers, who were empathic towards General Practitioners.

[GP1]: "I would say there was something about them being important enough that those people were really engaged and exciting. I think we can't undervalue that part because we were being ignored in some ways in the context of the Covid response and the funding etc."

[GP4]: "Well, I really enjoyed it and valued the opportunity to listen to someone like that but I suppose maybe it makes you feel that, yes, this is serious. These people are taking the time to address these groups of local GPs."

Creating the right atmosphere was considered important.

[GP3]: "It was the opportunity to raise any issues and questions. That was a forum that, sort of, provided that. Although there was usually a speaker or a local Consultant, or an update from somebody, there were always maybe a few minutes at the end. "Anybody got any issues?" So, there was that opportunity for a bit of a chat."

[GP4]: "In general, it's fine for people to have maybe slightly differing opinions or to raise issues to get answers."

[GP5]: You could feel relaxed and just listen, and think, yes, that's a very good point, or whatever. Didn't feel pressure to speak.'

There was also a sense that **ownership and autonomy** expressed.

[GP1]: "I just found it very empowering. That view, forewarned is forearmed. You felt like you had all the tools and were also reassured that we were all doing a similar thing."

[GP1]: "Unity and ownership and support and teamwork. I got a total buzz out of it."

[GP2]: "As a Locum, that felt amazing to feel included. At the start I thought, "Oh, God, I'm the Locum here. I'm going to be the only one." Then, there were other people added in. It was really nice to feel part of something and not just, sort of, on the edge."

BUILDING FUTURE DIRECTION

All participants agreed that this method of providing support to General Practitioners has a role to play in the future, and many offered ideas about **longer-term function**.

[GP5]: 'Now, it's all so anonymised and so much less personal. That's where the peer group meetings, I think, are important.'

[GP1]: "I think that GPs aren't great at selling themselves and their voice isn't heard well. I think we really need to consider actively pursuing PR support, somebody who is our public relations representative."

[GP5]: 'Our services are pretty broken in Northern Ireland. I mean, they were so poor before this. I do feel there needs to be a complete turnaround. I know loads of people are working really hard at that and I do think communication between primary and secondary care is important in trying to move forward with the Service here. So, there's that but the communication between primary and secondary care was useful.'

Participants also reflected on how to **capitalise on lessons learned**. There was a sense that Continued Professional Development (CPD) is more acceptable to GPs than explicit emotional support but that CPD, when done well, can be emotionally supportive. It was also considered important that the value base of General Practitioners is reflected when deciding the topics that should be covered, and that having a local focus is helpful to maintain engagement.

[GP1]: "I think now we've seen what we can do ourselves, we don't necessarily need that reassurance. I think we can do it all for each other."

[GP3]: "Short. It has to be short."

[GP3]: *"What GPs want is to be able to sort things for their patients. If you can sort things for your patients quickly and efficiently, your life's a lot easier."*

[GP4]: "There could potentially be a role, monthly, two-monthly, for updates or a forum for people to bring questions."

[GP2]: "They kind of go hand-in-hand, really. I don't know that I would value one over the other but I suppose, by our nature, as doctors you kind of like information, guidelines and facts. So, I'd probably be going with the clinical guidelines that were particularly useful in the first instance. I'm feeling that's what I need to do my job. The other [peer support], *I suppose, is also very important but perhaps you don't recognise it as important and you think that the guidelines are the first thing that you need. But also, you do need the support as well and that's a nice thing that comes with it."*

DISCUSSION

The findings of this study demonstrate that the Covid-19 pandemic had a measurable effect on the emotional well-being of a group of General Practitioners in Belfast. Memories of learning about and responding to the pandemic were expressed using the language of trauma and of war, and GPs recounted having to take responsibility for a range of professional and personal challenges. In North and West Belfast, a community of General Practitioners felt that the impact of the pandemic on primary care and on General Practice was not being given due consideration, and so came together, in the spirit of practice-based group learning [11], to support one another in a virtual educational meeting. Careful consideration was given to the type of information needed by General Practitioners at the time and speakers were carefully chosen to meet the needs of the profession. As well as providing invaluable education, the virtual meetings were also a source of emotional support and affirmation. They fostered a sense of camaraderie and empathy for peers and colleagues, and the visual connection of seeing faces was clearly important. The meeting provided a sense of support and reassurance, which created unity and a flattening of professional hierarchies. The role of the facilitator in providing a calm, containing, positive atmosphere where people felt safe to remain quiet, to ask questions or to disagree with one another was paramount. Attendees felt supported by the speakers, who they perceived had empathy for them. Both the attendees and the organisers felt buoyed by taking ownership and adopting a position of autonomy in the face of a worldwide crisis.

Because of the constraints imposed by the pandemic, it was not possible for the research team to meet in person, which meant the methodology had to be adapted to suit the needs of a virtual team. Nevertheless, the themes that emerged from the interviews were strikingly consistent and as such, the analysis was straightforward. Accordingly, we believe the themes identified are broadly representative of the views of GPs who attended the Covid-Zoom meetings, though we are mindful no male GPs volunteered to be interviewed.

The call to support the resilience and emotional well-being of General Practitioners has received widespread support [12]. This study demonstrates that a virtual support forum can bolster professional resilience at a time of crisis. It was felt that this type of meeting does have utility in the future, both to support general practice and individual General Practitioners.

The authors of this paper believe it is likely that GPs across the country would identify with the themes that emerged in this research. In contrast to other well-intentioned statutory support initiatives, which are often delivered top-down, this initiative harnessed the instinct to meet a crisis by 'coming together' with people with common links and culture. It was noted that CPD is more acceptable to GPs than initiatives explicitly providing emotional support, but that, when it is done well, CPD can be emotionally supportive. This finding is particularly important as funding for CPD has been progressively diminished over time.

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Ethical approval: Ethical approval was granted by the Research Ethics Committee for the Faculty of Medicine, Health and Life Sciences, Queen's University Belfast (Reference: MHLS 20_86).

Competing interests: The authors have declared no competing interests.

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Clinical Paper

Follow up for COVID-19 in Belfast City Hospital

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Background:

During the COVID-19 pandemic of Spring 2020, Belfast City Hospital functioned as Belfast's Nightingale facility. Evidence published during this time focused mainly on the acute management of the condition. Guidance on follow up and long-term management for patients recovering from COVID-19 was sparse. A specialist COVID-19 follow up service was devised in Belfast City Hospital led by a respiratory physician with physiotherapy and psychology input.

Methods:

Data was collected on all patients admitted to Belfast Nightingale unit. Patients admitted to Intensive Care at any stage in their admission were followed up separately by Intensive Care. Initial consultation was via telephone call for all eligible patients six weeks post discharge, followed by face-to-face consultation for those with symptoms at next available appointment, and a further face- to-face consultation at twelve weeks post hospital discharge. Patients were seen by respiratory physician, physiotherapy and psychology at each appointment. All patients who had initial changes on chest radiograph had 12 week follow up radiograph requested as per British Thoracic Society guidelines.

Results:

29 patients were followed up after hospitalisation with COVID-19. Of these, 10 were brought for face-to-face consultations. Patients at clinic were all functionally independent with a median Medical Research Council dyspnoea score of 2 and a subjective assessment of their current health of median 50, on a visual analogue scale 0-100. Fatigue was common with all patients. Depression, anxiety and post-traumatic stress disorder were all reported from psychological review. Chest radiograph showed signs of improvement in 100% of clinic attendees. 90% of patients seen in clinic had normal or chronic obstructive patterns on spirometry, with one patient having a reduced transfer factor.

Conclusion:

Majority of patients did not require face-to-face review and were recovering well. Of the 10 patients seen in the respiratory led clinic, the main issues reported were fatigue and psychological issues. Respiratory symptoms were significantly improving in 9 out of the 10 patients seen. All patients have been introduced to psychology service whilst at clinic and will continue to receive necessary support.

Introduction

At the time of writing, there have been 33,722,075 confirmed cases of infection with SARS-CoV-2 (severe acute respiratory syndrome – coronavirus - 2), otherwise referred to as COVID-19, worldwide 1, with 11,952 of these in Northern Ireland 2. While a lot of focus has been on logistical and clinical management of the pandemic, there has been little guidance on follow up of patients with COVID-19 after they have been discharged from hospital.

Given the extent of respiratory involvement during the peak of the illness, a clear concern lay around the potential for chronic respiratory illness as a result. The clinical severity across those infected with the SARS-CoV-2 virus was broad, ranging from those who remained asymptomatic to those who required critical care support for multi-organ failure. Due to this, there will also be a range of psychological and rehabilitation needs following discharge from hospital. This greatly differs from typical respiratory discharges and so a new follow up service was developed specifically for this patient cohort.

During the COVID-19 pandemic, Belfast City Hospital (BCH) was restructured to function as Belfast's Nightingale Hospital. This was required for a 7 week period over April – May 2020. Each patient initially presented to another hospital within the Belfast Health and Social Care Trust, where they had a confirmed positive SARS-CoV-2 nasopharyngeal and / or oral swab, and were transferred to the Nightingale facility. In total, 113 patients were admitted under the Nightingale Medical team.

Methods

A database was compiled and maintained on all patients admitted to the Nightingale facility. Data was collected on patient demographics, smoking history, co-morbidities, clinical frailty score3, ventilation requirements, need for

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renal replacement therapy, and incidence of delirium and mortality.

Conference calls facilitated discussion between the respiratory, intensive care, psychology and physiotherapy departments across the trust to devise a structured approach for the COVID-19 follow up clinic. The six week follow up approach was designed across respiratory and intensive care to facilitate appropriate care for all patients, allow comparisons of outcomes and to enable safe transfer of care from intensive care to respiratory if required following the initial follow up period. Patients admitted to intensive care at any stage in their admission were followed up by the intensive care team for 12 weeks following discharge and any patients not admitted to intensive care were followed up by the respiratory team. This article focuses on the initial 12 week respiratory follow up service. Assessments were carried out virtually with a holistic approach to cover not only medical needs, but also addressing need for psychological and physical rehabilitation requirements.

The first step of follow up consisted of a telephone call with screening questions to assess patients and determine the need for a subsequent face-to-face consultation at post COVID-19 follow up clinic. We aimed to complete phone calls by six weeks following hospital discharge.

Any patient requiring critical care support on Intensive Care Unit during their admission was contacted by an intensive care physician for their 6 week virtual review. Patients who had not required intensive care were contacted by a member of the respiratory team at 6 weeks. Following Electronic Care Record (ECR) review, patients were excluded if aged 90 years or older, or if they had a clinical frailty score of greater than 5. Excluded patients' notes were then passed to our respiratory specialist nurse to review and assess if any additional support would be required. Asymptomatic incidental presentations with normal chest radiograph at presentation were also excluded.

A proforma was drawn up for the phone call to ensure key questions were asked and phone calls all made by a member of the respiratory team.

Following the telephone discussion, outcome options were clinic appointment arranged or no follow up required. If the patient reported persisting symptoms from any section of telephone screen, they were offered a clinic appointment. If, however, they were recovering well with no symptoms but had changes on chest x-ray (CXR) during admission, then as per British Thoracic Society (BTS) guidelines, they were offered a 12 week follow up CXR. For the patients with no lasting symptoms and no CXR changes during admission, no follow up was arranged 4.

For those requiring face-to-face respiratory consultation, they were invited to a multidisciplinary post COVID-19 clinic where they had follow up CXR, lung function tests, ECG, blood tests to include full blood count, kidney function and NT-proBNP. Each patient was assessed by respiratory team, physiotherapy and psychology. Degree of breathlessness was measured using the Medical Research Council (MRC) Breathlessness Scale 5. Physiotherapy assessment consisted of the Fatigue Impact Scale (FIS) 6; The QOL EQ5DL7, a quality of life questionnaire; The Duke Activity Status Index (DASI)8; Post-COVID-19 Functional Status (PCFS) Scale9 and the 30 second sit to stand test in which the heart rate and oxygen saturation was taken pre- and post-testing. The EQ-59 score includes a visual analogue scale by which patients rated their perceived current health compared to their best score, on a 0-100 scale.

Questionnaires were sent to patients to complete prior to clinic attendance to allow calculation of various symptomatology scoring systems. Psychology questionnaires sent included the PHQ9 score for depression10, the 7-item Generalised Anxiety Disorder Scale GAD-7 for anxiety11 and the Posttraumatic Stress Disorder (PTSD) Checklist PCL-5 score 12.

Results

This patient cohort totalled 113 patients, comprised of 69 male patients (61%) and 44 female patients (39%), with a median age of 66 years(IQR 53.5 – 78). 98 patients (86%) were of white Northern Irish ethnicity, with the remaining 14% comprising 7 different ethnicities. Only 2 patients were current smokers, 31 ex-smokers and 61 patients had never smoked. Smoking status was unknown in 19 cases. 79 patients (70%) were direct admissions from home via an Emergency Department, 13 (11%) were admitted from 24-hour care facilities and the remaining 21 (19%) were transferred from other hospitals following positive swabs for SARS-CoV-2. The median length of hospital stay was 10 days (IQR 5 – 21).

Table 1: Patient demographics

	Total (n=113)	ICU	Non-ICU
Age (years)	66 (53.5 – 78)	55 (49 – 63)	74 (64 – 86)
Sex			
Male	69 (61.06%)	33 (80.49%)	36 (50%)
Female	44 (38.93%)	8 (19.51%)	36 (50%)
Smoking			
Current smoker	2 (1.77%)	0 (0%)	2 (2.78%)
Ex-smoker	31 (27.43%)	11 (26.83%)	20 (27.78%)
Never smoker	61 (53.98%)	21 (51.22%)	40 (55.56%)
Unknown	19 (16.82%)	9 (21.95%)	10 (13.88%)
Length of stay	10 (5 – 21)	22 (12 – 39)	7 (3 – 12.5)

Data are n (%), or median (IQR)

Out of a total of 113 patients admitted to the Nightingale facility at BCH, 29 met eligibility criteria for follow up under respiratory team. We had a 19% mortality rate, excluding

21 patients from follow up. 36 patients were admitted to intensive care and had initial follow up with the intensive care team. Frail, elderly (>90years) patients (n=24) were not reassessed at clinic but were offered a follow up CXR if changes on initial scan. Any incidental cases of positive SARS-CoV-2 swabs who were asymptomatic with normal CXR were not contacted for follow up (n=5).

We aimed to complete initial telephone call for these 29 patients within 6 weeks of discharge. We were able to contact 28 (97%) patients (Figure 1). The median time from hospital discharge to initial telephone conversation was 42 days and median time to initial face-to-face consultation 56 days.

Of the 28 patients contacted for virtual respiratory telephone review, 9 patients (32%) reported persisting breathlessness, 4 (14%), ongoing cough and 3 (11%) had chest pains. 12 patients (43%) were off their baseline mobility with reduced exercise tolerance. 7 patients (25%) reported low mood since discharge from hospital, 5(18%) reported anxiety or panic attacks and 5(18%) reported a disrupted sleep pattern or nightmares. 2 patients had new cognitive decline – 1 patient had new memory impairment and 1 patient, currently a nursing home resident, had new fluctuating mild confusion.

In total, 12 patients were identified as requiring face-to-face consultation. 2 patients remain inpatients in a rehabilitation facility and so have had their initial face-to-face consultation arranged for 12weeks post discharge so a total of 10 patients were reviewed in the multi-disciplinary six week follow up clinic. 16 patients are listed for a 12 week CXR. 7 patients reported good recovery and have not required follow up at this time.

Of patients brought to clinic, 40% were obese with a median BMI of 30.2 (27.2 – 33.55kg/m2). The median dyspnoea score was 2.

All patients who attended clinic were functionally independent with no physical limitations to strength or balance. However, fatigue was common with all patients seen and this was reflected in the FIS questionnaire scores. Patients reported a fatigue impact score median 65 out of total 160 and DASI score median 21.4 points METS 5.38, demonstrating moderate impairment of functional status. Of the patients who were seen on a second review and re-tested, the FIS scores had shown an improvement of 19% and the DASI functional impact score showed an improvement of 54%. Physiotherapy assessment included 30 second sit to stand with patients managing a median result of 13 in this time frame. Post-COVID-19 Functional Status (PCFS) Scale showed an improvement in the second review of 37.5%. EQ-5D-5L Visual Analogue Scale showed an improvement in the second review of 27.2%.

Psychological assessment showed overall moderate severity depression with median PHQ9 score of 10 (4 -15) and mild severity anxiety with GAD7 median 7 (2 -11). The median PCL-5 score, the screening tool used for PTSD, had a median score of 28.5 (3 – 33.75), which would not meet criteria for PTSD clinical caseness. Cognitive assessment was completed using the Montreal Cognitive Assessment (MoCA) tool in 4 patients with a median result of 24.5 (23 – 26), which is in normal range. However, it is important to note that there was considerable variation in responses to the psychological questionnaires. On review of the data there were 3 clear outliers, which consistently differed significantly across all questionnaire responses thus deflating the other scores.

Patients graded their current health on day of clinic as a median of 65 (56.25 – 71.25) on a virtual analogue scale of 0-100, 100 being their best health.

At presentation, 111/113 (98%) patients had a CXR. Of these, 66 (59%) showed changes typically seen with SARS-CoV-2, 25 (23%) had a radiograph showing changes unlikely to be due to SARS-CoV-2 infection and 20 (18%) were normal. At this stage, we have repeated CXRs in patients brought for face-to-face consultation, however the remainder of patients with abnormal CXRs on admission will have their CXR arranged at twelve weeks post discharge. CXRs showed significant improvement by time of clinic review in 100% (n=10).

10 patients had spirometry and transfer factor measured. These were in normal range for 6 patients. Out of remaining four, three patients had obstructive spirometry with known history of chronic obstructive respiratory conditions and one patient had new reduced transfer factor. This patient has had further investigations and follow up arranged with the respiratory team.

ECG was reviewed with no abnormalities detected, in sinus rhythm for eight of the ten patients seen in clinic and was not performed in the remaining two patients. NT-ProBNP blood test was in normal range for seven patients, high in one patient and test not performed for two patients.

Discussion

We have reviewed the design and outcomes of the first stage of ongoing follow up in the care for patients discharged from hospital following infection with SARS-CoV-2.

Data will continue to be collected on lasting physical and psychological symptoms, chest radiography and lung function following hospitalisation. Patients who were not discharged following 6 week face-to-face review will be seen again at the twelve week post discharge point, and patients assessed by intensive care teams at six weeks have been invited for a face-to-face review.

At this early stage, it is good to see that 54% of patients did not require face-to-face review and report they are recovering well from COVID-19. Of the 10 patients seen in the respiratory-led clinic, the main issues reported were fatigue and psychological issues. Respiratory symptoms were significantly improving in 9 out of the 10 patients seen. All patients have been introduced to the psychology service whilst at clinic and will continue to receive necessary support.

Patients presented with expected and normative distress given both their personal experiences and the ongoing wider societal perceived risks and ongoing restrictions and concerns. Many reported being very grateful for having survived and for the care they received and potentially this may have reduced initial reporting of psychological symptoms. All those seen at clinic reported feeling very reassured in having the opportunity to discuss and normalise their feelings and some preliminary, lower level psychological advice was given. All will be reviewed at 12 weeks.

There was no physiotherapy follow up needed for any patients seen with most given advice with pacing their activities to help with fatigue with home exercises programs as needed. The participants were shown the COVIDcare NI APP which has information and guidance on recovering from COVID-19 amongst other advice.

This approach is in keeping with BTS guidance for early integration with ICU follow up and the requirements of a 'post-COVID-19' holistic assessment, however we did decide to facilitate earlier follow up for all patients than the suggested 12 weeks4. In those still symptomatic, it offered early opportunity for referral to appropriate services. Patients were reassured knowing they weren't alone in the problems they were facing and that support was available. We feel this will affect long term outcomes and overall patient satisfaction. We have now developed a patient satisfaction questionnaire which we will email to patients following 12 week review to address if they found this helpful.

