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Ulster Med J 2022;**91(3):**121-122

Editorial

A secular age

Michael Trimble

One of my duties within the university is teaching on the year 1 medical ethics course. This has become more challenging in recent years. In the ethics tutorials it has become increasingly apparent that the basic presuppositions held by the students have undergone a paradigm shift. Not so long ago, when considering contested topics such as abortion or the right to euthanasia, there was tension and argument but at least the terms of the debate were agreed. Gradually, the balance has shifted, with increasing numbers of students favouring unrestricted access to abortion and many supporting the right of patients to access medically supervised euthanasia. However, not only have the conclusions changed but so have the underlying patterns of thought.

Traditional ethics in Western Medicine owes much of its heritage to Classical Greek thought,[1] from Aristotle's Nicomachean ethics,[2] to the Hippocratic Corpus, not least the famous Oath. However, as philosopher Luc Ferry notes, a radical new element was to be introduced into the Western mindset with the advent of Christianity and its concern for the individual. [3] Historian Tom Holland goes further and suggests that so much of what we now take for granted as part of a modern liberal worldview actually has its roots in Christian thought and practice.[4] However, the world is changing and, as philosopher Charles Taylor reminds us, we now live in a secular age. In his 800 page *magnum opus*, he attempts to answer the question

> Why was it virtually impossible not to believe in God in, say 1500 in our Western society, while in 2000 many of us find this not only easy, but even inescapable? [5]

That we live in a secular age has profound implications for ethics. Henry David Aiken describes our approach to ethical issues as occurring on one of four levels: At the most superficial is our emotive response, that is our gut reaction, the "boo" or "hurrah" that comes without thought or reflection. A more considered response concerns the rules as applied to the situation at hand. Sometimes the rules may not apply or may even conflict; sometimes the rules are called into question and, at such times we need to consider the principles that underlie the rules. Finally, at the most fundamental level there are our basic convictions. [6] It is at this most basic level that the impact of the secular is felt. Medical ethicist Tristram Engelhardt analyses the effects of the loss of the Christian consensus. [7] In particular, he notes that issues such as abortion and euthanasia are often now no longer viewed in terms of morality and are rather seen as lifestyle choices and therefore a wholly personal matter. Indeed, the immorality is held to be in questioning such choices. Value judgements are replaced by individual feelings. Regular readers will have noted my fondness for the writings of CS Lewis. In his short book the *Abolition of Man*, Lewis predicts this development and notes that when ultimate values are no longer recognized it is a perilous situation for humanity.[8] Lewis highlights what he terms the Tao - his term for *natural law*. He notes the common features of ethical systems through the ages and across the world. Lewis does not deny that there are differences between moral systems and in another of his popular works he notes that

> The moment you say that one set of moral ideas can be better than another, you are, in fact, measuring them both by a standard, saying that one of them conforms to that standard more nearly than the other. But the standard that measures two things is something different from either. You are, in fact, comparing them both with some Real Morality, admitting that there is such a thing as a real Right, independent of what people think, and that some people's ideas get nearer to that real Right than others. Or put it this way. If your moral ideas can be truer, and those of the Nazis less true, there must be something – some Real Morality – for them to be true about. [9]

The mention of Nazi morality in the above quote links to a disturbing example of Lewis's thesis from the *Abolition of Man*. I was recently taking a session on an elective course on the history of medicine for year 1 medical students. My topic was medicine in the Nazi era. Many physicians were members of the Nazi party and the involvement of physicians in wartime atrocities is well documented. [10] As part of the discussion following the presentation, I asked the students if they thought the Nazi physicians were evil or mistaken. The conversation took an unexpected turn as the majority of students felt that evil was not a valid concept in these circumstances.