We continue to run separate intensive care and respiratory follow up clinics until 12 weeks post discharge with frequent communication between teams to address any issues encountered and update on progress. Following the 12 week review, a follow up pathway has been designed for further follow up needs. If symptoms are improving as expected for a patient following a severe viral pneumonia, no evidence of lasting CXR changes and/or physiological impairment, they will be discharged from medical follow up. Other members of the multidisciplinary team will arrange follow up as required. If the patient has an abnormal CXR or physiological impairment, defined as abnormal lung function tests, raised NT-ProBNP, or symptoms out of keeping with resolving pneumonia, they will have further investigations arranged based on suspected diagnosis. Based on investigation results, patients will be triaged by an allocated respiratory/intensive care consultant to follow up. New interstitial lung disease cases will be seen at a respiratory physician led clinic and follow up of chronic thromboembolic disease / pulmonary hypertension at a pulmonary vascular disease clinic.

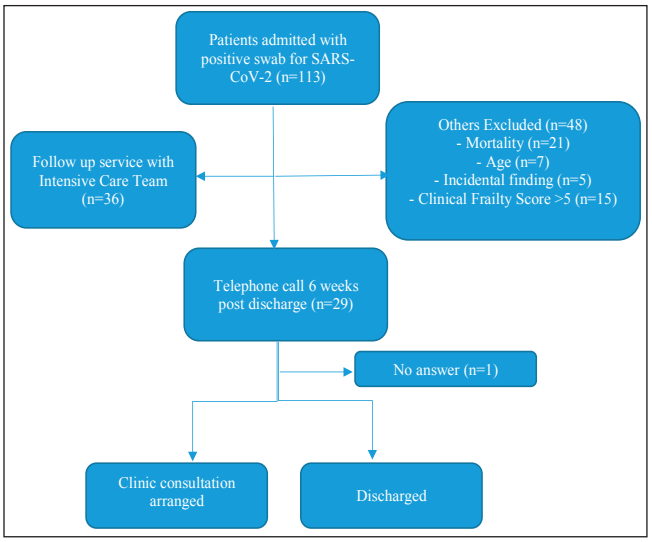
The COVID-19 outbreak is posing considerable challenges to healthcare systems worldwide. Throughout the pandemic, understanding of the acute phase of the disease has rapidly expanded, however, there is still little known about the long-term consequences following clinical remission. Information on the long-term effects of other coronavirus diseases is limited, and we still do not know to what extent this data can be applied to COVID-19 13 14.

It is possible that the COVID-19 pandemic may result in ongoing psychological distress for many survivors with the potential for some to develop significant mental health issues. Post trauma symptoms and, in the longer term, development of PTSD, can be a common pathological outcome of a wide variety of traumatic events, from natural disasters to road traffic accidents15. Core symptoms of PTSD, as defined by the Diagnostic and Statistics of Mental Disorders, the fifth edition (DSM-5) of the American Psychiatric Association, include persistent avoidance of stimuli, persistent intrusion symptoms, negative alterations in mood or cognition, and marked alterations in arousal and reactivity, all associated with the experienced traumatic event16. PTSD results in clinically significant distress to the individual, as well as impairment in normal functioning. Epidemiological data indicate that the median time for PTSD to recover is 36 months for individuals who sought help for any mental health problem and about 64 months for individuals who never sought help for a mental health problem17.

Infectious disease epidemics result in a psychological trauma. While most of these mental health problems will fade out after the epidemic, symptoms of PTSD may last for a prolonged time and result in serious disability. Issues such as a pre-morbid history of mental health difficulties, physical morbidity sequelae and wider life impacts (such as impact on employment) and admission to ICU can all be contributing factors in ongoing distress. A systematic review of psychological consequences of infectious disease outbreak indicates that the average prevalence of PTSD among health professionals was approximately 21%18. A study of the long-term psychiatric morbidities among SARS survivors revealed that PTSD was the most prevalent long-term psychiatric condition. 47.8% of SARS patients were diagnosed with PTSD, and 25.5% of these patients continued to meet PTSD criteria at 30 months post-SARS19.

An already large and still increasing number of people have been exposed to COVID-19. It remains a cause of increased social anxiety, with high visibility in terms of media coverage and strong public health messaging, some of which is promoting increased vigilance and increased safety behaviours (which post traumatic event could be interpreted as trauma reactions). It is very important, therefore, to gain an understanding of the ongoing natural progression of expected psychological distress, normative psychological impact and the longer term likelihood of developing PTSD and other mental health issues. This will allow better understanding of the workforce needs and service developments needed to best support individuals and families during and in the aftermath of the pandemic.

Figure 1: Flowchart showing COVID-19 follow-up pathway



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Clinical Paper

Outcomes of older COVID-19 patients in Acute Care at Home, Southern HSC Trust, Northern Ireland, from March - June 2020

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ABSTRACT:

Introduction: The older population has been most affected by COVID-19, with mortality rates of around 27%. The Acute Care at Home (ACAH) team aims to improve outcomes in the older population by preventing hospital admission or facilitating early discharge, allowing patients to be treated in their own environment. During the COVID-19 pandemic, the ACAH team administered oxygen therapy, antibiotics, anticipatory medications and other vital interventions to combat the ill effects of COVID-19.

Method: An observational approach has been used in this study. Patients were included if they were admitted to ACAH during March-June 2020 for treatment of COVID-19. Biochemistry, oxygen saturations and co-morbidities are among the studied parameters. Lymphocyte count and serum magnesium were compared with a non-COVID-19 cohort. Trends within parameters and associated mortality were analysed and tabulated.

Results: 70% of admissions were lymphopenic, whilst 54% were hypoxic. There was a 28-day mortality rate of 35%, with an 18% increase in mortality rate when comparing residence in long-term care facilities (LTCF) to personal residence. All patients had existing co-morbidities.

Conclusion: The data indicates that hypoxaemia, hyperferritinaemia and hypermagnesaemia are associated with early mortality in the older population infected with COVID-19. National Early Warning Score and frailty score are predictive of mortality in this cohort, with higher scores correlating to worse outcomes. Those living in LTCF are at an increased risk of mortality. However, ACAH mortality rates are comparable to those admitted to hospital, validating the concept of ACAH. The highlighted trends can be used to improve outcomes in future admissions.

Key Words: Covid-19, older population, mortality, acute care at home, Southern HSC Trust Northern Ireland.

Introduction:

Over 2 million people worldwide have died from COVID-19 [1]. Mortality is highest among older populations, with a case fatality rate of up to 27% [2]. Older people have experienced increasing anxiety about hospital admissions and death [3]. This paper presents data and findings recorded by the Acute Care At Home (ACAH) Team in the Southern Health & Social Care Trust in Northern Ireland. It is a multidisciplinary team led by Consultant Geriatricians, treating older people in the community. Acute care is provided to patients within their own homes or within a long-term care facility (LTCF). Each patient is assessed comprehensively. Treatments include intravenous (IV) fluids, antibiotics, pain relief and home-oxygen therapy. Ultimately, ACAH aims to prevent hospital admission or facilitate early discharge from secondary care. During the first wave of the COVID-19 pandemic, data was collected on COVID-19 patients admitted to ACAH: patient demographics, alongside information about their presentation, co-morbidities, blood results and clinical outcome. This paper analyses the data collected in search of trends.

Method:

Data were collected retrospectively, for the time period of March to June 2020, using two electronic information management systems routinely used within ACAH; Northern Ireland Electronic Care Record (NIECR) and PARIS. ACAH doctors suggested certain parameters for analysis from their clinical experience. Microsoft Excel was used to collate this data and trends within the population were identified and assembled in a results sheet. Information gathered includes patient demographics, COVID-19 PCR result, place of residence, frailty score, presenting complaint, past medical history, smoking status and biochemistry results at different stages of patient care.

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Biochemistry results on admission included:

- Lymphocyte percentage (reference range 20-40%)
- Lymphocyte count (reference range 0.9-2.9 x10^9/L)
- Lactate dehydrogenase (LDH) (reference range 135-214 U/L)
- Ferritin (reference range 30-400 ug/L)
- D-dimer (reference range 0-0.5 mg/L)
- Serum magnesium (reference range 0.7-1.0 mmol/L)
- Haemoglobin (reference range 115-160 g/L)
- Platelet count (reference range 150-450 x10^3/mL)
- Total white cell count (reference range 4-11x10^9/L)
- Serum albumin (reference range 35-50 g/L)
- Alanine aminotransferase (ALT) (reference range 0-33 U/L)

Estimated glomerular filtration rate (eGFR) and oxygen saturation were recorded on admission and on discharge, with the lowest result during admission also being recorded. Creatinine and C-reactive protein (CRP) were measured on admission and on discharge, with the highest result of each during admission also being recorded. If a patient had an acute kidney injury (AKI), according to the AKIN classification [4], this was also recorded. The need for supplemental oxygen, antibiotics, subcutaneous/IV fluids and palliative medications were also recorded.

Patients were counted as deceased if they died during admission or within two weeks of discharge, which was considered to be in line with the national UK practice of being within 4 weeks of a positive COVID test*.

Patients were included in the study if they met the following inclusion criteria:

1. Admitted to ACAH between 1st March 2020 and 30th June 2020 AND;
2. Positive COVID-19 PCR OR;
3. Negative COVID-19 PCR but clinically symptomatic (with fever, cough, dyspnoea or hypoxia) and treated as COVID-19*.

If a patient received multiple admissions during this time period, these were recorded as separate entries.

Data were also collected from a pre-pandemic population so comparisons of certain parameters could be made. This population encompassed ACAH patients between 1st March 2019 and 30th June 2019. It was assumed that these populations were demographically similar as the acceptance criteria to receive care from the team remained the same.

Patients consented to their NIECR and PARIS being accessed by healthcare professionals and their anonymised data being used for research purposes.

Results:

123 admissions met the inclusion criteria. Of these, 92 (74.8%) received positive COVID-19 PCR tests and 31 (25.2%) received negative COVID-19 PCR tests, but were clinically treated as COVID-19. The age range of patients was 23-98 years old, including 115 (93.5%) patients over the age of 65. 88 (71.5%) patients were permanent residents of nursing homes, 26 (21.1%) were cared for at home, 4 (3.3%) were in supported living, 3 (2.4%) were in elderly mentally infirm units and 2 (1.6%) lived in residential homes.

The 28-day mortality rate was 35%, with 45% of those living in LTCF recorded as deceased, compared to 27% of patients living in their own homes.

44 (36%) patients had three or less co-morbidities and 79 (64%) had more than three co-morbidities. 46 (37.4%) patients were current or ex-smokers and 77 (62.6%) were non-smokers.

Table 1 Common presenting complaints by percentage

Presenting complaint	Percentage of patients (%)
Low oxygen saturations	54
Decreased oral intake	46
Cough	42
Fever	35
Dyspnoea	33
Neurological symptoms	25
Lethargy	24

The most common presenting signs and symptoms are shown in Table 1. 54% of patients had low oxygen saturations, defined as saturations of <94%, with 54% of those patients requiring supplemental oxygen and only 36% of those put on supplemental oxygen having returned to their normal levels on discharge. Less common reasons for referral included hypotension, decreased mobility and agitation, with only 2.5% of patients describing a loss of taste and smell (ageusia and anosmia) on admission.

The biochemistry results of the patients on admission to ACAH are recorded in Table 2 . Notably, 70% of patients had below the normal range of percentage lymphocytes, while 37% were below the normal range of absolute lymphocyte count and were therefore lymphopenic. Furthermore, 63% of patients had a raised CRP beyond the normal range. Also, 33% had a raised ferritin level and 66% had a raised D-dimer. Haemoglobin was low in 40% of patients and albumin had dropped below normal in 20% of patients.

Furthermore, 44.7% of patients required subcutaneous fluids, while 15.4% required IV fluids. 72.3% required antibiotics during their admission to ACAH. Ceftriaxone was the most common antibiotic prescribed, with 43.1% of all patients receiving ceftriaxone only, while 11.3% received a combination. 45.5% of patients were prescribed palliative/ anticipatory medication.

Table 2 Biochemistry results on admission of COVID-19 cohort

Test	Reference Range	Range of abnormal results	Low	Normal	High	Not recorded
Total White Cell Count	4-11 x10^9/L	L: 2.9-3.8 H: 11.3-37	6 (4.9%)	85 (69.1%)	26 (21.1%)	6 (4.9%)
Percentage Lymphocytes	20-40%	L: 1.8-19.8 H: 40.3-56.1	86 (69.9%)	31 (25.2%)	2 (1.6%)	4 (3.3%)
Absolute Lymphocyte Count	0.9-2.9 x10^9/L	L: 0.18-0.89 H: 4.09	45 (36.6%)	73 (59.3%)	1 (0.8%)	4 (3.3%)
CRP	0-30 mg/L	32.27 - 450.13	N/A	42 (34.1%)	77 (62.6%)	4 (3.3%)
Ferritin	30-400 ng/mL	420.1 - 6747	2 (1.6%)	67 (54.5%)	41 (33.3%)	13 (10.6%)
D-dimer	0 – 0.5 mg/L	0.52 – 16.82	N/A	11 (8.9%)	81 (65.9%)	31 (25.2%)
Serum Magnesium	0.7-1.0 mmol/L	H: 1.01 - 1.72 L: 0.53 – 0.67	9 (7.3%)	74 (60.2%)	18 (14.6%)	22 (17.9%)
Haemoglobin	Females: 115-160g/L Males: 130-180g/L	H: 168 (F) L: 56-127 (M), 87-114 (F)	50 (40.6%)	66 (53.7%)	1 (0.8%)	6 (4.9%)
Platelets	150-450 x 10^9/L	H: 453-630 L: 74-149	14 (11.4%)	95 (77.2%)	8 (6.5%)	6 (4.6%)
Albumin	35-50 g/L	L: 9-34	25 (20.3%)	88 (71.5%)	0 (0%)	10 (8.2%)
ALT	M: <50 U/L F: <35 U/L	H: 42-333	0 (0%)	84 (68.3%)	18 (14.6%)	21 (17.1%)

For certain biochemistry results, comparisons were made between the COVID-19 cohort and a non-COVID-19 cohort from 2019. When studying lymphocytes, 37% of those with COVID-19 were lymphopenic, compared to 28% of those without COVID-19. In regards to serum magnesium, more patients in the ACAH COVID-19 population had high magnesium (16.0%) than in the ACAH non-COVID-19 population (5%). Furthermore, 29% of COVID-19 patients who were recorded as deceased had hypermagnesaemia, compared to only 6% who survived.

Table 3 presents the percentage of patients deceased by the end of the study and their corresponding National Early Warning Score (NEWS) on admission to ACAH. Generally, as the score increases, the greater the percentage of patients deceased. 100% of patients admitted with a score of 12 or above had died by the end of the study period. NEWS of 7 confers an uncharacteristically low mortality rate of 11% due to the low number of patients with this score.

Table 4 represents the percentage of the deceased population who had abnormal biochemistry and oxygen saturations. Notably, 65% of the deceased population had low oxygen saturations, 63% had a low eGFR and 53% had a high creatinine.

Furthermore, the distribution of D-dimer results within the ACAH patient cohort is seen in Figure 1 (reference range

Table 3 NEWS on admission and the corresponding mortality rate

NEWS	Mortality rate
1	9%
2-3	34%
4-6	52%
7	11%
8-10	64%
>10	100%

0-0.5mg/L). The 28 day mortality rate of the patients with a D-dimer >0.5 mg/L was 27% (23/85). However, there is a stark rise in mortality rate when D-dimer rises above 2 mg/L, with 45.8% of patients being recorded as deceased.

Clinical Frailty Score is a graded scale from 1 to 9 which can categorise patients from very fit, 1, to terminally ill, 9. Frailty is defined by the World Health organisation as "a progressive age-related decline of body functions resulting in vulnerability and reduced resilience to physical and mental stressors with an increased risk of negative health outcome"[5]. This study found that 47.6% of people who had a clinical frailty score of greater than or equal to 7 were deceased, compared to 25% of those who had a frailty score of less than 7.

Discussion:

The findings have demonstrated many trends in the presentation of COVID-19 within ACAH patients. 64% of patients had more than three co-morbidities, with 100% having at least one. This indicates that having co-morbidities increases the likelihood of requiring medical admission when infected with COVID-19. A 2020 study by Ejaz et al concluded that the presence of co-morbidities, particularly COPD, hypertension, diabetes and heart disease, is linked to more severe symptoms and a higher mortality rate due to COVID-19, when compared to their counterparts without co-morbidities[6].

Table 4 Percentage of deceased population and abnormal parameter

Abnormal parameter	% of deceased population
Raised ferritin	47
Low oxygen saturations	65
Lymphopenia	43
D-dimer <0.5mg/L	27
D-dimer >2 mg/L	46
Low eGFR	63
High creatinine	53
Hypermagnesaemia	29

On analysis of ferritin levels, it was discovered that 47% of the deceased patients had an abnormally high ferritin level. Another study by Cheng et al, 2020, concluded that ferritin levels were significantly increased in more severe COVID-19 patients when compared with non-severe COVID-19 patients [7]. Furthermore, it has been shown that those with at least one co-morbidity, of which 100% of the patients in this study had, are more likely to have a high ferritin level. Consequently, these patients are more likely to have clinically severe COVID-19 [7].

45% of those living in LTCF were recorded as deceased, which is quite disproportionate compared to 27% of those living in their own homes within the same time period. Research conducted by The European Centre for Disease Prevention and Control (ECDC), published in June 2020, revealed that LTCF across Europe, including the UK, were home to 31-66% of all COVID-19 related deaths, with the average in Scotland being 46% [8]. As the ages and co-morbidities of patients living at home are comparable to those in LTCF, this could indicate that there are higher mortality rates when

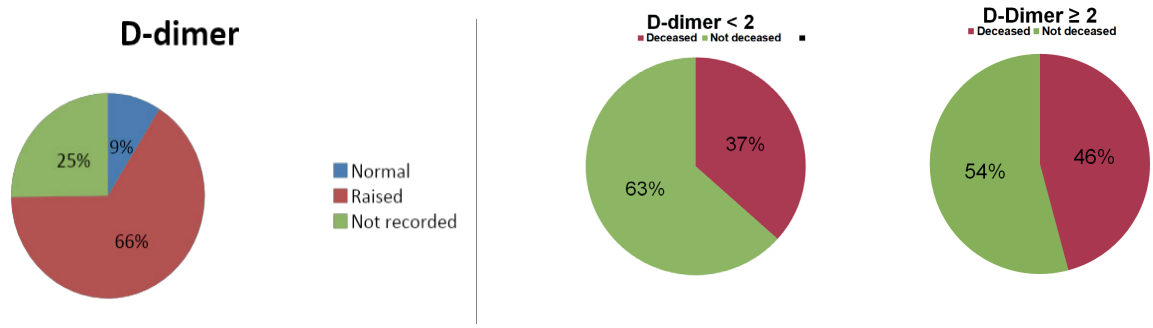

Figure 1: Percentage of study population with normal, raised and not recorded D-dimer results and mortality percentage of those with raised and normal D-dimer

living in a LTCF, compared with at home, when infected with COVID-19. There may be many different reasons for this, such as LTCF staff not being appropriately trained in infection control measures, a greater number of people coming in and out of LTCF, resulting in greater infection risk, and a lack of personal-protective equipment (PPE).

Furthermore, 65.3% of those who were recorded as deceased had low oxygen saturations (<94%). It has previously been discovered that hypoxaemia is independently associated with higher mortality when infected with COVID-19 [9]. Supporting this, a 2020 paper by Mejía et al discovered that an oxygen saturation below 90% on admission is a strong indicator for mortality in patients with COVID-19 [10]. These findings suggest that hypoxaemia may be a reliable indicator of mortality in COVID patients.

Moreover, 43% of deceased patients were lymphopenic. This may be due to the COVID-19 virus directly targeting lymphocytes or lymphatic organs, but many reasons are possible. However, it has been concluded that lymphopenia is a reliable indicator into the severity of COVID-19 within hospitalised patients [11]. 28% of patients admitted to ACAH for reasons other than COVID-19 were lymphopenic compared to 37% of those admitted with COVID-19 in the same time period.

64% of patients who had a NEWS of 8-10 on admission were deceased by the end of the study. This rose to 100% when filtered to a score of greater than 10. This strongly indicates that the NEWS is a reliable prognostic indicator for deterioration of COVID-19 patients. Several other studies have gathered similar conclusions, which would encourage early interventions to resolve the affected parameters, in an effort to prevent fatal outcomes [12].

When looking at the incidence of ageusia or anosmia within this population, it was discovered that 97.5% of people had an intact sense of taste or smell on admission. This contradicts the findings of other studies such as the 2020 paper by Lee et al which found that 15.3% of people had either anosmia or ageusia in a population of 3,191[13]. It has been shown that these symptoms are beneficial when diagnosing COVID-19, especially at earlier stages of the disease [13]. Perhaps, in an older cohort with COVID-19 anosmia and ageusia are less common. However, the reduced incidence in this cohort could be due to under-reporting as many patients had a history of dementia or presented with delirium and may have been unable to alert staff of these symptoms.

It has been widely reported that coagulopathy is common in critically ill patients with COVID-19 and associated with cardiovascular events and poor outcomes [14]. Raised D-dimer values (>2 mg/L) have an associated increased mortality where P=0.041 as shown in a study by Yao et al, which supports the results of this study, where 45.8% of those with a D-dimer >2 mg/L were deceased, compared to 27% of those with a D-dimer >0.5 mg/L [15]. This suggests there is an association with mortality and D-dimers above 2 mg/L.

Moreover, when incorporating clinical frailty scores, there is a 22.6% increase in mortality rate in clinical frailty scores of greater than or equal to 7, compared to those less than 7. This would indicate that an increased frailty score is associated with a higher mortality in patients with COVID-19, as reported by Hägg et al, suggesting that frailty scores can help to identify those at risk of mortality, in order to prevent adverse outcomes [5]. However, a systematic review conducted by Cosco et al, 2020, included 2 studies out of 26 in which mortality was disproportionately high in the fitter population and less severe than expected in frail groups [16]. This suggests that caution should be exercised when applying prognostic significance to frailty scores alone, in the context of older people with COVID-19 [16].

63.3% of those who were deceased at the end of the study had a low eGFR and 53.1% had a high creatinine. This is similar to findings in other studies such as the 2020 study by Cheng et al. which found that deterioration was more likely in those who had kidney disease [17]. Elevated serum creatinine was also an indicator for admission to the intensive care unit. Overall, reduced kidney function was associated with an increased risk of death. Therefore, it is important to monitor those with altered kidney function in order for early intervention to take place and improve outcomes [17].

The majority of ACAH patients infected with COVID-19 had a normal magnesium level. 16% of patients with COVID-19 had hypermagnesaemia, compared to 5% within the non-COVID-19 comparison group. A study of 65,974 hospitalised patients in 2015 found that high magnesium was associated with respiratory disease, which supports the findings of this paper [18]. This is thought to be due to the anti-inflammatory, immunomodulation and airway relaxation properties of magnesium, therefore the body reactively increases magnesium levels to reduce inflammation, suggesting it is a response to severe infection rather than a cause of severe disease[18]. This may be particularly relevant in the 'cytokine storm' seen in Covid-19 infection. For example, a study by Tan et al found that significantly fewer Covid-19 patients required supplemental oxygen therapy when treated with magnesium, as magnesium is thought to relax the airway[11]. Furthermore, a higher proportion of ACAH COVID-19 patients who were deceased by the end of this study had hypermagnesaemia when compared to those who survived. Cheungpasitporn et al also found that hypermagnesaemia carries a comparatively worse prognosis when compared with hypomagnesaemia, as magnesium seems to rise in more severe COVID-19[18]. All of this information suggests that hypermagnesemia may be seen as a response to more severe infection rather than hypermagnesaemia causing respiratory distress.

Conclusion:

In conclusion, trends within the ACAH COVID-19 population are largely supported by other literature. Hypoxaemia is an early indicator of mortality, as is high ferritin and high magnesium. NEWS score is an effective early warning

indicator and a higher score on admission is associated with an increased mortality rate. Perhaps increased intervention in those patients with higher NEWS scores can improve outcomes. A positive correlation was found between higher frailty score and increased risk of mortality, indicating early recognition of a higher/increasing frailty score could allow for intervention in order to help improve patient outcomes. Regular COVID-19 testing of patients and staff in LTCFs, correct use of PPE and review of its availability could also help mitigate the risk within this vulnerable group. Furthermore, COVID-19 positive patients in LTCFs were remotely monitored for deterioration by the ACAH team, which allowed for early intervention. This likely resulted in improved outcomes, which has also been recommended in published literature[19].

The results of this study validate the concept of ACAH. Despite ACAH treating patients who were on average older and who had a higher frailty score, the mortality rate was only 2% higher than that in UK hospitals during a similar time period[20]. Whilst being similarly effective as hospital admission, ACAH allowed these patients to remain in their own home with their families or normal caregivers, mitigating the risk of hospital admission in older people. At a time when patients were often unable to have visitors, this is an important factor to consider. Many of the patients cared for were, by their own decision, not for transfer to hospital. This meant that ACAH was their only way to access acute medical care and prevent early and potentially unnecessary palliation in some cases, proving the value of the service, especially throughout the ongoing challenges of COVID-19.

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Clinical Paper

Discovery of inhibition of *Burkholderia cenocepacia*, *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* by the Brown Rot Basidiomycete Fungus, *Postia placenta*

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ABSTRACT

Antimicrobial resistance (AMR) has now emerged as a major global public health problem. Certain bacterial pathogens, particularly Gram negative organisms associated with patients with cystic fibrosis (CF), have become resistant to several classes of antibiotics resulting in pan-resistance, which creates a clinical treatment dilemma. This study wished to explore the production of antibacterial extracellular metabolites from plant pathogenic fungi. Fungal Culture Extracts (FCEs) were prepared from 10 fungi (*Armillaria gallica, Clitocybe nebularis, Fusarium coeruleum, Fusarium oxysporum, Fusarium poae, Hymenoscyphus fraxineus, Nectria fuckeliana, Phytophthora infestans, Phytophthora ramorum, Postia placenta*), which were tested for activity against the CF pathogens, *Pseudomonas aeruginosa* (PA) (n=8), *Burkholderia cenocepacia* (n=2) and *Stenotrophomonas maltophilia* (n=2). In addition, FCE were assessed for their ability to alter antibiotic susceptibility in PA (n=8), with six antipseudomonal antibiotics (ceftazidime, ciprofloxacin, colistin, meropenem, piperacillin/tazobactam, tobramycin). None of the FCEs showed inhibitory activity to the 12 bacterial isolates tested, with the exception of the FCE from *Postia placenta*, which showed inhibition against all 12 bacteria. An antagonistic interaction was observed, where a statistically significant decrease in mean zone sizes was noted with *Armillaria gallica* (p=0.03) and *Phytophthora infestans* (p=0.03) FCEs and their interaction with the fluoroquinolone antibiotic, ciprofloxacin. Given the increase in clinical morbidity and mortality associated with chronic lung infections with *Pseudomonas aeruginosa*, *Burkholderia cenocepacia* and *Stenotrophomonas maltophilia*, coupled with the difficulty in treating such chronic infection due to overwhelming antimicrobial resistance, any novel substance showing inhibition of these organisms merits further investigation as a potential future antimicrobial agent, with potential clinical therapeutic application.

INTRODUCTION

Antimicrobial resistance (AMR) has now emerged as a global health crisis, where it is estimated by the World Health Organisation (WHO) that in 2016, there were 490,000 persons infected with tuberculosis (TB), which was multidrug resistant[1]. Furthermore, the WHO states that AMR threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi, as well as indicating that without effective antibiotics, the success of major surgery and cancer chemotherapy could be compromised[1]. Whilst the burden of AMR is increasing with several organisms, it is particularly worrying in treating chronic Gram-negative infections in patients with cystic fibrosis (CF), where AMR has developed at an alarming rate, to the extent that there are some infections which are resistant to all classes of antibiotics presenting a treatment dilemma[2], Development of AMR in the causal bacteria of chronic infections may result in denial of lung transplantation and access to important clinical trials of new therapies.

Therefore, such clinical dilemmas create an urgent need to discover effective alternative antimicrobial agents that have proven *in vitro* activity against such bacteria and can translate into *in vivo* efficacy. This can be accomplished through accelerated drug discovery programmes, drug re-purposing and through revisiting antibiotics from fungi programmes, the so-called "Fleming II" approach. Fungi are a rich source of bioactive compounds in nature, including the antimicrobials, produced as secondary fungal metabolites[3]. and this, coupled with their biodiversity of an estimated 1.5 – 5.1 million existing species, they remain a potentially important source of discovering novel antimicrobial agents[3].

Therefore, the aim of this study was to examine the production of antibacterial substances from 10 plant pathogenic fungi

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and their *in vitro* effect on the Gram-negative CF pathogens, *Burkholderia cenocepacia*, *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia,* as well as examining the interaction of fungal culture extracts with conventional antibiotics.

MATERIALS AND METHODS

Description of environmental fungi and bacteria employed

Ten species of environmental plant pathogenic fungi were examined in this study (Table 1). Fungal organisms were isolated from diseased plant material. Fungal isolates were propagated in the laboratory at 22°C in Potato Dextrose Sabouraud Maltose Broth (PDSMB) consisting of equal volumes of Potato Dextrose broth (potato extract; 4g/L, glucose; 20g/L) and Sabouraud Maltose broth (Maltose; 20g/L, neo-peptone; 10g/L, $MgSO_4.7H_2O$; 1g/L, KH_2PO_4;1g/L). The identity of all species was confirmed by PCR amplification and sequencing of rRNA genes. The Gram-negative bacteria (n=12 isolates), including *Pseudomonas aeruginosa* (n=8), *Burkholderia cenocepacia* (n=2) and *Stenotrophomonas maltophilia* (n=2) were employed in this study. All bacterial isolates were part of the HSC Microbiology Culture Repository (MicroARK) housed at the Northern Ireland Public Health Laboratory, Belfast City Hospital. All isolates were originally isolated from sputum of adult patients with cystic fibrosis. All bacterial isolates were recovered on Columbia Blood agar (Oxoid

Table 1: Description of environmental macro- and filamentous plant pathogenic fungi examined in this study

Environmental fungi	Common name	Taxonomy (Phylum)	Description	Previous antimicrobial reports
Armillaria gallica	Bulbous Honey Fungus/White Rot Fungus	*Basidiomycota*	Macrofungus.Plant pathogen; Root rot of garden trees	None
Clitocybe nebularis	Clouded Funnel/ Clouded Agaric	*Basidiomycota*	Macrofungus. Saprophytic fungus found in under conifers	Antifungal activity [4]
Fusarium coeruleum	None	Ascomycota	Filamentous fungus. Plant pathogen causing dry rot of potatoes	None
Fusarium oxysporum	None	Ascomycota	Filamentous fungus. Plant pathogen causing a variety of wilt diseases	Antibiotic activity [5]
Fusarium poae	None	Ascomycota	Filamentous fungus. Plant pathogen causing Head Blight in wheat	Antibiotic activity [6]
Hymenoscyphus fraxineus	None	Ascomycota	Filamentous fungus. Plant pathogen causing Ash Dieback disease in Ash trees (*Fraxinus excelsior*)	None
Nectria fuckeliana	None	Ascomycota	Saprophytic fungus and plant pathogen causing apple canker, Nectria twig blight and coral spot in orchards. Flute canker.	None
Phytophthora infestans	Oomycete or potato blight mould	Oomycota	Filamentous fungus. Plant pathogen causing potato blight disease	Antibiotic activity [7]
Phytophthora ramorum	Oak blight	Oomycota	Filamentous fungus: Plant pathogen causing sudden oak death	None
Postia placenta	Brown rot disease	Basidiomycota	Macrofungus. Plant pathogen causing brown rot disease.	None

CM0031, Oxoid Ltd., Basingstoke, UK), supplemented with 5% (v/v) defibrinated horse blood for 48h at 37°C, under aerobic conditions and passaged a further three times, prior to use. Their identication was confirmed employing the MALDI-TOF (BioMerieux Ltd., UK), in accordance with the manufacturer's instructions.

Preparation of fungal culture extracts (FCEs)
Plant pathogenic fungi (Table 1) were inoculated in PDSMB, as described above and slowly agitated aerobically for six weeks at 22°C. Following this, FCEs were prepared by filter-sterilisation of the supernatant employing a Stericup-GP Sterile Vacuum Filtration system (150mL process volume) through a 0.22 µm filter. FCEs were stored in the dark at 4°C until employed.

Antibacterial susceptibility assays with FCEs

(i) **Direct Effect**: Inoculum (0.5 McFarland standard) of each of the 12 isolates described above were streaked individually on to the surface of individual Columbia Agar supplemented with 5% (v/v) defibrinated horse blood. The plates were labelled in sectors representing each FCE drug plus appropriate controls. FCE extracts (10 µl) were pipetted onto the media and left to dry. The plates were inverted and incubated at 37°C incubator for 48h. Any observed zones of inhibition (mm) in the region of FCE was measured and recorded.

(ii) **Indirect Effect**: Five plant pathogenic fungi from Table 1, including *Armillaria gallica*, *Clitocybe nebularis*, *Fusarium oxysporum, Nectria fuckeliana, Phytophthora infestans*[4,5,6,7] were included. FCEs were prepared individually for each of these fungi, as described above. FCE (50mls) was added to Mueller-Hinton agar (450mls) in order to prepare 10% [v/v] FCE-supplemented agar. Eight PA isolates, including six PA isolates from CF sputum and two PA blood culture isolates, were investigated and their antibiotic susceptibility to six anti-pseudomonal antibiotics (ceftazidime (30µg disk), ciprofloxacin (5µg), colistin (10µg), meropenem (10µg), piperacillin/tazobactam (110µg) & tobramycin (10µg)) was determined by disk diffusion assay employing Clinical and Laboratory Standards Institute (CLSI) methodology and interpretive criteria[8]. Plates where incubated aerobically for 48hrs at 37°C and zones of inhibition (mm) were recorded and compared to zone sizes of the control (with no FCE present). Each isolate was classified as sensitive, intermediately resistant or resistant, according to CLSI criteria[8].

RESULTS AND DISCUSSION

None of the FCEs showed inhibitory activity to the 12 bacterial isolates tested, with the exception of the FCE from *Postia placenta*, which showed activity against all 12 bacterial isolates tested (Figure 1). The effect on antibiotic susceptibility when employing Mueller-Hinton agar supplemented with 10% [v/v] FCE from five plant pathogenic fungi is shown in Table 2(a)-(f). Statistically,

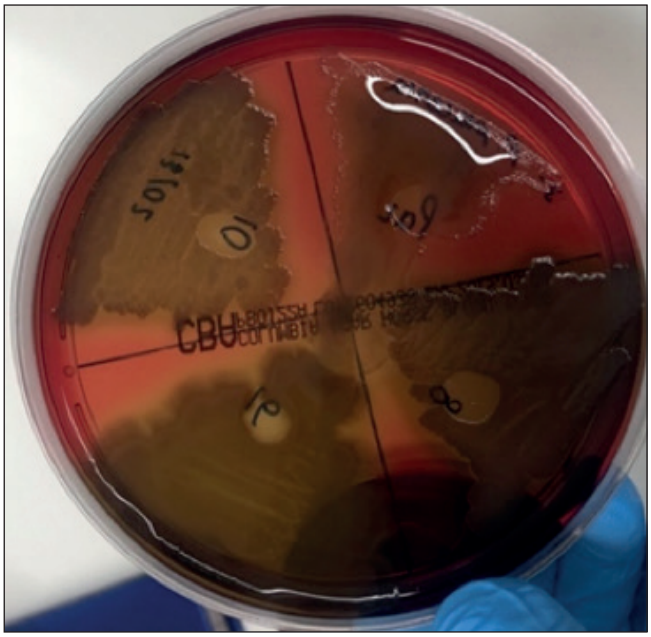

Figure 1:
Inhibition of four isolates of *Pseudomonas aeruginosa* isolated from sputum of patients with cystic fibrosis with Fungal Culture Extracts from the Brown Rot fungus, *Postia placenta*

there was significant differences in the eight PA isolates examined in mean zone sizes of the six anti-pseudomonal antibiotics with *Clitocybe nebularis*, *Fusarium oxysporum* and *Nectria fuckeliana.* [4,5,6,7] An antagonistic interaction was observed between two fungi and ciprofloxacin zone sizes, where a statistically significant decrease in mean zone sizes was noted with *Armillaria gallica* (p=0.03) and *Phytophthora infestans* (p=0.03) FCEs and their interaction with the fluoroquinolone antibiotic, ciprofloxacin, where zone sizes decreased from 25.3mm (control with no FCE added) to 19mm and 13.3mm, respectively. This is an interesting observation, in that these fungi are in some way interfering with the antibacterial properties of this fluoroquinolone by making it less antibacterial. At this stage, we are unaware of the constituent components of the fungal extracts which could account for this effect on the fluoroquinolone, but this antagonism may be due in part to the *in vitro* lowering of the pH and the release of cations (Ca^{2+}, Mg^{2+}).

Of all the environmental fungi examined, only one, namely *Postia placenta* showed to have antibacterial activity against all Gram-negative organisms tested. These bacterial pathogens were selected, as they can be difficult-to-treat clinically due to being multi- and, at times, pan-resistant to all antipseudomonal antibiotics available. Therefore, without an efficacious antibiotic available to clinically treat such cases, it is important to seek novel molecules that can inhibit the growth of these organisms.

Postia placenta, formerly known as *Rhodonia placenta*, is a brown rot macrofungus that is largely responsible for the decay of wooden structures by rapid depolymerisation of cellulose, where it is a cause of wood rot in ships, in mines

attacking wooden pit props and in the timber of buildings[9]. Taxonomically, this basidiomycete belongs to the Phylum*: Basidiomycota* - Class: *Agaricomycetes* - Order: *Polyporales* - Family*: Fomitopsidaceae.* Pathologically, this fungus acts on wood through cellulose degrading mechanisms, including the enzymatic degradation by small cellulases and through the generation of hydroxyl free radicals, via Fenton chemistry, where Fe(II) and H_2O_2 react to form hydroxyl radicals (OH^-) [$H_2O_2 + Fe^{2+} + H^+ \rightarrow H_2O + Fe^{3+} + OH$] [10]. Analysis of the *P. placenta* genome revealed few conventional cellulases suggesting that much of its cellulose degradation involves the production of free radicals[10]. The production of free radicals by *Postia* may account for its antibacterial activity against bacterial pathogens, which are susceptible to such oxygen scavenging species. Additionally, other genome, transcriptome and secretome analysis of this fungus have identified other antibacterial molecules, including quinones which may also add to its antibacterial activity.

Previously, there has been a report on a novel fungal immunomodulatory protein (rFIP-ppl) from *Postia placenta*, where antitumor assays demonstrated significant cell proliferation inhibitory activity and apoptotic effects in human tumour cells, particularly on gastric tumour cells (MGC823) than against hepatoma (HepG2) cells[11]. To date, there have been no reports of extracts of this polypore fungus demonstrating antibacterial activity, therefore the antibacterial activity against the Gram-negatives described in this report are novel and worthy of further investigation.