It is part of the teacher's job to encourage students to ask the right questions and in doing so help them to seek the truth. I realize more than ever the need for ethical and professional development. Education, particularly medical education must be less about imparting information and more about character formation. This must occur not just in the taught class but in the everyday practices in the surgery, in the clinic, and on the wards. Teaching has been described as a subversive activity[11] with the culture of the classroom teaching as much if not more than the curricular content. The day to day life of our teams and units provide a daily opportunity to for all of us to assist in the professional and moral formation of our students and trainees. James KA

Smith describes our day to day routines as cultural liturgies [12] and, just as religious liturgy shapes the life of the believer, even such secular liturgies impact the mind and behaviour of these who practise them. To return to where we began with Aristotle, these cultural liturgies form in us the ideal of the good life to which we aspire. When students see us in our work environment, what is the ideal we represent? To what do we aspire, for ourselves, for them and for our patients?

ENDNOTES

1. MacIntyre A. A short history of ethics: a history of moral philosophy from the Homeric age to the 20th century. London: Routledge; 2002.
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Editor's business

Student and trainee roles

Looking to the future of the journal, I am delighted to welcome Drs Hannah O'Hara, Jonathan Winter, and Jake Clements on to the team. They will be helping update the journal's social media presence and developing visual abstracts and new material aimed at increasing the journal's relevance for students. This issue includes prize-winning abstracts and posters from the QUB Scrubs academic conference.

Forthcoming vacancy

I plan to step down as editor following the publication of the January 2023 issue. If anyone is interested in taking up the reins, they can contact me by email at editor@ums.ac.uk .

For further information, I would suggest reading my predecessor's article, So you want to be UMJ editor (Ulster Med J 2019;88(3):141-142) which is available on the UMJ webpage https://www.ums.ac.uk/umj088/088(3)141.pdf.

Ulster Medical Society Lecture Programme 2022-2023

Professor Nigel Hart

Professor Nigel Hart first graduated in 1990 from Queen's University Belfast (QUB) with a degree in Computer Science. He worked in the IT industry for several years working in the UK, Japan, Switzerland and North America. He had a change of direction and was enrolled to study medicine at QUB in 1994, graduating in 1999. He completed his JHO year in the Belfast City and Royal Victoria Hospitals. He commenced GP training in 2000, enrolling in the GP Academic Research Training Scheme (GPARTS) and subsequently completed an MD in Stroke Risk Factors. He became a GP partner in a rural Practice in 2007 and was appointed to the position of Senior Lecturer (part-time) at the School of Medicine at QUB later that year. In 2015 he moved to a full joint appointment in the Centre for Medical Education in the School of Medicine where in 2016 he was appointed as Associate Director for General Practice and Primary Care to lead expansion of General Practice within the undergraduate curriculum. He has been in leadership roles in undergraduate education, GP Training, clinical research and quality improvement. He currently leads the GPARTS programme and is co-lead for the Primary Care group of the Northern Ireland Clinical Research Network.

UMS Lecture/Meeting Dates

Date	Lecture	Speaker & Subject	Venue	Time
Thurs 6th Oct	Presidential Address	**Professor Nigel Hart** ***Professor of General Practice and Primary Care, QUB*** "The remarkable potential of Primary Care"	*North Lecture Theatre Medical Biology Centre QUB	Lecture 8pm
Thurs 20th Oct	Sir Thomas and Lady Edith Dixon Lecture	**Professor Brian Dolan OBE** ***Director of Health Service 360/Hon. Professor of Leadership in Healthcare*** "Dear Deconditioning: Recognising and addressing the other pandemic"	*Lecture Theatre Trust HQ Ulster Hospital	8pm
Thurs 10th Nov	UMS/QUB/NIMDTA Joint Meeting	**Trainee Research Day** **Guest Speaker Professor Phil Evans** **NIHR CRN Deputy Medical Director & National Specialty Lead for Primary Care**	Online Virtual	9am to 12.30pm
Thurs 10th Nov	UMS	**Dr Austin O'Carroll** ***HSE Clinical Lead for Dublin Covid Homeless Response and Founder of Safetynet*** "Making sense of street chaos: access to healthcare for people experiencing homelessness"	*South Lecture Theatre Medical Biology Centre QUB	8pm
Thurs 17th Nov	UMS	**Ms Marie-Louise Connolly** ***BBC NI Health Correspondent*** "Reporting on health with fairness and impartiality - my role as BBC NI's health correspondent"	*BCH Postgrad Centre	8pm
Thurs 1st Dec	UMS	**Dr Sarah Burke** ***Assistant Professor of Health Policy, TCD*** "Reflections on health reform in Ireland (Sláintecare): through a health policy and health systems' lens"	*Lecture Theatre Craigavon Area Hospital	8pm
Thurs 15th Dec	UMS/DoH/QUB Joint Meeting	**Professor Sir Michael McBride, Professor Sir Chris Whitty, Professor Sir Gregor Smith, Sir Frank Atherton** ***Chief Medical Officers*** "In conversation with the four Chief Medical Officer's: Reflections on a Pandemic"	QUB	Refreshments 7pm Lecture 7.30pm
Thurs 12th Jan	Joint Meeting with Ulster Obs & Gynae Society	**Professor David McCance** **Consultant Physician and Honorary Professor of Endocrinology** "Diabetes in pregnancy"	*BCH Postgrad Centre	8pm
Thurs 26th Jan	UMS: The Robert Campbell Oration	**Professor Susan Smith** ***Professor of General Practice, TCD*** "Practice-embedded research will ensure evidence-informed primary care delivery"	*BCH Postgrad Centre	8pm
Thurs 9th Feb	The Desmond Whyte Lecture	**Dr Helen Bevan** ***Strategic Adviser, NHS Horizons*** "The healthcare system of the future: how do we get better at getting better?"	*Centre of Medical & Dental Education & Training, Altnagelvin Area Hospital	Buffet 6pm Lecture 7pm
Thurs 23rd Feb	The Gary Love Lecture Joint meeting with Ulster Society for History of Medicine	**Professor Emeritus Alun Evans** ***QUB*** "The UMS: From an Old Museum to a New Institute"	*BCH Postgrad Centre	8pm
Thurs 9th Mar	UMS	**Dr Davog McCaffrey** ***F1 and Former President QUB GP Society*** "Remembering your why… - putting the spark back into your medical career" **Dr Niamh Woods** ***Leadership Fellow UK Foundation Programme*** "Who's still willing to fight for a national health service?"	*Med Ed Centre Bretten Hall Antrim Area Hospital	8pm
Thurs 23rd Mar	Joint meeting UMS with BCH	**Dr Jonny Acheson** ***Emergency Medicine Consultant, Parkinson's Advocate, Artist*** "Drawing on my experience of Parkinson's Disease"	*BCH Postgrad Centre	Buffet 7pm Lecture 8pm
Fri 21st Apr	UMS	**Annual Dinner**	The Great Hall QUB	7.30pm
Thurs 4th May	UMS	**AGM**	UMS Rooms	5pm

All lectures can be booked via Eventbrite for in-person or *streamed at https://www.eventbrite.com/cc/ulster-medical-society-lectures-1108089 or by emailing administrator@ums.ac.uk

Ulster Med J 2022;**91(3):**124-129

Presidential Address

A history of cancer and its treatment

Presidential Address to the Ulster Medical Society. 7th October 2021

Many people know me as a Clinical Oncologist, whereas I see myself as a cyclist on a 35-year detour into Oncology. The picture shows me in Roncevalles, on the border between France and Spain and the signpost shows my destination, Santiago de Compostela, 800 kilometres away. When I joined Oncology, I felt like I was setting off on a similar lengthy pilgrimage to change the world.

Figure 1.
The author at Roncevalles, Spain,
on a cycle to Santiago de Compostela

Identifying the first recorded case of cancer is a challenge, as the diagnosis was vexing in ancient times. Atossa, around 520 BC, was a Persian queen who developed a "tumour" in her breast. It discharged and expanded within the breast. Democedes was a captive Greek slave in her royal household, and a renowned healer. He offered her a cure for her problem if she would grant him whatever he requested. She agreed, and he got to work with poultices and balms. The "cancer" resolved. As agreed, he made his request, that she ask her husband, king Darius, to invade Greece. Darius agreed, and Democedes volunteered for the advance scouting party. On reaching the Greek border, Democedes skipped across and was home and free. All were happy, but I have doubts. The discharging and enlarging lesion could have been a bacterial or tuberculous abscess, and not a cancer[1]. This lack of histological proof bedevils the early accounts.