In conclusion, FCEs from the brown rot fungus, *Postia placenta*, inhibited these important CF Gram-negative pathogens on all occasions, whilst similar FCEs from nine other pathogenic plant fungi did not show any antibacterial activity. Given the increase in clinical morbidity and mortality associated with chronic lung infections with *Pseudomonas aeruginosa*, *Burkholderia cenocepacia* and *Stenotrophomonas maltophilia*, coupled with the difficulty in treating such chronic infection due to overwhelming antimicrobial resistance, any novel substance showing potential in inhibiting these organisms merits further investigation as a potential future antimicrobial agent, with potential benefits in the treatment of such difficult-to-treat infections.

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The data in this paper is the product of a collaborative alliance on drug discovery between colleagues at Plant Pathology, AgriFood & Biosciences Institute (AFBI), Newforge Lane, the Northern Ireland Public Health Laboratory, Belfast City Hospital, and the School of Medicine, Dentistry and Biomedical Sciences, QUB and wishes to report on a NI project which contributes to developing novel antimicrobials in the fight against AMR.

CONFLICT OF INTEREST

None

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Table 2a-f: Zones of inhibition created by six antibiotics on PA strains (n=8) when grown on Muller-Hinton agar supplemented with 10% [v/v] Fungal Culture Extracts (FCEs).

The tables are colour coded depending on whether the strain showed sensitivity, intermediate resistance or resistance to the antibiotic according to CLSI criteria. If a strain susceptibility classification was altered when grown on a media including fungal supernatant when compared to the Standard Muller Hinton control (Table 2a), the zone of inhibition is outlined. Zones of inhibition where analysed using a two-tailed paired student t-test with significant p values (p=<0.05) noted in red. Tables titled according to FCE incorporated.

Key as per CLSI standards	Sensitive	Intermediately resistant	Resistant	Different from Control Plate	PA = *Pseudomonas aeruginosa*

Table 2a – Mueller-Hinton Control (no Fungal Cultural Extract added)

Isolate	Zone of inhibition (mm)					
	Ceftazidime CAZ30	Tobramycin TOB10	Colistin CT10	Meropenem MEM10	Ciprofloxacin CIP5	Piperacillin/ Tazobactam TZP110
PA CF/05/11	30	26	16	28	26	14
PA CF/96/06	28	28	8	0	10	28
PA BC/07/658	0	22	12	34	32	28
PA CF/96/49	22	24	14	32	18	18
PA CF/05/49	36	24	16	34	38	24
PA CF/96/33	34	30	18	18	10	38
PA CF/05/56	26	28	18	0	32	30
PA 91/BC/07	16	24	0	26	36	16
Mean	24	25.75	12.75	21.5	25.25	24.5

Table 2b - *Nectria fuckeliana*

Isolate	Zone of inhibition (mm)					
	Ceftazidime CAZ30	Tobramycin TOB10	Colistin CT10	Meropenem MEM10	Ciprofloxacin CIP5	Piperacillin/ Tazobactam TZP110
PA CF/05/11	46	0	20	36	28	34
PA CF/96/06	28	28	18	28	0	26
PA BC/07/658	0	20	14	10	32	0
PA CF/96/49	22	20	10	32	16	0
PA CF/05/49	28	22	12	40	32	26
PA CF/96/33	0	34	14	20	8	24
PA CF/05/56	20	32	10	36	30	36
PA 91/BC/07	18	24	0	26	32	20
Mean	20.25	22.5	12.25	28.5	22.25	20.75
Individual antibiotics (p=)	0.48	0.37	0.81	0.32	0.06	0.51
All antibiotics (p=)	0.50					

Table 2c - *Phytophthora infestans*

Isolate	Zone of inhibition (mm)					
	Ceftazidime CAZ30	Tobramycin TOB10	Colistin CT10	Meropenem MEM10	Ciprofloxacin CIP5	Piperacillin/ Tazobactam TZP110
PA CF/05/11	36	30	14	26	0	36
PA CF/96/06	0	28	0	24	0	0
PA BC/07/658	26	24	0	20	0	28
PA CF/96/49	22	0	14	30	0	0
PA CF/05/49	ND	24	16	36	26	0
PA CF/96/33	28	32	0	16	8	26
PA CF/05/56	28	32	0	36	36	26
PA 91/BC/07	18	26	14	26	36	20
Mean	22.57	24.50	7.25	26.75	13.25	17.00
Individual antibiotics (p=)	0.96	0.72	0.19	0.39	**0.03**	0.24
All antibiotics (p=)	0.10					

Table 2d – *Fusarium oxysporum*

Isolate	Zone of inhibition (mm)					
	Ceftazidime CAZ30	Tobramycin TOB10	Colistin CT10	Meropenem MEM10	Ciprofloxacin CIP5	Piperacillin/ Tazobactam TZP110
PA CF/05/11	38	30	8	28	30	34
PA CF/96/06	26	34	0	24	0	28
PA BC/07/658	16	24	0	14	36	0
PA CF/96/49	18	24	14	32	0	0
PA CF/05/49	28	26	16	36	26	26
PA CF/96/33	30	32	0	0	0	28
PA CF/05/56	32	0	18	36	30	26
PA 91/BC/07	0	0	14	26	30	18
Mean	23.5	21.25	8.75	24.5	19	20
Individual antibiotics (p=)	0.89	0.37	0.28	0.67	0.06	0.41
All antibiotics (p=)	0.13					

Table 2e - *Clitocybe nebularis*

Isolate	Zone of inhibition (mm)					
	Ceftazidime CAZ30	Tobramycin TOB10	Colistin CT10	Meropenem MEM10	Ciprofloxacin CIP5	Piperacillin/ Tazobactam TZP110
PA CF/05/11	36	28	10	30	28	0
PA CF/96/06	20	28	22	20	0	26
PA BC/07/658	0	22	14	26	32	28
PA CF/96/49	22	0	14	34	18	26
PA CF/05/49	26	22	0	36	0	28
PA CF/96/33	26	34	20	20	0	26
PA CF/05/56	36	0	16	38	32	28
PA 91/BC/07	20	24	14	28	36	18
Mean	23.25	19.75	13.75	29	18.25	22.5
Individual antibiotics (p=)	0.78	0.22	0.78	0.19	0.18	0.48
All antibiotics (p=)	0.48					

Table 2f - *Armillaria gallica*

Isolate	Zone of inhibition (mm)					
	Ceftazidime CAZ30	Tobramycin TOB10	Colistin CT10	Meropenem MEM10	Ciprofloxacin CIP5	Piperacillin/ Tazobactam TZP110
PA CF/05/11	0	28	0	28	28	34
PA CF/96/06	20	30	18	24	0	22
PA BC/07/658	0	24	12	28	30	14
PA CF/96/49	18	24	14	34	0	18
PA CF/05/49	ND	0	16	38	32	26
PA CF/96/33	ND	32	18	16	0	32
PA CF/05/56	36	28	0	36	28	26
PA 91/BC/07	16	22	12	26	34	16
Mean	15	23.5	11.25	28.75	19	23.5
Individual antibiotics (p=)	0.38	0.50	0.70	0.21	**0.03**	0.78
All antibiotics (p=)	0.42					

The tables are colour coded depending on whether the strain showed sensitivity, intermediate resistance or resistance to the antibiotic according to CLSI criteria. If a strain susceptibility classification was altered when grown on a media including fungal supernatant when compared to the Standard Muller Hinton control (Table 2a), the zone of inhibition is outlined. Zones of inhibition where analysed using a two-tailed paired student t-test with significant p values (p=<0.05) noted in red. Tables titled according to FCE incorporated.

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Annual Oration

The Rime of the Ancient Imager: Plato's Cave and Other Shadows Royal Victoria Hospital, September 2019

Barry Kelly

Accepted July 2021

Picture the scene. It's a wedding and the guests are milling around in the garden outside the church. Suddenly, a wizened old man appears in their midst and makes a beeline for one of the guests.

It is an ancyent Marinere,
And he stoppeth one of three.
'By thy long grey beard and glittering eye,
Now wherefore stoppest me?

The mariner locks eyes on a young man and he can't escape. The mariner presses on:

At length did cross an Albatross,
Thorough the fog it came;
As if it had been a Christian soul,
We hailed it in God's name.

However, as he tells his story, the mariner speaks in an increasingly agitated tone, which concerns the wedding guest…

'God save thee, ancient Mariner!
From the fiends, that plague thee thus—
Why look'st thou so?'—with my cross-bow
I shot the Albatross!

The mariner has ensnared the young guest and continues to tell his story; the mistakes he has made, and the lessons learnt. Now his life's penance is to find the person who is about to do the same, tell him what he has learnt and warn him.

I pass, like night, from land to land;
I have strange power of speech;
That moment that his face I see,
I know the man that must hear me:
To him my tale I teach.

My pleasant task today is to address those of you about to begin your clinical studies. I thought that, like that flawed and wizened old mariner, I would offer some pointers, as I have learnt them.

Part 1: Fiat Lux

Let's start at the very beginning. Where do we live? How long have we been here? Our home, our galaxy - The Milky Way – is named for the milk of the goddess Hera. We live, as Douglas Adams wrote, in its *unfashionable* Western spiral arm. Our galaxy is between 150 - 200,000 light years across. The speed of light is 186,000 miles/sec; so, in a year, it travels 5.9 trillion miles. Our nearest star is Proxima Centauri, 4.3 light years away. We orbit an unimportant star with our eight neighbours. Approximately 800 of our little solar systems would fit into one light year. Feeling small enough, yet?

How long have we lived here?

The universe is infinite. Its explosive and inflationary origin was first proposed in 1927 by George Lemaître, a Belgian mathematician and Jesuit priest working at MIT. His mathematics had led him to conclude that a primeval 'atom' had burst forth into light, like fireworks, in what he himself called 'A Day Without Yesterday.' For subsequent decades of the 20th century, like *West Side Story's* Sharks and Jets, inflationary theorists argued about this with their steady-state opponents. One of the latter, Fred Hoyle in a radio broadcast, coined the term 'Big Bang', to pour scorn on it.

The problem for inflation theorists was leftover radiation. If, as Lemaître and the other inflation proponents argued, the universe had burst forth from *a singularity*, the energy generated should have left a residue. Given the enormity of time and space involved, it had been calculated that this would now be three degrees of microwave radiation. "Where is the radiation?" taunted Hoyle, "You can't find it because it isn't there."

Actually, a Russian astronomer named George Gamow had already, in a 1949 scientific paper, predicted precisely how this radiation might be identified and from where. It required a very specific piece of equipment and there was only one place that had it; The Bell Antenna. His paper unfortunately was in Russian, and the main players outside Russia hadn't read it.

In 1965, two astronomers, Arno Penzius and Robert Wilson inadvertently discovered a mysterious hiss in the night sky. It was constant and ubiquitous. It proved to be that elusive three degrees of microwave radiation; the last piece of evidence, making The Big Bang a fact. They had been working at the

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Bell Antenna in New Jersey and using the specific telescope that Gamow had suggested in his Russian paper 16 years earlier. We will learn more of Bell laboratories later.
A few weeks before he died in June 1966, hospitalised with leukaemia, news reached Lemaître of Wilson and Penzius' discovery, thus confirming the validity of his Fireworks Theory.

When did we make our entrance?
Archaeological evidence suggests the following timeline for us: tools were in use by our ancestors two million years ago; fire first burned 300,000 years ago; we began to speak 80,000 years ago; agriculture began 10,000 years ago and we began to write, only 5000 years ago.

That's a lot of information and the numbers given are so large that it they are difficult to process. Suppose, as Carl Sagan has suggested in *Cosmos*, we consider this slightly differently. What if we compress the 13 billion year history of the universe into one calendar year? If this calendar were the size of a football pitch, all of human history would be the size of your fist. Our current location is 31 December and we are approaching midnight. Our starting point is January 1st. In this Cosmic Calendar, each month represents 1.25 billion years; each day, 40 million years; each hour, 1.8 million years; each minute, 30 thousand years and each second, 500 years.
On January 1st, The Big Bang happens (13.8 billion years ago). On January 10th, the first stars are born. On January 13th, stars coalesce to form galaxies. On May 15th, The Milky Way is formed. On August 31st, our sun is born. On September 15th, the earth is born (4.5 billion years ago). On September 21st: life begins on earth. On December 24th the dinosaurs appear. On December 28th, the dinosaurs disappear again just as our first flowers bloom.

As we approach December 31st, things get busy. Just over two hours ago, at 9.45pm; our ancestors, the first hominids, stand upright. One hour ago, the first tools are made. Fifteen minutes ago (450,000 years ago) the Neanderthals arrive (and disappear 1.3 minutes ago. I regret to inform you that we probably ate them.) Fourteen minutes ago, at 11.46pm, fire is tamed. Twelve minutes ago (350,000 years) *Homo sapiens* appears. Three minutes ago (80,000 years) we begin to speak. Forty seconds ago, we domesticate plants and animals. Twenty-five seconds ago, we build our first cities. Only sixteen seconds ago, writing begins. As Carl Sagan wrote, "All of recorded history; everyone about whom we have ever known; every hero and coward, every saint and sinner are contained within the last 16 seconds of our cosmic year." Ten seconds ago, we invent the wheel. Seven seconds ago, Moses is born (1700 BCE). Six seconds ago, Buddha is born (500 BCE). Four seconds ago, Jesus is born. Three seconds ago, Mohammad is born. One second ago, Martin Luther and Galileo are born. Finally, one-fifth of a second ago, radiation is discovered.

So first we had The Geosphere, our planet; next The Biosphere, when life began to bloom (mid-September) and then The Noosphere, a termed first used by the French philosopher and paleontologist, Teilhard du Chardin, when we began to *think*. To paraphrase du Chardin, 'We are the animals who know, and *know* that we know.' We do indeed. We are a young species, fragile and curious. Drilling down into our world of human endeavour, we now approach our own particular discipline: medicine.

Part 2: Medicine

The Origins of the National Health Service
In the early part of the 20th century, a young Glaswegian doctor began working as a GP in a South Wales mining town. His name was Archibald Joseph Cronin. Later in his career he would write *The Adventures of a Black Bag* that many of us remember as *Dr Finlay's Casebook*. But let us return to South Wales. Cronin was appalled by the inequality of what he saw and in 1937, he wrote a semi-biographical novel: *The Citadel*. This book is considered by many to be the single most important literary work that inspired Aneurin Bevan to create the National Health Service in 1948. Cronin wrote:

"I have written in *The Citadel* all I feel about the medical profession; its injustices, its hide-bound unscientific stubbornness, its humbug. The horrors and inequities detailed in the story, I have personally witnessed. This is not an attack against individuals, but against a system."

Bevin continued, "No society can legitimately call itself civilised if a sick person is denied medical aid because of a lack of means. Illness is neither an indulgence for which people have to pay, nor an offence for which they should be penalised, but a misfortune the cost of which should be shared by the community." Interestingly, Bevan anticipated that his great social experiment would last for about five years. By that time, he reasoned, most diseases would be cured. As you will have observed, ladies and gentlemen, that has not proven to be the case.

What makes a doctor?
I believe that a good doctor requires only three attributes: industry, integrity and compassion (or sympathy, if you prefer). Sympathy is the perception, understanding and reaction to the distress or need *of someone else*. Empathy is the capacity to understand or *feel* what another person is experiencing. Empathy is currently often prioritised by medical educators but I am wary of this. For me, empathy is being able to step into the shoes of another person, or indeed, having been in those shoes oneself. It is challenging to accept that a young medical graduate, often from a privileged background, could really have commonality with the life experiences of a much older person, possibly from a different social and economic group. As Seamus O'Mahony has said in his book *Can Medicine Be Cured*, "Hold my hand while you misdiagnose me." However, it is very possible and indeed desirable to be sympathetic. There is an older and less fashionable word for this: compassion. Words are our scalpels. We need to be careful with them.

Knowledge and Wisdom

What is the difference between knowledge and wisdom? According to Myles Kington, knowledge is knowing that a tomato is a fruit. Wisdom is not putting it in a fruit salad. It is disconcerting to think that today's expert may become tomorrow's relic. Age, however, can bring experience and often wisdom with it; both useful attributes for the young to seek out in the old.

The Failing Doctor

The moving finger writes; and having writ, moves on.
Nor all thy piety nor wit;
Shall lure it back to cancel half a line
Nor all thy tears wash out a word of it.

The Rubáiyát of Omar Khayyám

The past cannot be undone and we all make mistakes. That's the price we pay for being human. I console myself with the thought that it is very difficult to make an original mistake. As far as I know, just over 170 doctors were erased from the GMC register last year. The question is: how many were erased for technical failures and their inability to carry out their specialist skill? The answer is, practically none. The vast majority of doctors erased from the register, were so for reasons we often don't like to discuss or even admit, exist. At least ten percent of medical students and doctors have significant psychological issues. These are widespread and various but include addiction, personality issues, stress, burnout and so on. Two percent of us are bipolar and we know that one percent are potentially suicidal. There are about 300 people in this audience, so you can all do the mathematics.

If you work in a department with nine other people, the chances are that one of them will fall into this psychological category. If you can't think of who that person might be, it just might be *you*. In my view, historically this is an area about which we have devoted little time. Graduate medical students for example are particularly susceptible. Focused, dedicated, tenacious and usually successful, they will also have debt, may have several jobs, a partner and children, so therefore are much more likely to come to grief than the wide-eyed school leavers, excited to explore their new freedom and the extra-curricular possibilities of third level education

The 'at risk' practitioner isn't necessarily an obstetrician about to embark upon an emergency procedure, it can simply be the person staring at a normal ECG or unable to don their surgical gloves. Worse, it might be the person in the hospital car park, catatonic with dread, that is at most risk. We know that this problem is ubiquitous and increasing, particularly for junior doctors due to what has been named the Toxic Environment of Uncertainty. In their earlier school and university days there was always a solution and they would find it. In our chaotic world of 21st-century medicine with its multifactorial problems, understaffing and budgetary restrictions, they can crumble all too easily. We need to do much better here.

Plato's Cave

Imagine that you are in a cave. You and others are chained to a wall within the cave, facing its back wall. Onto it, project the silhouettes of the outside world. This is all you have ever known. Those dancing black-and-white shadows are your comprehension of the world. One day, a mysterious individual comes and unchains you. He takes you outside and demonstrates reality. Life in all its variety, colours and dimensions is revealed to you for the first time. This, of course, is overwhelming and extraordinary. Suddenly, you are brought back into the cave and, once more, chained to the wall. "Where have you been?" asks one of your companions. "I've been outside" you reply. "But there is no outside," he laughs. With increasing desperation, you explain that the shadows visible on the cave wall are simply that; a two-dimensional reflection of our three-dimensional world. The allegorical story illustrates the philosopher's frustration when she has an epiphany into the cosmos's workings. Despite her protestations, those around her dismiss her as a lunatic. Such is the philosopher's lot. However, I would suggest that Plato's cave also works as a metaphor for radiology. The shadows that we see on the wall aren't *real*, but simply represent the sketchy shadows of our actual patients. So, it's to Radiology next that we turn.

Part 3: Radiology

A question I occasionally ask non-clinical medical colleagues is, 'What did your mobile phone look like when you were last on call in an acute hospital?' That telephonic metaphor: the older the phone; the quainter the view of radiology, reflects the rapid advances made due to Gordon Moore and his eponymous law, to which I shall return. When I qualified, the dictum was, 'This patient is too sick to go to radiology.' Now it's, 'This patient is too sick <u>not</u> to go to radiology.' Radiology is technologically driven and is advancing ever faster. Godfrey Hounsfield's first CT brain image took hours to produce but now an abdominal CT takes about 20 seconds.