The evidence from mummies in ancient Egypt, spanning the three millennia BCE, is more definitive. Mummies were desiccated and their visceral organs removed and replaced by linen, so metastatic lesions in bone are diagnosed based on lytic and sclerotic bone lesions on imaging, with missing soft tissue primary tumours. Many mummies have had CT scans, with a small number of bone lesions found. This is not surprising, given that their age at death was around forty years. In a reconstructed lumbar spine CT scan, there were distinctive sclerotic bony lesions[2] and my colleagues specialising in prostate cancer would readily call this as metastatic prostate cancer. The Daily Mail newspaper in 2011 labelled this as the "earliest case of prostate cancer in the world".

The aetiology of cancer has been a topic for philosophical and scientific debate. In early times the causes were conjectural. Hippocrates, a Greek physician around 400 BCE, described the body as containing four fluids (humours) which were blood, phlegm, yellow bile and black bile. He associated an excess of black bile (so-called melancholy) with cancer. He was very influential, and his theory predominated until about the 11th century[3]. Virchow was an astute pathologist and in the 1840's he made fundamental observations on cancer cells[4]. These were new insights. He described them as autonomous cells derived from previous cells. He suggested that cancer cells resembled cells in the tissue from which they arose; for example, breast cancer cells resembled a normal breast cell. This became widely accepted by the start of the 20th century.

The next insight was the discovery of DNA by Watson and Crick[5]. I was a medical student in 1975, only 20 years after DNA was discovered, and DNA division and base pairs were "cutting-edge" new science, The modern understanding that cancer is a disease of DNA, and that DNA mutations lead to loss of control of cell proliferation, was in its infancy.

Why has cancer become so common? Firstly, in the 20th century, fatal infections began to wane, due to public health measures. Typhoid disappeared and tuberculosis declined. In the 1940's antibiotics arrived, treating many previously fatal infections. However, as well as fewer deaths from infection, there were many more cases of cancer. The UK data presented by Cancer Research UK have shown that cancer incidence of cancer rises dramatically with increasing age, being at least 5 times more likely for people in their eighties compared to those in their forties, as illustrated in the figure. Data on life expectancy over the centuries are interesting. Before 1850, life expectancy was stubbornly around 35 years, but in the last century it has increased dramatically, now reaching into the 80's. Before the mid-19th century, there were virtually

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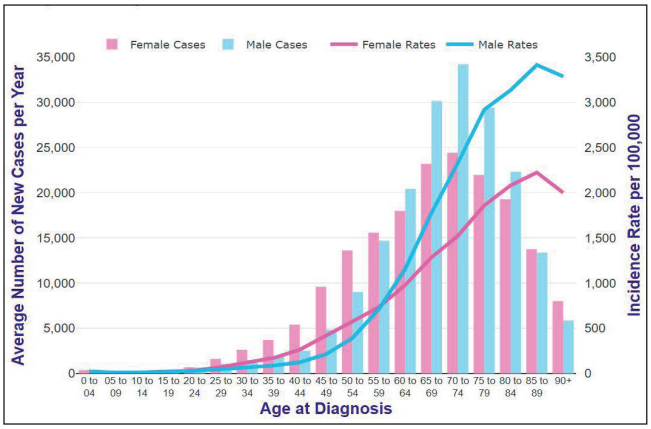

Figure 2.
Cancer cases and incidence by age in the United Kingdom. Credit: Cancer Research UK. https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/age#ref [August] [2022]

no middle aged or elderly people around to get cancer, and therefore cancer was quite rare. As the elderly population increases, cancer is more common, and this upward trend will continue.