Discrepancy and Error

Radiology is primarily a visual medical specialty operating on the basis of pattern recognition. It helps to understand the code. In this 15th century woodcut by Albrecht Dürer, one sees Adam and Eve in the Garden of Eden. But if one looks carefully, the artist has included symbols of both allegory and The Four Humours. (*Fig 1a, and b*. *Adam and Eve in the Garden of Eden, Albrecht Dürer,*) There are several animals. There is a parrot, an ox, an elk, a goat, a cat, a mouse and a rabbit. The artist's contemporaries would have understood this code. The parrot's call was believed to sound like 'Eva Ave' ('Hail Mary') and the bird, symbolic of the Virgin Birth. The goat represents the Bible's scapegoat, ritually burdened and routinely banished. The others are the four humors: the elk is black bile or melancholia; the cat is choleric or yellow bile; the rabbit is blood and the ox, phlegm. Dürer is telling us that the four humours are momentarily balanced, and the goat is still on his hill; representing a moment of perfection and harmony. Not knowing this code is termed an error of cognition.

Fig 1a. Adam and Eve

Now let us consider errors of perception. Here are two chest radiographs, each concealing a cancer. The question is: where is it? In this first case, there is loss of normal apical symmetry. (*Fig 2 a,b,c. Left apical tumour).* This is

Fig 1b. Adam and Eve decoded

not unusual and is often quite innocent. A second, simple, apical view demonstrates however that there is a mass. The subsequent CT confirms this and no doctor in this room would miss it. In the second case, all appears well. (*Fig 3. a, b. Right basal tumour*). There is however a concealed ten-centimetre tumour at the right lung base, where there is a density that shouldn't be there. Again, the CT makes it obvious.

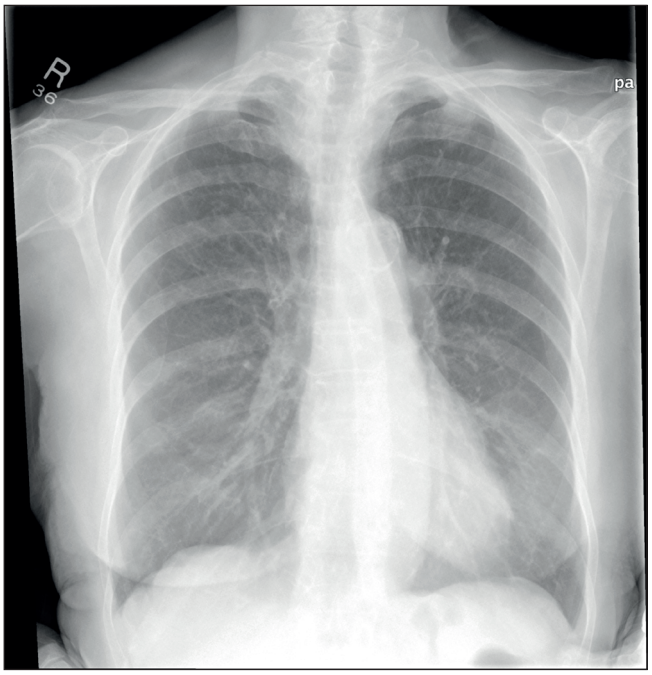

Fig 2a. left Apical Tumour, chest radiograph

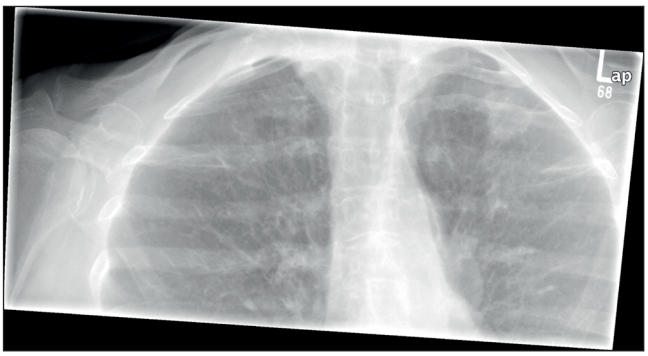

Fig 2b. left Apical Tumour, apical projection

Fig 2c. left Apical Tumour, CT imag

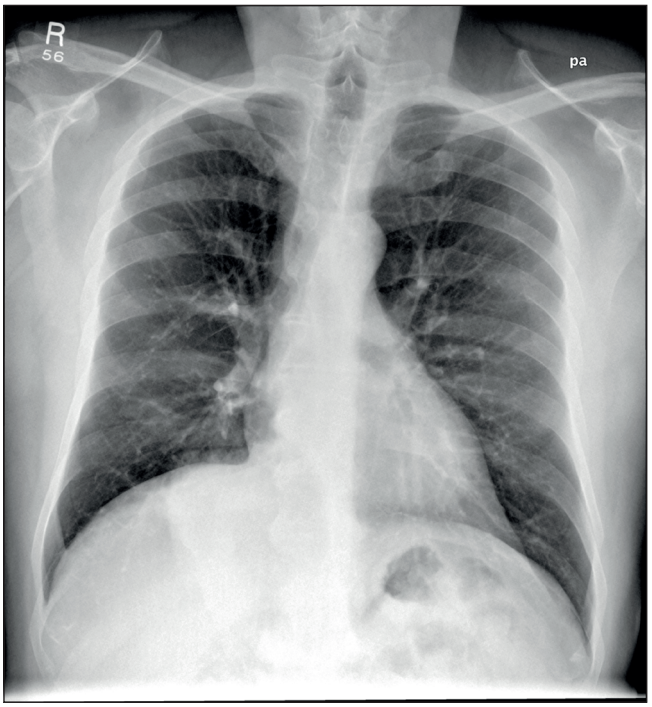

Fig 3a. Right Basal Tumour, chest radiograph

Fig 3b. Right Basal Tumour CT

Sometimes though, we see things that simply aren't there. Unsurprisingly, if you look at a chest radiograph for less than five seconds, you will miss things. However, if you look for more than 60 seconds you may start to imagine shapes that aren't there. This phenomenon is called Pareidolia. Pareidolia is our tendency to interpret a vague stimulus as something known to the observer, such as seeing shapes in clouds, seeing faces in inanimate objects or abstract patterns, or hearing hidden messages in music. It is not confined to humans. Scientists have for years programmed computers to use visual clues to 'see' faces and other images.

Part four: Technology and The Future.

What are humanity's most important inventions? I will suggest three. The first is the sewing needle, probably about 50,000 years old, which allowed us to make clothes that kept us warm and survive the ice ages. The second is the wheel about 5000 years ago which got us on the move. The third would completely change the world.

Its inventor was a man named Johannes Gansefleisch (John Gooseflesh). He was a serial inventor with a variable success rate. His current invention was so radical that he thought his name Gansefleisch wasn't appropriate. So, he changed it to the street in which he now lived, Gutenberg Street. The invention was, of course, the printing press with movable type. The exponential explosion of information that emanated from the press marked the dawn of The Information Age.

In 1854, George Boole, professor of mathematics at University College Cork, published *The Laws of Thought* and this contained his Boolean Logic. Boolean Logic is credited with laying the foundations for The Information Age. It is based on entirely on two numbers: one and zero (true and false) and would become the basis for all computer language. Although Charles Babbage conceptualised and built the first mechanical computer in 1833, modern computing really began with in 1936 with Alan Turing. In 1948, Claude Shannon, the Father of Information Theory, postulated that electrical switches could open and close as per Boolean logic. William Shockey, at Bell Laboratories, subsequently devised solid state energy-efficient semiconductors, thereby replacing the cumbersome vacuum tube. He came from, and returned to, a small town in California; Palo Alto, founding Shockley's Semiconductors and Silicon Valley. His silicon transistor, a word that is a composite of *trans conductance* and *varistor*, used approximately one millionth of a vacuum tube's power. For this discovery, he was awarded the Nobel prize. Two of his coworkers, Robert Noyce and Gordon Moore left to form a new company which they called Integrated Electronics. We now know this company as Intel. Their new integrated circuits were known as microchips or microprocessors. In 1965, Gordon Moore propounded his famous law that "Processing speed or capacity will double every 18-24 months."

The pernicious advance of Artificial Intelligence (AI)

Chess had always been considered the apotheosis of human intelligence and therefore the defeat of a human by a computer marked a watershed. In 1996, Garry Kasparov was defeated by IBM's Deep Blue. To give some idea of the permutations (known as game tree complexities) involved, in chess this is calculated to be 10 to the power of 120 moves. By comparison, the number of atoms in the universe has been calculated at 10 to the power of 80. These numbers incidentally are called Shannon Numbers, after Claude Shannon. Deep Blue could calculate 200 million chess moves a second. In 2016, all of that computing power was available in a Sony PlayStation. All that in 20 years, or, if you prefer, ten to thirteen 'Moores.'

In 2011, IBM's Watson computer competed on the US quiz-show, *Jeopardy* against two reigning champions and won. Watson could process the equivalent of a million books per second. In 2016, Google's Deep Mind computer, Alpha Go defeated the reigning world champion at the ancient Chinese game of Go. Go, considered the world's toughest game, is played on a 19 x 19 square board and has 10 to the power of 360 moves. The Universe, remember, has 10 to the power of 80 atoms.

Deep Blue had been built for one purpose; to play chess. It couldn't do anything else. Google's Alpha Go on the other hand was built *to learn*. Six months before it played Go's world champion, it had been ranked 400th in the world. In six months, it had taught *itself*. It had learned and improved to the extent that it had beaten the world champion.

There is no question that medicine like every other discipline will be changed utterly by computers However, at the heart of what we do, one constant will always remain: a doctor and a patient. Both will be flawed and exhibit human frailty, but the relationship will be charged with our one unique advantage: humanity. I suggest that the impact of AI on medicine can be summarized as follows: numbers, pictures, gloves and hunches. I would like to consider each of these in turn.

Numbers

Noam Chomsky observed that, "a computer winning chess is no more surprising than a forklift truck winning a weightlifting competition." So it is with numbers. Number-based medical specialties (e.g. nephrology) will utterly transform within the next five years.

Pictures

The algorithms required to interrogate pictures are more complex, but as we all know from facial recognition and our mobile phone thumbprint access, this isn't science fiction. Radiology, histopathology and dermatology sit within this group. Our imaging now is almost exclusively digital, therefore Boolean and increasingly easily deciphered by computers. Radiology will change dramatically in the next decade and I caution our trainees that they must put on a pair of gloves to have a career. This brings me to the next section.

Gloves

Practitioners and specialisms that routinely use gloves like surgery, obstetrics, anaesthetics, interventionalists and endoscopists require more complex and intricate motor skills than computers can currently provide. Besides, even if they could replace the practitioner, we generally appreciate a human pilot on our plane!

Hunches

Hunches are a much higher order event. Many here will remember walking into a room, seeing a patient and instantly thinking "This lady is really sick." Our diagnosis has been made in milliseconds. How do we do this? We know it because experience, non-verbal cues, non-linear, non-Boolean information stored in our frontal lobes and memory centres inform us that - no matter what the results and tests say - there is *something badly wrong* here. It is, in effect, a hunch. Medical specialties that work with rapid diagnosis and intuition sit here: a GP is required to make her diagnosis within minutes. Emergency Medicine is another. Perhaps one of the most interesting specialties to consider is psychiatry, where the diagnosis is formulated based on what the patient is saying (or not saying); how they are saying it; how they are sitting; what their eye contact is like and a host of other human factors that, as matters currently stand, are very difficult for a computer to evaluate. It will take some time for AI to get there.

The Flaw in The Law.

Moore's Law is predicated on the fact that computers are built by us. The premise therefore follows that when computers are building *themselves* and are self-learning, Moore's doubling times are very likely to contract. Because I learn to ride a bike, it doesn't mean that *you* can benefit from *my* knowledge. Tesla cars on the other hand, upload what they've learned each night to The Cloud, so that *every* car learns.

The point at which all physical laws break down is called The Singularity. At the beginning of time, with the creation of our universe, the first singularity was replaced by these laws. At the end of time, they will once again dissolve. Some devotees of artificial intelligence called The Rationalists describe another singularity. This is when artificial intelligence, computing speeds, machine learning and neural nets all converge. What space will there be then for us? The answer is likely to be the same as that received from Zhou Enlai in 1971 when the Chinese politician was asked what the consequences of the French Revolution were. Although he may have been referring to the French riots of 1968, the famously silky reply was, "It's too early to tell."

The Imager, whose eye is bright,
Whose beard with age is hoar,
Is gone and now the Wedding-Guest
Turned from the bridegroom's door.

He went like one that hath been stunned,
And is of sense forlorn:
A sadder and a wiser man,
He rose the morrow morn.

But let's not be despondent. Like that bright-eyed mariner, we will proceed optimistically. I would like to finish with a quick story from an old friend and what happened during his final radiology exams. He was shown a spinal radiograph that demonstrated a fracture. "What would you do next?" He replied that he would perform a CT study, which he was duly given. This confirmed the fracture. "Now young man, you are told that the patient has neurological symptoms. Is there any other test you could do?" He suggested an MRI, which unfortunately confirmed that the bone had pushed against the spinal cord. "Very good. Now what would you say to the neurosurgeon?" He thought for a moment and replied, "I think I would say …. well, that's me off home then."

Thank you all very much for your very kind attention.

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Medical History

Early Irish Brain Surgery and Antiseptic Agents (1889).

Tracy Freudenthaler

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Key words: Dr. Henry O'Neill, historic antiseptics, antiseptic surgery, early brain surgery, Ulster Medical Society

INTRODUCTION

Ulster Medical Society (UMS) President, Dr. Henry O'Neill (1891-1892), championed the use of antiseptics for more than 25 years of medical practice. Curiously, the author's recent purchase of an unassuming and worn journal from an antique dealer has returned attention to Dr. O'Neill's career and public health advocacy efforts in Ireland. This article provides a snapshot of O'Neill's specific antiseptic practice recommendations, and provides a transcript of his hand-written guide for brain surgery from July of 1889.

Dr. Henry O'Neill (1853-1914)- "Health"

Dr. O'Neill was remembered in his British Medical Journal 1914 obituary[1]: his 'Indomitable spirit drove him on to work which would have put a strain on a much younger man'. He earned a nickname of "Health" at some point, perhaps for his radical views[2], or perhaps simply for his commitment to public hygiene[3]. He was a 'a voluminous writer, chiefly on sanitary and professional matters.'[1] Briefly, his service to the medical profession includes House-Surgeon and Surgeon at Belfast Royal Hospital, President of North Ireland Branch of the British Medical Association, and Ulster Medical Society President (1891-1892). His contributions to Belfast were spirited and impressive. He was a physician then city councilman, an advocate for adequate public housing and nutrition, a pathologist that practiced public health law.

Antiseptic treatments (1891) - A call for action

O'Neill lauded Joseph Lister for his understanding of germ theory. Historically, there was an existing premise that air was a mass with disturbing properties referred to as miasmas theory. Lister embraced a shift in thinking that there "… was something in the air, not the air itself, which caused fermentation and putrefaction…".[5] In 1907 Franklin Clark published a brief history of antiseptic surgery, noting during Lister's time: "the air contained morbific elements, capable of inducing inflammation and suppuration, a problem which as yet had not been solved[5]". Lister believed that attempts to control the wounded area would prevent these minute particles in the air from introducing the inflammation and pus formation (suppuration). Lister said, these minute particles are '…the germs of various lowest forms of life…'.[5]

In eagerness to advocate for this germ theory, O'Neill's 1891 opening Presidential speech to the Ulster Medical Society (UMS) records his call for action for use of antiseptics[4]. In his address to UMS, he made these significant statements regarding Lister's impact:

- '…antiseptic surgery, by the evolution and perfecting of which he (Lister) has done more to relieve the suffering and to diminish the mortality in surgical cases than has been accomplished by any other surgeon during the last century'.
- '*(Lister knew the…)* difficulty of killing germs, after they had once made their way into the tissues, it was absolutely necessary that such organisms should be prevented from gaining access to the wounds at all.'

There was expressed concern over the origin of 'germs' and the source of infections that occur pre and post-surgery. The verbiage aligns with the prevailing thoughts of the time. O'Neill stated '…pus formation was the result of the action of germs falling from the surrounding air into a wound.'[4] He likened the process of pus formation to that of 'fermentation'. Like Lister, his messaging to colleagues called for prevention of the germ from entering the surgical field; '…since germs were floating in the air, were suspended in water, and were attached to the instruments and bandages that were used in the treatment of wounds,'[4] there must be action to kill the germs before contact.

Historic antiseptic agents varied. According to O'Neill, Lister had recommended 'a solution of double cyanide of mercury and zinc' for his surgeries. 'Germicidal reagents' were valued in both pre-operative preparations; and during surgery, intended for both 'wounds and suppurating surfaces.' Table 1 presents a list of O'Neill's '…necessary antiseptic treatments.' Shaving of the surgical area was absolute. Most wounds were encouraged to be washed with soap and water; however, turpentine, ether, and alcohol were favorable for the first washing. The value of some agents over others lied within the ordering of the application. Some agents appear to counteract the effects brought on by the previous agents.

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Table 1:
'Necessary Antiseptic' Agents (Dr. O'Neill 1891)[4]

Antiseptic Agents:
Turpentine
Ether
Alcohol
Carbolic acid solution
Corrosive sublimate (mercury)
Mercury
Germicidal reagents
Soap and water
Boiled clean water
Bicarbonate of soda (for instruments)

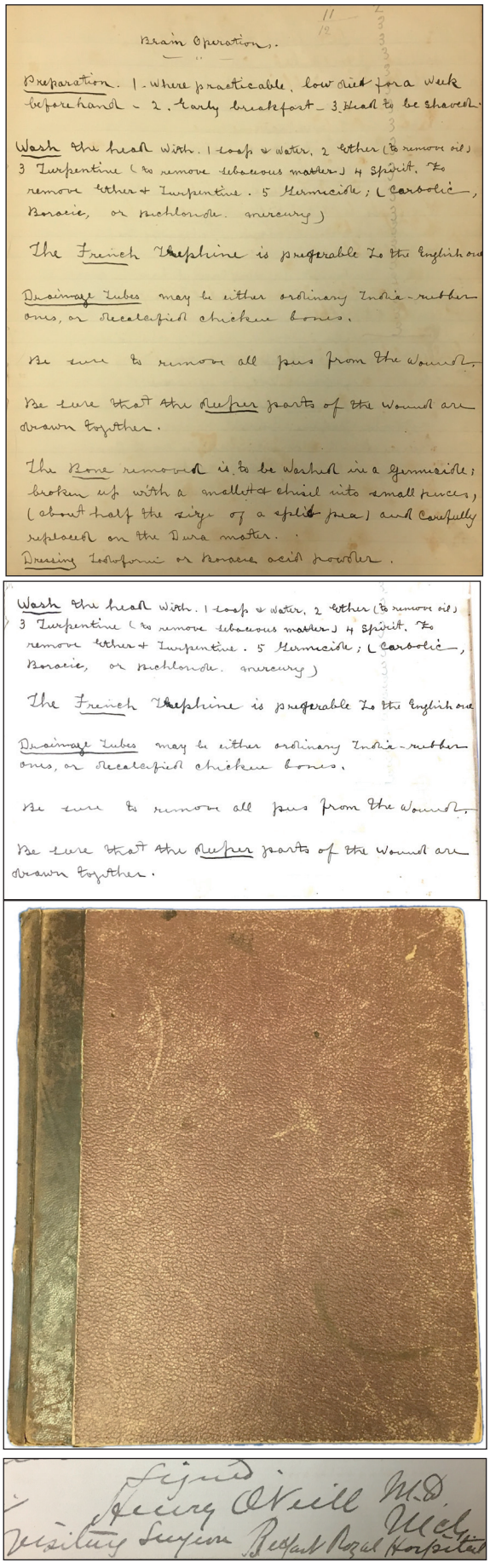
Dr. O'Neill believed the use of antiseptic treatments would allow for advancement of surgeries '…successfully performed in regions which were looked upon by the older surgeons as entirely outside the range of surgical operations.' [4] O'Neill explained in his1891 UMS speech the need for hygienic care before, during, and after the surgical procedure. The following is an excerpt of his suggested a pre-surgery hygienic procedural routine in his own words:

- 'Hands of the operator and his assistants should be purified by washing and brushing them in warm water and soap, and then with corrosive sublimate solution 1 in 1,000, or carbolic acid solution 1 in 40, and, lastly, in alcohol.'
- 'Instruments should be steel, with metal handles, nickel plated, so that they can be readily boiled in clean water, or with 1 per cent. Bicarbonate of soda added to the water.'
- 'Patient should be laid on a dry linen sheet' and covered with a similar sheet, except over the parts to be operated on.'