What is the role of environmental factors? I suggest that this follows a pattern. A factor is identified, its impact is mitigated, and after a lag period, related cancer cases decline. For example, Sir Percival Pott identified the first occupational cancer. He associated scrotal cancers with young boys working as chimney sweeps. Soot was a chronic irritant and its presence in the scrotal skin caused these rare, but often fatal, cancers. The public outcry over this led to massive improvement in working conditions for the boys, although many more actually died when smothered in soot falls in the chimneys. Public opinion responds to drama more than simple numbers!

Doll & Bradford Hill reported in 1964 that doctors who smoked were more likely to get lung cancers[6]. Despite this revelation, smoking remained very prevalent, due in part to the suppression of evidence by tobacco companies. Eventually the message has emerged, leading to fewer smokers who each smoke less. Lung cancer incidence is now declining, after the expected time lag.

A key environmental factor in Belfast was asbestos, widely used in ship building and engineering. Asbestos is a light irritant fibre which enters the airways and lodges deep in the alveoli. It causes asbestosis, pleural plaques, lung cancer and mesothelioma with a latency of up to 40 years[7]. The fascinating aspect here is the timeline. The first compensation case was settled in the 1920's. Industry research quantified the issues in the 1930's, medical research came in the 1960's and then big settlements in the 1970's. Only then was asbestos banned, but cases are still arising. Of note, the most common cancer due to asbestos is lung cancer, not mesothelioma, because combined exposure leads to a dramatic increase in lung cancer risk.

Currently obesity is the key reversible factor. It is a chronic pro-inflammatory condition, and cancer incidence is around 30% higher in obese people (BMI > 30 kg/m^2). Its association with endometrial cancer was long known, but recent studies have shown that incidence of oesophageal or kidney is doubled, breast and colon cancer are 30% more common, and with lesser increases for other sites. As obesity is becoming more prevalent, it will cause more cancer[8].

Cancer treatment has evolved remarkably. The early surgeons had no anaesthesia, so surgery was barbaric, with patient tolerability the limitation of this approach. Surgery in that era caused horrific morbidity and little benefit. Therefore, in this era most treatment came from Physicians. They diagnosed, purged, bled and poisoned, to treat the mythical black bile. In summary they were no more effective, but perhaps caused less harm.

The arrival of anaesthesia in the late 19th century, followed by antiseptics, heralded more effective cancer surgery. Halstead, an American Surgeon, tackled breast cancer and, at the end of the 19th century, he developed "Halstead's radical mastectomy". This extended from full mastectomy, to include pectoralis minor, then pectoralis major, and regional lymph nodes. Despite considerable functional and cosmetic issues, it controlled disease, and was widely adopted[9]. Less extensive surgery eventually became feasible, when accompanied by adjuvant radiation or chemotherapy. Uptake of the non-surgical approaches was slow, but by the 1990's this became accepted as best practice. Surgery cures more cases, radiation therapy comes next, and chemotherapy is catching up quickly. The role of surgery will diminish even more in future.

Cancers of breast and prostate are usually sensitive to hormone manipulation. This was achieved surgically in the past by oophorectomy and by orchidectomy. George Beatson, a Scottish surgeon, was a pioneer, reporting a clinical trial, in which three women with advanced progressive breast cancer had oophorectomy: one was cured and two got excellent remissions of limited duration[10]. The treatment was therefore effective, even with the limited numbers. I doubt that modern therapies would get approval from this scale of trial, no matter how effective!

In his laboratory in Wurzburg, Germany in 1895, Roentgen noticed an extraordinary glow around a cathode ray tube, which he named "X-rays"[11]. These "ionising" radiations caused DNA damage, impacting on cell division. Their value was recognised promptly, and, within a year, X-rays were used to treat cancer. In 1902, Marie Curie and her husband Pierre isolated radium, which was a radioactive element. By 1906 radium needles were used to treat cancer. Sadly, there was no awareness of the risks, and no radiation protection. This caused the death of many radiation pioneers from diseases relating to over-exposure. Marie Curie died of radiation-induced aplastic anaemia and there is a memorial in Hamburg to 159 radiation martyrs.