Antiseptic practices with brain surgery

O'Neill attested to 4 brain operations in a handful of years, all with positive outcomes. Indeed, he believed through careful antiseptic treatment, 'cerebral surgery' would be 'no exception' to the types of surgical procedures that could be performed. O'Neill concluded the '…the greatest importance in the success of any operation, … can only be accomplished when the surgeon secures for the wound and everything that is brought into contact with it a thoroughly aseptic condition.'[4] Table 2 presents the procedure for brain surgery from his 1891 address.

A handwritten journal drafted by Dr. O'Neill was discovered online and purchased by the author of this article in April of 2021. The small journal was manufactured by R. Carswell & Son Manufacturing Stationers, Belfast; the label still holds tightly, the binding intact. The journal is worn, with pages missing, and begins with a list of patient admissions and


Brain Operation.

Preparation. 1. Where practicable, low diet for a week before hand – 2. Early breakfast – 3. Head to be shaved.

Wash the head with. 1 soap & water, 2 ether (to remove oil) 3 Turpentine (to remove sebaceous matter) 4 Spirit. To remove ether & Turpentine. 5 Germicide; (Carbolic, Boracic, or Bichloride. mercury)

The French Terebene is preferable to the English one

Drainage Tubes may be either ordinary India-rubber ones, or Decalcified chicken bones.

Be sure to remove all pins from the Wound.

Be sure that the Deeper parts of the Wound are drawn together.

The Bone removed is to be Washed in a Germicide; broken up with a mallet & chisel into small pieces, (about half the size of a split pea) and Carefully replaced on the Dura mater.

Dressing Iodoform or Boracic acid powder.

Wash the head with. 1 soap & water, 2 ether (to remove oil) 3 Turpentine (to remove sebaceous matter) 4 Spirit. To remove ether & Turpentine. 5 Germicide; (Carbolic, Boracic, or Bichloride. mercury)

The French Terebene is preferable to the English one

Drainage Tubes may be either ordinary India-rubber ones, or Decalcified chicken bones.

Be sure to remove all pins from the Wound.

Be sure that the Deeper parts of the Wound are drawn together.

Signed
Henry O'Neill M.D.
Visiting Surgeon Belfast Royal Hospital

Table 2:
Brain surgery procedure excerpts from UMS 1891 address, (Dr. O'Neill 1891)[4]

Procedure:
• 'The shaved and disinfected scalp before the skull is exposed'
• Position of lesion marked by 'puncture perforation of the scalp'
• 'After all hemorrhage has been arrested the skull is opened, either by using a trephine or a chisel'.
• Bone is placed in antiseptic solution
• '…exploring syringe, with a fine needle about 4 inches long, is best suited for the purpose.'
• Forceps for the removal of abscess
• 'A fine drainage tube passed along the track to the abscess cavity'
• '2 per cent. Boracic Acid solution' applied to area of abscess
• Drainage tube inserted
• 'Flap is now secured by sutures of sterilized silk, catgut, or horsehair'
• 'In wounds of the brain rest is secured by keeping the room dark and quiet'

Quote marks identify Dr. O'Neill's own words

discharges. The entries span the years of 1889 until fall of 1899 including diagnosis criterion, admissions and payments received, various remedies and medicinal preparations. Figures 1-3 present original images of the journal and his writings.

Page two presents a carefully articulated brain operation procedure dated 1889. He purposely orders the steps of preparing the patient, handing of the removed bone, and antiseptic measures. Table 3 presents a transcription of these two journal pages in his words. His written procedures align with his opening address to UMS where he similarly presents brain operation. Note the discussion of washing of the head with a multi-step regimen where ether, turpentine, and spirits were necessary agents. Randomly, he indicates the 'French trephine is preferable to the English one', but offers no explanation for his opinion. He concludes his entry with caution to surgeons that 'every head case should be considered as serious, few should be looked on as hopeless'.

SUMMARY

Dr. Henry 'Health' O'Neill served as Ulster Medical Society (UMS) President from 1891-1892, during the evolving shift in physician thinking regarding germ theory. 'We are

Table 3:
Transcript of Dr. O'Neill's July 11th 1889 medical journal entry: Brain Operation

Brain Operation
Preparation: 1. Where practicable, low diet for a week before hand, 2. Early breakfast, 3. Head to be shaved.
Wash the head with 1. Soap and water, 2. Ether (to remove oil), 3. Turpentine (to remove sebaceous matter, 4. Spirit to remove ether and turpentine, 5. Germicide (carbolic, boracic, or bichloride mercury).
The French trephine is preferable to the English one.
Drainage tubes may be either ordinary India-rubber ones, or recalcified chicken bones.
Be sure to remove all pus from the wound.
Be sure that the deeper parts of the wounds are drawn together.
The bone removed is to be washed in a germicide; broken up with a mallet and chisel into smaller pieces (about half the size of a split pea) and carefully replaced on the Dura matter.
Dressing Iodoform or Boracic acid powder
Put on enough dressing to last for one, two, or three weeks, and leave undisturbed as long as possible.
Treatment: Keep the head high, and cool (illegible and ice-cap) Exclude light and noise. Keep movements regular.
Diet: milk, beef tea, and chicken soup.
Bad symptoms: 1. High temperature 2. Pain in the head 3. Rigors 4. Fits 5. Vomiting.
When any of these occur, take off the dressing and examine again.
A surgeon must be very careful how he gives a certificate that there is no danger to life in a head wound, however apparently slight. What appears a scalp wound may be a fractured skull, Erysipelas too may ensue. He should never certify before 2 weeks and seldom before four. Every head case should be considered as serious, few should be looked on as hopeless.

rapidly approaching the time when we shall become health officers, our duties then being to prevent rather than cure disease.' Newly recognizing organisms in the air as causative agents for '…disease and fermentation…', O'Neill called for physician action through: '…antiseptic surgery, which rapidly revolutionized the treatment of wounds'. Through his UMS Presidential address and his personal journal O'Neill memorialized a variety of early 1890's antiseptic agents, a summary of hygienic surgical practices, and rare account to cranial surgery procedures and patient aftercare in 1889. In conclusion, O'Neill's obituary states he was dedicated to the field of public health, and it was his life-work. [1] His nickname, 'Health', alludes to the breadth of community health contributions to Belfast and the citizens of Ireland during his lifetime.

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Medical History

THOREAU, TOLSTOY AND WALDEN WOODS: THE CLINTONS AND BELFAST

Authors: John Hedley-Whyte[1], Debra R. Milamed [2]

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Provenance

INTRODUCTION

In late June 1940, we were told by the British Army that my[1] father, a Newcastle-upon-Tyne surgeon, was missing, presumed dead in the German conquest of France[1,2]. My maternal grandfather, Edward Nettleton, who had twice circumnavigated the world under sail in *Royal Forth*, 3,130 tons launched 1893, told me that I was now head of the Hedley-Whytes and had better read the works of Henry David Thoreau. Grandfather and I knew that his daughter Nancy, my mother, possessed Thoreau's books and had read them. I did as bid[3,4,5,6].

In late July 1940, we went to meet my father in Leeds. A month earlier in Saint-Nazaire, the Chief Radiographer of my father's RAMC 8th General Hospital had approached my father. The Radiographer had been a prisoner of war in Germany during World War I. This experience he did not wish to repeat. "Let's capture a ship. What about *The Glenaffric* in dock here?" The dock master refused to open the locked gates to release *The Glenaffric.* He was shot. The gates were opened. The 8th RAMC General Hospital British patients and Staff loaded with the Chief Radiographer as Acting Navigation Officer. This officer had been a Shipping Pilot before becoming a Chief Radiographer. After picking up survivors from the sunken Cunard Liner, the *Lancastria,* in July they reached Plymouth[7,8].

After Leeds we, as a family, took the Stranraer to Larne Ferry arriving in Belfast for Christmas 1940. Transport and clearance of the twenty-four volumes totaling nearly one hundred pounds of the 1939 edition of *Encyclopaedia Britannica* which had been my father's gift to me that year caused grumbling and an excessive workload for the Customs Officers at Stranraer and Larne.

WARTIME BELFAST EDUCATION

From then until August 1942 most of the tuition I remember was in the form of set tutorials at Musgrave Park Hospital by RAMC Officers and staff. From March 1942 I was tutored by members of the U.S. Army Harvard 5th General Hospital[9,10]. After each lesson I had to write up a summary for my father[3,4,5,6]. I remember we covered blood transfusion[11,12],

1 This and subsequent first person singular and plural references are to the first author.

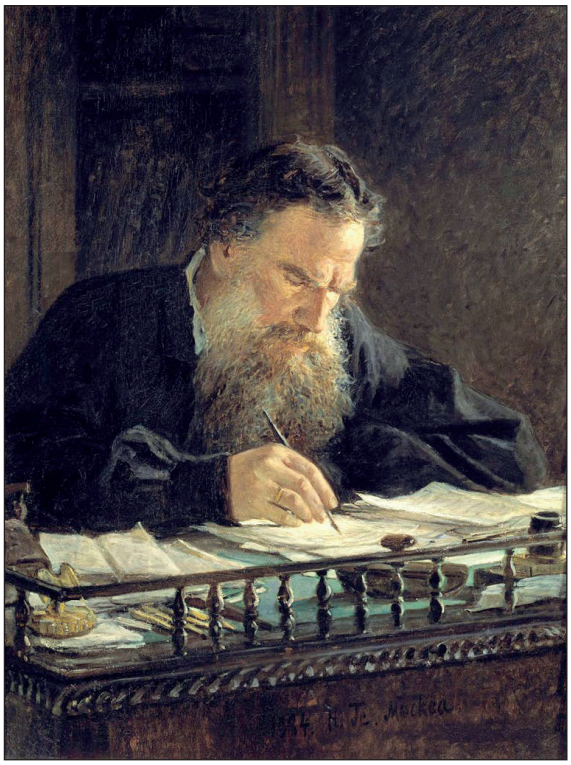

Figure 1.
Portrait of Count Leo Nikolaevich Tolstoy (1828-1910), 1884, by Nikolay Nikolaevich Ge (1831-1894). Oil on canvas, 96.2 cm x 71.7 cm. From the collections of the State Tretyakov Gallery, Moscow, Hall 31, No. 2637. Reproduced with their permission exclusively for this Medical History. This famous painter of portraits became a close friend of Tolstoy.

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vitamin A[13], Tolstoy's (Fig.1) *Anna Karenina* and *War and Peace*[14,15]. Thoreau's *Walden* and *Civil Disobedience*[16,17], Pandemics, and why Nobel Prizes are awarded.

In the early spring of 1942, Theodore L. Badger, Head of Medicine as well as Pathology at Musgrave Park, took over the domiciliary management of the tuberculosis of my sister, my brother and myself[18,19,20,21]. Ophthalmologist Benjamin Rycroft, later knighted[13,22], had suggested that we read Tolstoy's *Anna Karenina* (translated by Constance Garnett) published in 1911[14,23,24]. The chapters describing the decline and death of character Nikolay Levin from tuberculosis were exceptionally moving, inspiring my admiration for Tolstoy. I learned from my tutors and later reading that this account was based on Tolstoy's personal experience with the death of his own brother, Dmitry, in 1856[25,26]. Badger suggested that I read *Walden*, which I did[16]. Rycroft then brought a copy of Thoreau's *Civil Disobedience*[17] , which he said had influenced Tolstoy who had read widely in several languages including English[25,26].

The Harvard Faculty at Musgrave Park also discussed with me their own publications and careers. When I had almost recovered from lobar pneumonia[22] I was told about Tolstoy's last days[25,26]. When I got tuberculosis and appeared healed[18] I was told of 1837 Harvard Graduate Henry David Thoreau's death from TB and the disease's courses in his brother and two sisters[27,28]. I could not help but recall my earlier reading of *Anna Karenina*. Tuberculosis was endemic in 19th Century New England, and was the largest single cause of premature death[27,28,29,30,31]. Physician- Statistician Edward Jarvis had reported "consumption" as the cause of 21 percent of all deaths in the town of Concord, Massachusetts, during the period 1828-1878[27]. Henry David Thoreau's paternal grandfather Jean Thoreau and father John had also succumbed, as had members of many prominent Concord, Massachusetts families including the Emersons and Ripleys[28,32]. At Musgrave Park my teachers reminded me of the long history of tuberculosis and the ongoing campaign to reduce its incidence and mortality in Northern Ireland[33,34].

Rycroft told me that in Lenin and Stalin's USSR you could not be promoted to a high level in the Soviet Army, Police or Ambassadorial Services unless you were conversant, not only with Tolstoy's writings, but also with the influence of Thoreau and of his landlord Ralph Waldo Emerson[35,36]. Lenin had attended the Imperial University of Kazan, founded in 1804, where Tolstoy had studied[25,26]. *Thoreau's Civil Disobedience* had been translated into Russian by the close of the Nineteenth Century[37,38].

KAZAN STATE UNIVERSITY IN THE 21ST CENTURY

While Secretary of State of the United States (2009-2013), Hillary Rodham Clinton visited this historic institution, now Kazan State University, which she described in her October 14, 2009 remarks as " a very excellent university" which "increasingly has a reputation beyond Russia"[39,40,41] (Fig. 2). Secretary Clinton's visit was intended to promote

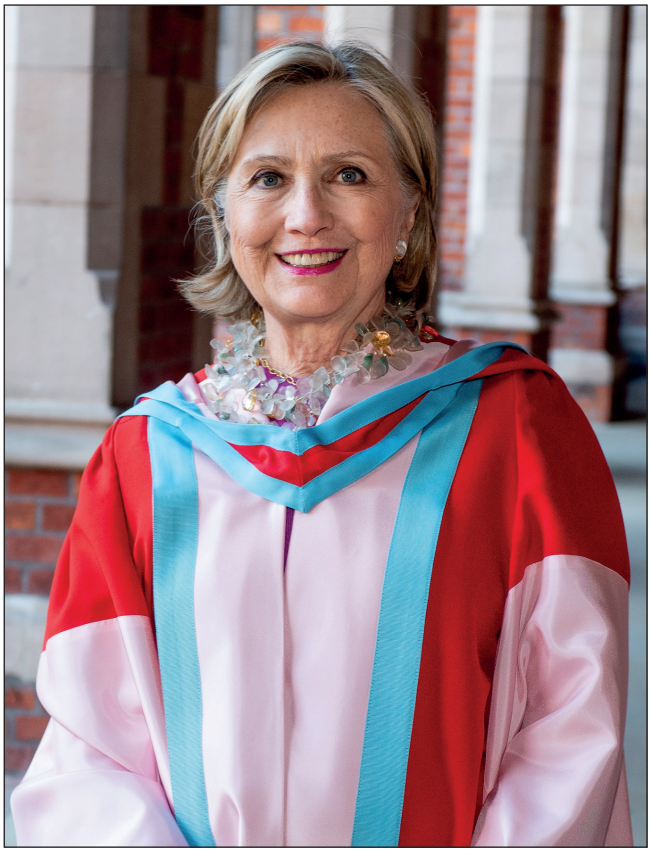

Figure 2.

Chancellor of Queen's University Belfast (QUB) , Hillary Rodham Clinton, 2020. Photograph by Andrew Towe, Parkway Photography Ltd., reproduced by permission of QUB. Chancellor Hillary Rodham Clinton wears the gown of her honorary degree of Doctor of Laws, QUB 2018.

intercultural dialogue and cooperation[42]. Immediately before her October 2009 trip to Moscow and Kazan, she had visited Belfast, a destination familiar from her years as First Lady of the United States. There she addressed a full session of the Northern Ireland Assembly with themes of devolution, disarmament and the common good[42].

Progress was evident in the January 2017 Conference held at the Kazan State University on "Literary Studies and Aesthetics in the 21st Century" which featured an American paper on classroom teaching of Thoreau's *Civil Disobedience*; this presentation "sparked a serious, albeit at times guarded discussion," about the Presidency of Russia[43].

HILLARY RODHAM 'S EDUCATION

At Wellesley College, Rodham became Valedictorian in 1969. She used to visit "nearby" Walden Pond[44]. Wellesley College in Wellesley, Massachusetts, was founded in 1870 to advance the higher education of talented women[45]. On May 31, 1969, Hillary Rodham (Fig. 2) delivered the Valedictorian's Address at Wellesley College's Graduation Ceremony. Rodham set aside her prepared remarks and reviewed the address of the previous speaker, Edward W. Brooke, Republican United States Senator for the

Commonwealth of Massachusetts, who served two terms from 1967-1979[44]. The impromptu but polished address by Rodham attracted wide attention and launched Hillary Rodham Clinton's career. Her career includes a plurality of popular votes of almost three million in the Presidential Election of 2016.

EUROPEAN ANAESTHESIA MEETING IN PRAGUE

On August 28th, 1970, as a newly-appointed Full Professor at Harvard University I flew to Prague as an invited speaker to the Annual Meeting of the European Society of Anaesthesia. At Prague Airport, I met Alex Crampton Smith, Nuffield Professor of Anaesthesia at Oxford University[46,47,48]. I hired a small Ford and we drove off to Alex's assigned hotel. I noticed we were being followed by a late model Soviet car known by its manufacturer's acronym, VAZ (Volzhskiy Avtomobilnyi Zavod, or Volga Automobile Plant), with two fierce-looking men inside. On arrival at the hotel we were arrested. The Warsaw Pact[49,50] Generals were having a meeting. Alex knew Russian from his World War II experiences. Professor Crampton Smith ordered our guards to carry my bags and take us to see the Senior Soviet General in the Hotel. This General apologized and invited us to the Warsaw Pact Military Leadership Reception where we were elegantly entertained with champagne, caviar and oysters. At the reception we were told by a Russian Army Staff Major that "A Dartmouth College graduate, a U.S. citizen, had recently been arrested in Prague." Fred Eidlin, the alleged U.S. spy, was being held by Czech Civil Authorities. "The spy was wrongly being held incommunicado," said the Staff Major. At a one-day trial in December 1970, Fred Eidlin was sentenced to four years hard labour. In February 1971 Eidlin was released[51,52,53]. He subsequently achieved a distinguished academic career in the United States and Canada[54].

Our Soviet host, arranged the change of my Anaesthesia Society Meeting scheduled abode in an inferior hotel to an elegant Swedish Houseboat on the Vltava River. There I was treated well under Russian Army control. They drove me each day to Alex's Warsaw Pact Generals and our meetings. Alex and the Senior Generals of course knew all about Tolstoy and Thoreau's *Civil Disobedience.*

To return to the West, I had to book a flight on Syrian Arab Airlines to Le Bourget Airport to the north of Paris. At Prague I had been escorted to the departing Syrian plane. As I ascended the stairs to the plane, a Soviet Army Major smartly saluted me and in French wished me "*Bon Voyage*". Syrian Arab Airlines thereafter ceased flying to and from Prague citing insufficient passengers.

INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, MOSCOW, 1987

On Saturday, August 29, 1987 my wife[55] (Fig 3) and I flew into Sheremetyevo Airport, Moscow, where I was to be leader of the United States Delegation to the Annual Meeting of the International Organization for Standardization (ISO) Technical Committee on Anaesthetic and Respiratory Equipment, as well as to chair the meeting of its Subcommittee on Lung Ventilators and Related Equipment, which included both Adult and Paediatric Intensive and Respiratory Care, Humidifiers and Patient Monitoring[56,57,58].