Radiotherapy developed quickly in the decades following

the discovery of X-rays. The radiation energy was low (up to 300kV), with poor penetration and quality control. This meant some cures but left many patients with severe side effects. In the 1960's machines using Cobalt-60 as a radiation source became available. Beam energy was equivalent to 1.25 MV, which was 5-10 times more penetrating. When I joined Oncology, Cobalt machines were still common, but we had our first linear accelerator with beam energy of 6MV. Energies are now up to 15MV, with electronic refinements. Computer beam distribution planning came next, first 2D, then 3D and now even 4D, accounting for respiratory motion during the exposure. When I started at Belvoir Park Hospital, the computer could plan only a single CT slice, taking several hours. Now we plan on hundreds of slices, with multiple beams, almost instantaneously. Modern Linear Accelerators (Linacs) use highly modulated beams and giving precisely targeted volumes, with minimal dose outside the target areas. They perform CT scans during treatment, and soon they will deliver MR scanning during treatment. Images from CT, MRI and CTPET can be fused, to improve target definition. Radiotherapy is now more effective and much safer, and it is now expected to cure many cancers. Radiotherapy after surgery improves outcome most obviously in breast and rectal cancers, but also in many other cancers. It can also be combined with chemotherapy, and soon immunotherapy, to enhance cure rates. Stereotactic ablative body radiotherapy (SABR) is very precise localised radiation therapy, which can cure small early lung cancers. SABR practitioners are confident that it will displace surgery in this setting[12].

Systemic therapy, including chemotherapy, are treatments, usually given orally or intravenously, which circulate throughout the body and attack the tumour cells, wherever they are. The original chemotherapy agents were cellular poisons, targeting the phases of the cell cycle in the dividing cell. This targeted the most rapidly dividing cells, of which cancer had the highest proliferation rate. Bone marrow and mucosal cells were at risk, so neutropenia, infection, mucositis and diarrhoea were very common side effects. Chemotherapy was first used in acute leukaemia, with aminopterin producing dramatic responses but relapse followed in a few months. The regimens were refined, adding other drugs. Chemotherapy started to show cures in leukaemia and lymphoma over the next few decades, but progress was poorer against solid tumours.

Chemotherapy made modest progress in the 1960's, but in 1971 President Richard Nixon, as a distraction from the Vietnam war, promoted his National Cancer Act. It funded a major research drive to "win the war on cancer". It brought a sizeable boost to cancer research and clinical trials activity. Progress was still slow and the only solid tumour showing early promise was testicular cancer in the 1970's. In other tumours many physicians viewed it as futile and toxic.

As a medical student in Trinity College, Dublin, in the late 1970's, my base hospital was Mercers Hospital, near St. Stephens Green. Doctor Peter Daly, a Medical Oncologist joined the staff. He was a man of dynamic style and character, newly returned from training in the United States. He introduced chemotherapy, to mixed reviews! I remember a ward round with him. The style was impressive, Matron, staff nurses, and the complete medical team from registrar to intimidated medical students. An elderly man was looking wan after chemotherapy for metastatic stomach cancer. He reported nausea and a cough. On sitting forward for chest examination, he retched and brought up his entire stomach contents, over the leg of Peter's sharp suit and shiny leather shoes. Chaos ensued, and an unsympathetic Matron sniffed "Serves you right for giving him that poison!".

Oncologists started to report some success. Larry Einhorn published a trial in 1977 on 50 patients with advanced testicular cancer[13]. Patients received cisplatin in a 3-drug chemotherapy combination and nearly all were cured (75% with chemo alone and a further 20% converted to complete response by surgery). I saw this paper as a medical student, and it really enthused me that chemotherapy and oncology were the future.