On Monday morning August 31, 1987, I as US Delegation Leader was introduced to my personal Intourist Liaison Officer. She had been a ballerina and then graduated from Moscow State University, founded in 1755 as Imperial Moscow University[59]. She had written about Dickens' visits

Figure 3.

E. Tessa Hedley-Whyte, A.M. Hon., Harvard, M.B.B.S., Durham, M.D. Newcastle, Honorary Fellow, Newcastle University. Oil on canvas, 24" x 28.5", 1992, by Kathleen E. Williams, who arrived in the UK as a refugee in 1943.

to the United States. On the basis of her University grades she could determine the horse that she rode. I showed the ballerina two photographs of myself on my mare, Lorraine's Choice, one taken in Northumberland and the other in Concord, Massachusetts. She immediately spotted the change in locale and asked how I had managed the transatlantic move. I replied Lorraine's Choice had flown "Standby" from Heathrow to Kennedy, and then been transported to quarantine at Ithaca, New York. The ex-ballerina reported this information to her supervisor. Our Liaison Officer had also just finished her training. The resulting acquaintance of my wife and myself with this ex-ballerina led to a Soviet Army Major being assigned to assist us with the conduct of

the ISO meeting. He was needed. The orders flew for Army radios, copiers, two Soviet Army translators, and more and more copiers. They arranged for my wife and I and other Heads of National Delegations to dine at privately owned restaurants: apparently a first for Moscow.

LENINGRAD

After the meeting in Moscow, my wife and I were flown to Leningrad. At the Hermitage Museum, my wife and I were inadvertently locked one evening in an upstairs gallery among works by Cezanne, Degas, Gauguin, Van Gogh, Matisse, Monet, Picasso, Pissarro, Renoir, and Toulouse-Lautrec. We reckoned that this collection approached a billion pounds sterling[60]. With mixed feelings we were released by outside authorities. We were taken to the Summer Palace. This palace was being rebuilt after heavy damage during World War II. Here again, the Soviet Army would get things done with expertise and optimal speed.

WALDEN, CONCORD, MASSACHUSETTS

My wife and I live in Walden Woods in Concord, Massachusetts (Fig. 4). It is a mile's walk to Henry David Thoreau's Cabin. A brick from the Thoreau Cabin was used to finish building the Institute and Museum-Library which was dedicated by President Bill Clinton and his wife Hillary Rodham Clinton, now Chancellor of Queen's University Belfast (QUB)[61,62]. Much of the millions of dollars raised to preserve Walden was due to Don Henley's efforts as Drummer of the Eagles with the support of the Concord Conservation Association and two official visits of the Clintons. In early June 1998 President Bill Clinton 's remarks at the dedication ceremony included his favourite quotation from Henry David Thoreau's *Walden,* Chapter II, "Where I Lived and What I Lived for":

Figure 4.

Fairhaven Bay on the Sudbury River at the southeastern foot of Fairhaven Hill and the adjacent Walden Woods. JH-W on Binn Pleasant, by Pleasant Colony out of Coal Binn. They look toward Fairhaven Bay Island; oil on canvas by Bridget Garrett (1966-), 1999, dimensions 18" x 22".

"Let us settle ourselves and work and wedge our feet downward through the mud and slush of opinion, and prejudice, and tradition, and delusion and appearance… until we come to a hard bottom and rocks in place which we can call reality..."[16,62].

In 2012 the Walden Woods Project, founded 1990, honoured President Bill Clinton with its Inaugural Global Leadership Award[63,64]. Also in 2012 the Walden Woods Project started "World-Wide Waldens" to connect and encourage school-aged students and their teachers to visit and preserve their Walden-like areas of environmental importance.

During the last decade, the planning for construction of a six-to-eight lane highway through part of Walden Woods was proposed to the Massachusetts State Legislature and Administration. I knew that the proposed route was over a marked Pre-Colonial Era Graveyard of Indigenous Peoples. As Chairman of the Fairhaven Preservation Association I met with my Executive Committee. I was directed to a suitable Concord attorney. We, the Fairhaven Preservation Association, documented the risk of starting a pandemic by disturbing such a graveyard[65,66]. This information was used to prevent building of the proposed highway.

RALPH WALDO EMERSON, HARVARD PROFESSOR

Ralph Waldo Emerson (1803-1882), was 1837 Harvard graduate Henry David Thoreau's landlord, friend, financier and Harvard Professor. After barely a year of their marriage, Emerson's first wife, Ellen, died, aged nineteen, of tuberculosis. Also, his two brothers, Edward and Charles, succumbed to tuberculosis at an early age. His own chronic infection had a major effect on his career and activities[28,32]. Emerson twice visited Britain for long stays and interchanged Moral Philosophy with Thomas Carlyle, a Scot[67,68].

Renowned philosopher, author, landlord, plutocrat and America's Harvard Professor, Ralph Waldo Emerson survived almost to the age of eighty, supported by Transatlantic and Caribbean yachting and visits to Italian sun as recommended by Henry Ingersoll Bowditch[29,30,31], whose father, Nathaniel Bowditch, pioneered modern oceanic navigation[69].

In 1867 Ralph Waldo Emerson first published the poem "Terminus":

"…I trim myself to the storm of time,
I man the rudder, reef the sail,
Obey the voice at eve obeyed at prime:

'Lowly faithful, banish fear,
Right onward drive unharmed;
The port, well worth the cruise, is near,
And every wave is charmed.'[70,71]".

The Stranraer and Larne Customs Officers did not open Volume 8 of my *Encyclopaedia Britannica* to that quotation from Emerson's poem on our 1940 trip to Belfast, nor during our 1942 return with the 31st General Hospital to their new

quarters at Hatfield House. Under its contiguous oak, Queen Elizabeth I accepted the Crown of England. The Cecils were most hospitable.

ACKNOWLEDGEMENTS

We thank the Copyright and Permissions Staff and Ms. Natalia Alexandrovna Kazak of the State Tretyakov Gallery, Moscow, for assistance with the portrait of Count Leo Nikolaevich Tolstoy. We thank the Development and Alumni Relations Office of QUB for permission to reproduce the photograph of Chancellor Hillary Rodham Clinton. We thank Ms. Anke Voss, Curator, William Munroe Special Collections, Concord Free Public Library, Concord, Massachusetts, for assistance with historical newspaper accounts of the 1998 and 2012 visits of the Clintons. We thank Ms. Sarah Walker of the Walden Woods Project, Lincoln, Massachusetts, for updating us on the mission of her organization.

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Game Changers

AXIOS STENTS: TRANSFORMING THE MANAGEMENT OF PANCREATIC FLUID COLLECTIONS

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Pancreatic fluid collections (PFCs) are frequent complications of acute pancreatitis. These are divided into 4 subtypes as per the revised Atlanta classification: acute peri-pancreatic fluid collections (APFC) and acute necrotic collections (ANC) when occurring less than 4 weeks following an episode of acute pancreatitis; pseudocysts and walled-off pancreatic necrosis (WOPN) if greater than 4 weeks interval.

Classically the management of PFCs involved open cyst-gastrostomy and/or necrosectomy. However, following the landmark PANTER trial[1] the focus has shifted to less invasive interventions. This Dutch study reported that a minimally-invasive 'step-up' approach was superior to open surgery in patients with acute necrotising pancreatitis. More recently, the TENSION multi-centre randomized control trial[2] has shown endoscopic transluminal stenting to be a viable alternative to percutaneous drainage, with lower rates of pancreatic fistula, shorter length of hospital stay and at a lower overall cost.

The evidence from these trials has been incorporated into the management of complicated pancreatitis at the regional Hepatobiliary unit in Belfast with the recent introduction of lumen-apposing self-expandable AXIOS stents. These stents are inserted under endoscopic ultrasound guidance and enable PFCs to be drained into the stomach; they incorporate a dual flange that prevents migration, and once placed can function as a port to facilitate debridement and irrigation.

In a recent study of 45 consecutive patients who underwent AXIOS stent placement in the Belfast Trust, the procedure was noted to be technically successful in 43 cases (95.6%) and clinically successful in 33 cases (73.3%). Only 5 patients (11.1%) required further surgical management within 40 days of stent removal. Overall the results have shown that AXIOS stents are an effective first line management of PFCs, avoiding the need for more invasive surgical procedures.

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MOVE YOUR FEET, LOSE YOUR SEAT

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At the onset of the COVID-19 pandemic, a "remote by default" strategy[1] was advocated for general practice consultations, which resulted in a seismic, and a likely long-lasting shift towards telemedicine in primary care.[2] This led to some doctors working in general practice to lament, "I didn't become a GP to work in a call centre!" The effect on the clinician-patient relationship has been discussed in detail,[1,3] however less attention has been paid to the impact this is having on the health and wellbeing of GP staff. Given that computer-work, paperwork, telephone and video consultations are all traditionally performed while sitting down, the reduction in face-to-face consultations has made general practice even more sedentary. Due to evidence linking excessive sedentary behaviour to many health problems, with a cumulative dose-response relationship with mortality risk,[4] the World Health Organisation advises individuals to minimise and break up periods of sedentary behaviour where possible.[5]

One way of minimising sedentary behaviour is by using an "active workstation," such as a height-adjustable sit-stand desk. In the general practice setting, active workstations allow clinicians to stand and/or move while undertaking computer-work, paperwork, telephone and video consultations (Figure 1). We researched the uptake of active workstations among GPs and GP Specialty Trainees in Northern Ireland, as well as exploring the opinions of GPs to their sedentary behaviour and physical activity. Among 320 participants, 18 (5.6%) reported having access to an active workstation in their practice, potentially allowing them to significantly reduce sedentary time. In subsequent interviews with GPs, multiple participants stated that they "hate sitting down all day long." This shows that not all GPs are happy with the current sedentary status quo, and some are now actively taking steps to reduce this.

We hope these findings will encourage other clinicians working in desk-based specialties to consider how their sedentary behaviour is affecting their health and to contemplate ways to reduce this where possible. The colloquial expression "Move your feet, lose your seat" is used as a justification when a person steals another's seat if they stand up or walk away from it. Is it time to reframe this statement for those working in General Practice as "Lose the seat, move your feet"? We plan to explore ways to help staff in primary care to be less sedentary and more physically active throughout the working day.

Figure 1. *A height-adjustable sit-stand desk in the primary care consulting room.*

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So you want to be a
Medical Student Technician?

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INTRODUCTION

In March of 2020, the COVID-19 pandemic brought life as we knew it to an abrupt halt and the world of medical education was no different. In-person clinical placements were temporarily suspended for medical students across the United Kingdom (UK) and worldwide. The Medical Schools Council promptly released guidance on employment or volunteering of medical students within the National Health Service (NHS) in the UK to support the pandemic response[1]. Within a day of this guidance being issued, discussions between the medical school at Queen's University Belfast (QUB) and the five Health and Social Care Trusts across Northern Ireland led to the establishment of the role of the "Medical Student Technician" (MST). Similar arrangements were seen across the UK[2], and indeed the world[3,4,5], with some medical schools even temporarily pivoting their entire medical curricula to aid the COVID-19 response, claiming that "medical students are needed just as urgently as ventilators"[6].

The wide-ranging implications of this nascent MST role are of interest to medical students, medical educators, healthcare service providers and patients alike. Here we present what the role has involved, some insights into being an MST and some reflections on how the role might evolve. It will reflect our personal experiences in addition to conversations with peers who participated in these roles. It is worth remembering that these roles were developed in a time of uncertainty and unprecedented flux.

WHAT IS A MEDICAL STUDENT TECHNICIAN?

The initial workforce appeal for MSTs cited an "urgent need of support" to "join the fight against COVID-19". It mentioned "working with colleagues" and "learning skills fundamental in patient care"[7]. The role was devised primarily for students in clinical years (third, fourth and fifth years) and, although it enabled access to clinical settings, it was not envisioned as a substitute for traditional clinical placements. Across all five Health and Social Care Trusts in Northern Ireland, the number of MSTs initially employed well exceeded one hundred. Some training for these roles was centralised, however, many MSTs received training locally in specific roles and on the job training.

The MSTs were placed in a diverse range of clinical environments including emergency medicine departments, various hospital wards, urgent care centres, maternity units, eye casualty, COVID-19 hubs and testing centres. Their responsibilities ranged from venepuncture, cannulation, and carrying out electrocardiograms, to helping prepare discharge summaries for patients. Many students considered themselves 'a spare pair of hands' for the teams they were based within. Less commonly and depending on the work environment, MSTs carried out specific tasks such as using equipment in the intensive care unit, log-rolling patients, performing ophthalmological assessments in eye casualty or suturing in emergency departments. No two posts were the same and daily activities varied widely. An entire day of venepuncture in an antibody testing facility was useful for refining venepuncture technique, but a role in a ward-based setting demanded a broader contribution to patient care. Many MSTs undertook important nursing and healthcare assistant activities such as patient observations or personal care. The position was designed with a clinical focus in mind, but a minority of students worked in non-clinical roles such as office-based work. Several MSTs also changed roles when different opportunities arose, or service requirements dictated this to be necessary. Shift patterns were generally variable, with many MSTs valuing flexibility in their work schedules.

The novel nature of the role meant many students found they had to use their own initiative to establish their place within different teams and find meaningful ways to contribute. This might be attributable to a job description that, in the circumstances, was left deliberately open. However, this was not necessarily a limitation as many students appreciated the need to adopt a more pro-active approach, which could have been beneficial in fostering their confidence and autonomy. These trailblazers have undoubtedly helped to better define the job role for the future.

THE BENEFITS OF BEING A MEDICAL STUDENT TECHNICIAN

Being an MST was more than just an extra source of income or an opportunity for students to legitimately leave the house during the months of lockdown. It has given medical students in QUB the unique experience of playing an active part in the pandemic healthcare workforce response. The sense of responsibility and belonging that resulted suggests that a more formal integration of medical students within the multi-disciplinary team could be a powerful way to develop future doctors' skills and professional identities.

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Immersion of medical students in clinical teams resulted in increased confidence, improved understanding of what will be expected from them as Foundation Programme doctors, improved situational awareness in clinical settings and even an appreciation of workplace etiquette and politics. These essential, non-practical skills are difficult to test and even harder to teach on medical school placements. In her book, "Your Life In My Hands"[8], Dr Rachel Clarke describes feeling wholly ill-equipped with some of these skills on her first night shift as a newly qualified doctor. Which team to call in a peri-arrest situation and knowledge of critical language used among healthcare staff could be considered more crucial for a newly qualified doctor than being able to list all the causes of acute pancreatitis*. It is difficult to acquire these skills without spending time embedded in a clinical team, something that was integral to the MST role. MSTs were afforded the opportunity to contribute to patient care and in so doing improved their relationships with staff and cemented their role as medical professionals. Healthcare colleagues could get to know the MSTs in a way not always possible with students on placements and it is possible that patients might look more favourably on busy MSTs than apparently 'loitering' medical students.

An important benefit of being an MST was, undeniably, the prospect of receiving a salary. Paid employment for medical students was not universal during the pandemic across the UK[9]. Nevertheless, in Northern Ireland, MST was a paid position which presented an alternative to jobs such as healthcare assistant or retail work. Aside from helping with the financial burden of being a student, remuneration allowed MSTs to be *learning while earning*. For some, it maintained clinical skills during time out of clinical training to undertake an intercalated degree, for others it provided a more fluid transition between fourth and fifth years of medical school and for a few it even replaced a cancelled elective.

Additionally, the benefits of employing medical students in place of agency staff is of possible economic interest to the NHS. Formally mobilising this relatively untapped resource could be one step towards addressing the intense pressure the healthcare system currently faces. However, we must be wary that employing MSTs is not seen as the only solution to workforce issues and ensure that no student feels obliged to participate in this voluntary role given the numerous personal factors that affect a student's choice to seek employment. Already having another job, having personal or family commitments or concerns regarding COVID-19 infection are just some reasons that might have influenced a student not to become an MST. In the interest of equal representation, it would be beneficial to gain further insight from these students.

REFLECTION AND FUTURE DEVELOPMENT OF THE MST ROLE

It is perhaps unsurprising, given the pace and circumstances under which these roles were developed that reflection and refinement at this stage will be prudent. As the roles were developed and launched within five independent Trusts, the organisational aspects including recruitment, payroll and training differed a great deal. With the variety of roles and clinical settings, the experiences of MSTs have been relatively heterogeneous, which, although giving rise to diverse learning opportunities, may have left some MSTs with unfilled expectations. Preparation, support and orientation is required on the part of MSTs and the employing Trusts to ensure the best experiences and outcomes for all involved. These observations should not undermine the huge potential that the development of the roles has brought about. As the dust settles, it will be crucial to reflect on the long-term value and sustainability of the MST roles.

Overall, from a student perspective, the arguments in favour of continuing MST employment are clear and abundant; anecdotally many MSTs were delighted to be paid to increase their confidence, knowledge and sense of professionalism whilst supporting a service under pressure. However, positive feedback from students is not enough evidence to advise replacing classical clinical placements with MST-like apprenticeships. The breadth of experiences within placements cannot be guaranteed in MST jobs and compared to placements, learning was ad hoc and fortuitous. Formal clinical placements involve prescribed learning objectives and in many clinical settings it would not be appropriate for a student to be seen as a worker rather than a learner. Nevertheless, the considerable growth in the MSTs' practical and interpersonal skills, and confidence in their identity as future doctors, is of great interest to medical educators and future medical students. Further exploration of how the MST format shapes clinical experiences and learning is necessary to formally assess the benefits, shortcomings and feasibility of such a scheme continuing.

CONCLUSION

The MST role was borne out of a challenging and uncertain time but given the very apparent value of MSTs to all involved parties, it is our hope that the position will be established further and made widely accessible to interested students. Nonetheless, benefits and drawbacks of the role must be further explored and weighed up against the logistical challenges such an offer would pose. Undeniably, these roles have provided useful experiential learning opportunities for students fortunate enough to be able to avail of them and in turn, a motivated and engaged workforce for the service. We propose, as an adjunct to traditional clinical placements, the MST role might better prepare future generations of doctors for the workplace challenges they will face.

** Idiopathic, Gallstones, Ethanol, Trauma, Steroids, Mumps/ Malignancy, Autoimmune, Scorpion bites, Hypercalcaemia/ Hypertriglyceridaemia, ERCP, Drugs*

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Letters

IMPACT OF THE COVID PANDEMIC ON RHEUMATOLOGY PATIENTS IN NORTHERN IRELAND - A WEB BASED CROSS-SECTIONAL SURVEY OF PATIENT REPORTED OUTCOMES

Editor,

Concern for the susceptibility of rheumatology patients to severe COVID-19 illness has been raised since the start of the pandemic. Rheumatic disease and their immunosuppressant therapies placed many patients into the 'clinically extremely vulnerable' group when the UK's shielding guidance commenced on 23 March 2020. The impact of DMARDs/glucocorticoids/biologics on COVID-19 remains under investigation[1]. A recent study suggested caution may be required with rituximab and sulfasalazine in COVID-19 patients [2].

The objective of our study was to evaluate the impact of the COVID-19 pandemic on rheumatology patients in Northern Ireland by assessing treatment, disease progression, shielding advice, access to primary & tertiary care, overall anxiety and incidence and severity of COVID-19 infection.

A web-based cross-sectional survey was completed in Northern Ireland between 23rd November 2020 and 22nd January 2021. The questionnaire included medication history, comorbidities, disease course, patient experience, shielding advice, COVID-19 illness, hospitalisation and effects on mental health. The survey was publicised by sending 6,032 Belfast Trust NHS patients a link via SMS and via NHS/Versus Arthritis social media platforms.

There were 2,615 responses and of these 2,539 had been completed and were suitable for analysis. The majority of respondents were aged 45+ (78.27%) and female (N=1819). Rheumatoid arthritis (41%) and psoriatic arthritis (29%) were the most common diagnoses. Just over one third (35.27%, N=896) of patients were on biological drugs. Most patients were taking methotrexate (28.04%) followed by hydroxychloroquine (15.20%) and adalimumab (12.52%). The majority (79.6%) continued treatment during the pandemic as recommended. There was evidence of disease 'flaring' in 30.75% of those patients who had stopped treatment. Of the respondents surveyed 7.8% (N=198), tested positive for Covid-19 and of these 77.55% reported that they had received adequate shielding advice. Less than one third of patients testing positive for COVID-19 had been treated with biological drugs (30.3%, N=60). Cardiovascular disease was the most prevalent comorbidity. Only 11.11% (N=22) of those who tested positive for Covid-19 required hospital admission and 2 patients required intensive care support. Both patients requiring ICU were not on immunosuppression. Of the 22 patients hospitalised with COVID-19, 13.64% (N=3) were on solitary sulphasalazine therapy, 13.64% (N = 3) were on solitary anti-TNF therapy, 18% (N = 4) were on methotrexate alone and one patient was on combination methotrexate and anti-TNF therapy. Anxiety and loneliness to varying levels was reported in the majority of patients.

The survey showed low levels of COVID-19 hospitalisation despite most patients continuing DMARD/biologic/glucocorticoid therapy. This has been replicated in other studies [1,2] however data continues to be gathered on the safety of some biologic drugs particularly rituximab [3]. Many patients expressed overwhelming anxiety and fear of mortality. This coupled with stringent restrictions and social isolation led to a detrimental effect on their well-being. Concern over the mental health of the rheumatology community within this pandemic has already been well recognised, and this current data highlights again the need for us as physicians to be proactive [4]. Our survey results also indicated high concordance with continuing prescribed treatments but highlighted the negative impact of interrupting treatment on disease control. Future data will inform our decision making regarding the safety of continuing with certain drugs [5].

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REVISITING PSYCHOLOGICAL AUTOPSY RESEARCH OF SUICIDE IN NORTHERN IRELAND

Editor,

A contemporary, scientific understanding of suicide is required to devise a meaningful prevention strategy in Northern Ireland. Psychological autopsy (PA) suicide studies comprise sensitive interviews with bereaved informants and clinicians (GPs, psychiatrists, etc), combined with meticulous scrutiny of records (coronial, healthcare, social care, etc).[1] For more than six decades these studies have contributed immensely to appreciation of the biopsychosocial complexity of suicide. The low incidence of suicide means that a case-control PA is the most pragmatic research design to identify risk/protective factors.

In the sole case-control PA study in Northern Ireland (suicides 1992-1993)[2] there was an estimated 38-fold increased risk of suicide linked to the presence of at least one current DSM-III-R[3] Axis I nemtal disorder (depressive disorders, primary non-affective psychoses, psychoactive substance use disorders). Other risk factors were: presence of at least one Axis II (personality) disorder; previous self-harm; mental health service contact ever, particularly current; current unemployment; manual social class; GP contact within 26 weeks; occurrence of at least one adverse life event during the previous 52, 26, 12 and 4 weeks, notably a "serious problem with close friend, neighbour or relative" (also "broke off a steady relationship", "problems with police or court appearance" and a "serious illness, injury or assault").[4] Axis I-Axis II comorbidity conferred a much higher risk compared with Axis I disorder(s) only. Exposure to civil disorder ("the Troubles") did not increase suicide risk. Higher religious commitment was protective against suicide.

Apart from the contributions of prevention, early diagnosis and effective treatment of mental disorders to suicide risk reduction, the Northern Ireland Suicide Study findings indicated that suicide prevention necessitated 1) high quality self-harm services; 2) minimisation/mitigation of unemployment; 3) public education/intervention regarding interpersonal problems; 4) recurrent suicide risk assessment/mitigation training for multidisciplinary practitioners within healthcare especially primary care, mental health services and general hospitals; and 5) recurrent suicide awareness/intervention training within the police service, the court service and the third sector. All of these remain relevant now.

The authors of a recent review of suicide in Northern Ireland recommended that suicide research/prevention should "focus on the transgenerational effect of the conflict ("the Troubles"), youth suicide, suicide prevention in minority groups, and the criminal justice context".[5] Northern Ireland needs another case-control PA suicide study soon. Study objectives may include: 1) updating the prevalence of mental disorders including comorbidity (noting temporal relationships) and disorder-specific suicide risk; 2) a more nuanced understanding of the suicidogenic impact of adversity including timing (distal/proximal, chronic, acute-on-chronic, anticipated) and dependence/independence of individual behaviour; 3) analysis of interactions between mental disorders and adversity; 4) scrutiny of the likely suicidogenic effect of physical illnesses (number, type, severity, chronicity, pain, disability, delay in diagnosis/treatment); 5) defining risk factors for different age groups; 6) measurement of suicide risk linked to social deprivation; 7) consideration of any suicide risk linked to the transgenerational legacy of "the Troubles"; 8) evidencing any suicidogenic impact of COVID-19; and 9) hypotheses regarding possible protective factors e.g. social connectedness, social support, educational attainment, religion/spirituality, engagement in sport, competent social problem-solving and willingness to seek help.

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A RARE CASE OF MULTILOCULAR PERITONEAL INCLUSION CYST IN A MALE PATIENT

Editor,

Multilocular peritoneal inclusion cysts (MPIC) are uncommon lesions, of which only around 20% of cases are reported in adult men. The mesothelial origin of MPICs was first demonstrated by electron microscopy in 1979, by Mennemeyer and Smith.[1] MPICs can occur anywhere along the peritoneal surface, arising from the peritoneal mesothelium, but are most frequently found in the pelvis as multiple, thin-walled, multi-locular cysts, that can form large intra-abdominal masses. [2,3] A 41-year old man presented as an emergency with a short history of pelvic pain and discomfort. He complained of bladder and rectal symptoms

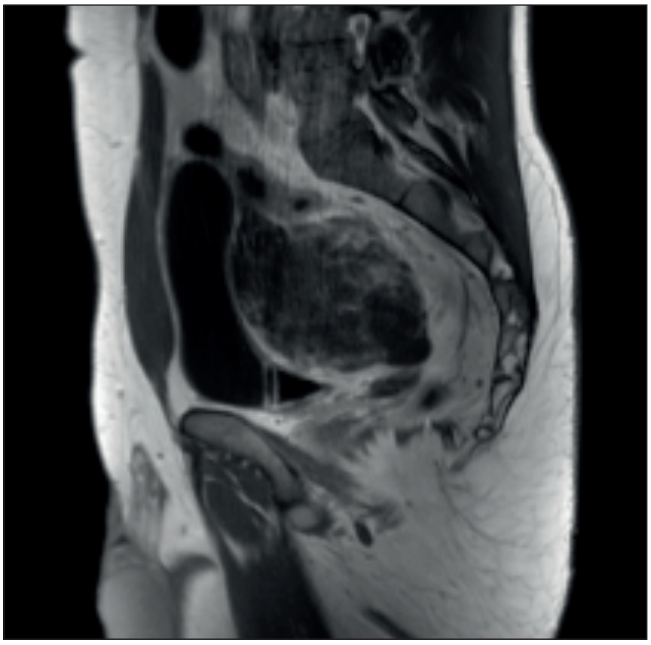

Figure 1 MRI Pelvis

including difficulty bladder voiding and marked tenesmus. The patient's past medical history includes Guillain-Barré syndrome secondary to CMV infection. CT and MRI scan showed a large mass between the rectum and bladder (Figure 1) measuring 8.6x8.5x8.5cm. A flexible sigmoidoscopy was performed and no mucosal abnormality was detected. Blood test and tumour markers (CA125, PSA, CEA, CA19-9 and AFP) were all within normal limits. At laparotomy, a large multi-cystic mass was situated between bladder and rectum. The mass appeared to arise from the mesentery of the sigmoid colon (Figure 2). Therefore, in addition to resection

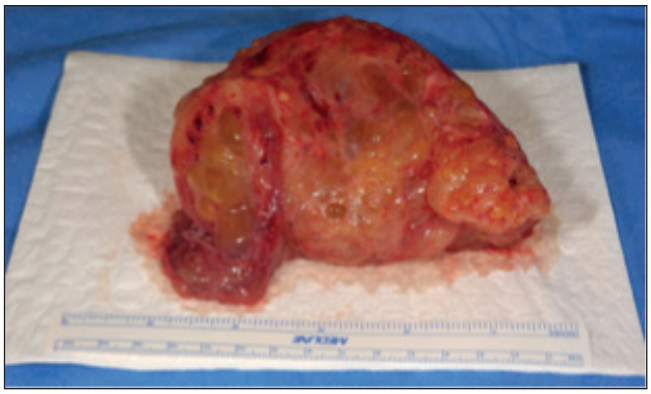

Figure 2 Dissected multi cystic mass

of the multi-cystic mass, a sigmoid colectomy with a primary anastomosis and an appendicectomy were performed. No other abnormality was detected in the rest of the colon, small bowel, stomach or gallbladder. Pathology showed a large multi-cystic mass measuring 112 x 87 x 47mm and weighing 290g. On sectioning, the mass consisted of numerous thin-walled cysts of varying size containing serous fluid. Histopathology showed a multilocular peritoneal inclusion cyst; each locule was lined by bland mesothelial cells and the septae contained fibrovascular connective tissue with

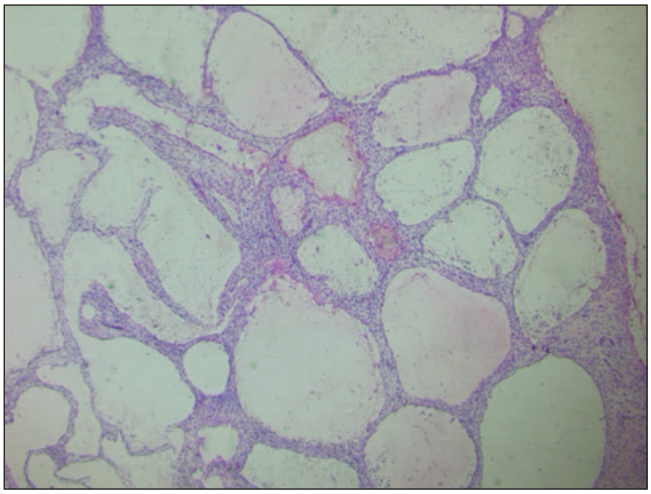

Figure 3
Numerous cysts lined by bland mesothelial cells with fibrovascular septa containing chronic inflammatory cells

a chronic scattered inflammatory cell infiltrate (Figure 3). There was no malignancy. Using immunohistochemistry, the cells lining the cysts were shown to express WT1 and CK5/6 in keeping with mesothelial lineage. Within the distal sigmoid colon specimen, there was a localised area of haemorrhage and a separate 12mm diameter nodule of multi-locular peritoneal inclusion cyst was present on the serosal surface. The appendix showed pinworm infestation but no evidence of dysplasia or invasive malignancy. The patient made a good post-operative recovery and was discharged home six days after surgery. The patient was reviewed 6-weeks after surgery and all symptoms had resolved. A repeat CT scan of his abdomen and pelvis, 6 months after surgery showed no recurrence. We plan for annual patient follow-up. MPIC are generally considered a benign reactive mesothelial proliferation developing secondary to endometriosis, trauma, inflammation or pelvic inflammatory disease (2,3). This patient cohort would suggest that MPIC is a reaction to chronic irritation stimuli with mesothelial cell entrapment, reactive proliferation and cystic formation. Some consider MPIC to be mesothelial neoplasms with the potential for malignant transformation. The uncertainty and debate surrounding these lesions is reflected by the limited evidence available.[3,4] MPIC has a high rate of local recurrence and surgical resection remains the mainstay of treatment to avoid local recurrence. [5] It is this infrequency, which makes its origin, pathogenesis, diagnosis and therapy challenging.

Consent Written informed consent was obtained from the patient for publication of this case report and any accompany images. A copy of the written consent is available for review from the journal's Editor-in- Chief.

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MY MEMOIRS OF THE ROYAL VICTORIA HOSPITAL PACEMAKER IMPLANTATIONS IN THE WEST WING OVER HALF A CENTURY AGO!

Editor,

In 1964 I became a Senior House Officer in Dr. Pantridge's Wards 5 & 6 at the Royal Victoria Hospital, Belfast. In the course of my many duties, I became interested in Pacemaker Implantation, which was becoming increasingly employed in the management of patients affected by atrio-ventricular block and other cardiac abnormalities.

During this time (and until 1987) I had access to the Radiology facilities in the R.V.H. 'West Wing', which was known as the 'ACG Theatre'. This clinical theatre was situated near the far end of the 'West Wing' corridor, adjoining the main R.V.H. Corridor.

This sterile room housed equipment required for electrocardiographic monitoring of the patients, in addition to the radiology equipment, which was expertly operated by a full-time radiographer – Tom Littler, who hailed from the North of England and performed his work with military precision. There was also the large DC Defibrillator (Oh for one of today's portable machines!)

Having access to this Facility enabled me, with the assistance of a trained R.V.H. nurse, to introduce and position the pacing electrodes with high precision. During the Sixties I implanted the first cardiac pacemaker in Northern Ireland (Ulster Medical Journal, Volume 59 No. 2, pp. 131-136, October 1990.) This procedure entailed proximal fluoroscopic venous canulation, employing a suitable accessible subclavian or supraclavicular vein, with shaping of the proximal portion of the electrode to facilitate conduction along the course of the vessel.

The patients who were scheduled for pacemaker implantation were admitted to the Cardiology Unit on the previous day. The male patients were prepped by having their chests shaved, and were prescribed mild sedation on the evening before. The procedure was explained to the patient and the consent form was signed. Nil by mouth was permitted from midnight. I did not require the assistance of an anaesthetist but instead I prescribed heavy sedation prior to the implantation. After the procedure the patient was wheeled on a trolley and returned to the Cardiology Unit.

During the mid-1960s I did not have the option of continuous monitoring equipment, but the patient's vital observations were monitored and charted. ECG Recordings were made frequently during the first twenty-four hours. An ECG Technician pushing a mobile cart containing a large ECG Machine with print-out capability was employed during this period. After a few days in hospital - and provided the patient's condition was stable, the patient would be discharged with a letter for his/her doctor and a follow-up appointment.

The patients fitted with these early Pacemakers had to have them replaced every two years because of limited battery longevity.

In the early 1970s, however, the pacemakers themselves were lighter in weight and smaller, and - very importantly - were fitted with rechargeable batteries. This new development was a great boon for the patients. Moreover, the rapid technological developments that permitted them to experience such a convenience certainly underlined the point that this was, indeed, a noteworthy era in Medicine.

The above Memoirs are my recollections of Pacemaker Implantation performed in the ACG Theatre, West Wing, Royal Victoria Hospital, Belfast over Half a Century ago.

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SINGLE CENTRE OUTCOMES OF ENDOSCOPIC FULL THICKNESS RESECTION (EFTR) OF COLORECTAL LESIONS USING THE FULL THICKNESS RESECTION DEVICE (FTRD)

Editor,

We write to you to with the results of our Endoscopic Full

Thickness Resections (EFTR) with the Full Thickness Resection Device (FTRD) at the Ulster Hospital. The detection and removal of colorectal polyps is a fundamental part of colonoscopy and reducing the rates of colorectal cancer. A number of endoscopic techniques exist to aid their removal, including snare polypectomy, endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). These methods are well established; however concerns have been raised at both the piecemeal fashion of removal, typically associated with EMR and the high perforation rate (up to 20%) with ESD.[1,2] Piecemeal excision can lead to a recurrence of greater than 20%.[2] Additionally, non-lifting lesions may not be amenable to EMR or ESD. T1 cancers are often co-incidentally found after endoscopic resection of a non-suspicious polyp. There is controversy over the further management of early T1 cancers with current guidelines recommending endoscopic treatment for those with low-risk histological features.[3] EFTR with the FTRD (Ovesco, Tubingen, Germany) was introduced into clinical practice in 2014. It offers additional therapeutic and diagnostic options, further aiding exact risk stratification and decision making for these early lesions. A large study by Kuellmer et al of 156 patients, specifically focusing on EFTR for adenocarcinomas was recently published.[4] Their R0 resection rate was 71.8% with an adverse event rate of 14.1%. The key finding of this study was the ability to discriminate between high and low-risk tumours and the avoidance of surgery in those deemed low risk.

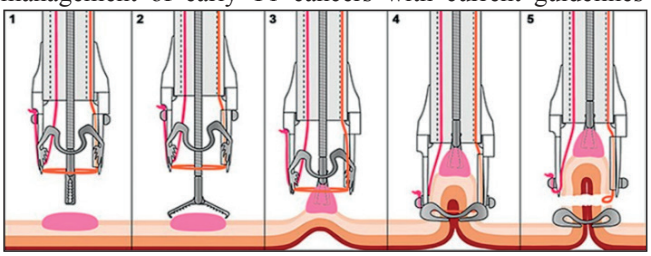

Figure 1
Illustration of the FTRD (www.ovesco.com) (1) and (2) the lesion is marked and grasping forceps are advanced through the working channel of the endoscope to grasp the lesion, (3) the lesion is pulled into the cap to incorporate a double full-thickness layer of colonic wall, (4) once the lateral margins of the lesion are pulled into the cap, the OTSC is deployed, (5) the pseudo polyp created by the OTSC is excised with a preloaded snare whilst the OTSC secures patency of the bowel wall.

Between June 2018 and September 2019, 12 EFTR were performed using the FTRD. All procedures were performed jointly by a consultant gastroenterologist and consultant colorectal surgeon who had received formal training with the FTRD. Procedures were performed under sedation and all patients were discharged the same day following a period of observation. Lesions were removed with the FTRD following the standardised method (Fig. 1).3 Follow-up was determined according to the histological findings, but generally repeat endoscopy was performed at 2 months.

Table 1: Resection site characteristics
Location

Location	Number	Size (range mm)
Caecum	1/12	20
Ascending colon	1/12	40
Transverse colon	1/12	40
Descending/left colon	1/12	25
Rectosigmoid colon	2/12	15-40
Rectum	6/12	6-40

Table 2: Adenocarcinoma characteristics

Site	T stage	SM level	Size (mm)	R status	Adverse Features	Previous attempts at resection
Rectum	1	2	33	0	Venous invasion	No
Rectum	1	2	18	0	Poorly differentiated	Piecemeal polypectomy
Rectum	1	2	25	1	Nil	No
Rectum	1	2	33	0	Nil	No
Rectum*	2	N/A	40	1	Nil	No
Rectum	1	2	15	0	Nil	Polypectomy

*Hybrid approach- Due to size of lesion, a piecemeal resection of the peripheral polyp was performed firstly followed by EFTR reducing the size from 40mm to 24mm.

Histology

Adenocarcinoma	6/12
Tubulovillous adenoma with low grade dysplasia	2/12
Tubulovillous adenoma with high grade dysplasia	1/12
Tubular adenoma with low grade dysplasia	2/12
Neuroendocrine tumour	1/12

The mean age was 70 and the median size of the lesion was 26mm (range 6- 40mm). Resection site characteristics and histology post EFTR are detailed in table 1. No patients suffered a post-procedural complication including perforation or bleeding. For the adenocarcinomas, 33% (2/6) had a R1 resection and went onto have subsequent surgery (table 2). One patient had no residual tumour, the other had no residual tumour however there was lymph node involvement. At the time of publication, no benign or malignant polyp recurrence had been identified at follow-up endoscopy.

The findings of both our data and larger studies is that, whilst EFTR looks promising, it needs to be approached with caution and longer follow-up data is required, particularly for pT1 adenocarcinomas. Its role can be developed for those patients not fit for surgical resection as was the case for a number of patients in our study. It is important to remember that surgery remains the gold standard treatment for invasive colorectal cancer.

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by Dr David Sweet, Consultant Neonatologist at the Royal Jubilee Maternity Hospital