As a Consultant, I had a special interest in testicular tumours, and I can give an illustrative example. A teenager had fatigue and a cough for two weeks, His chest X-ray (on the left) shows myriad rounded masses, confirmed as metastases from testicular choriocarcinoma with greatly raised levels of beta-human chorionic gonadotrophin (βHCG) at over 100,000 IU/L (reference range 0-4). He received 4 cycles of platinum-based chemotherapy, with virtually resolution of the lesions, as shown on the X-ray on the right. He remains well 15 years later.

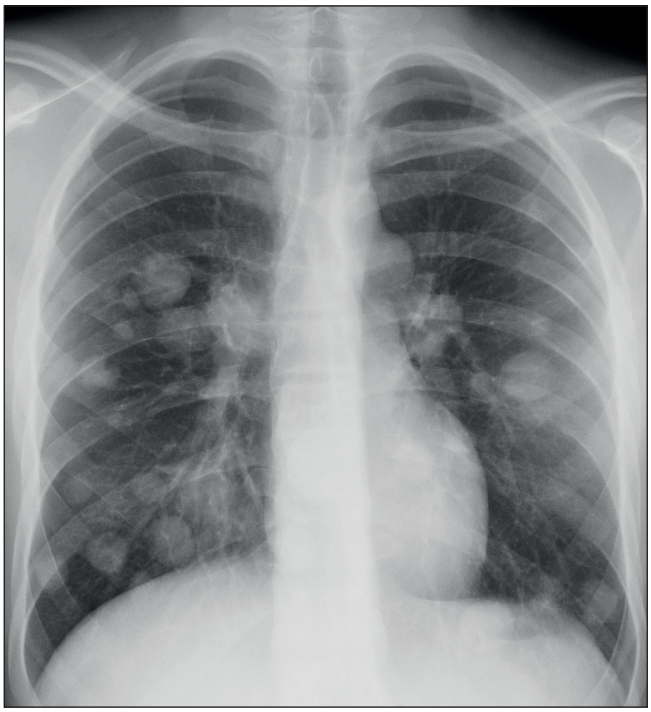

Figure 3a
Chest X-rays of a young man with advanced choriocarcinoma of testis. (a) at presentation, and (b) after 4 cycles of chemotherapy. The patient has granted permission for publication of these anonymised images.

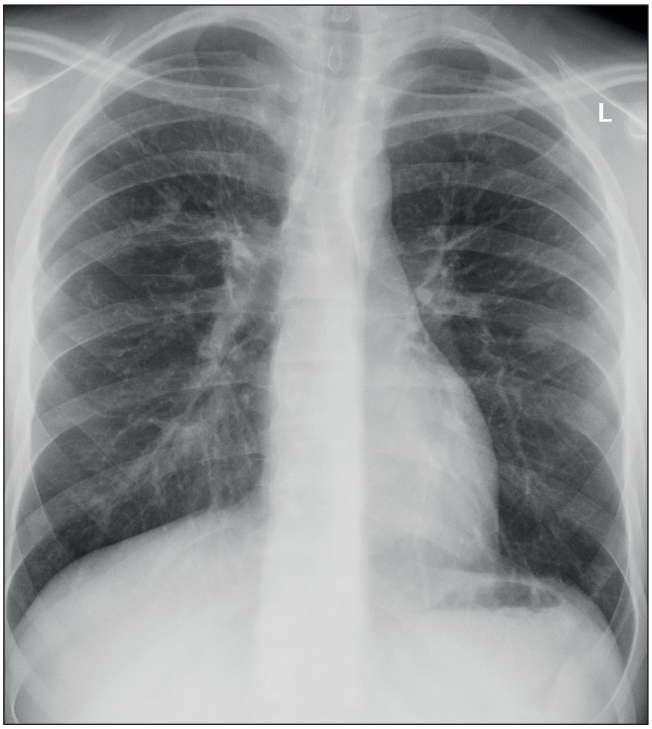

Figure 3b

Nowadays, chemotherapy has been refined and contributes to cure in many rapidly growing tumours. It can be combined with radiation for cure, it can improve the cure rate of surgery and can effectively palliate advanced cancer from many sites. Therapeutic index is still an issue, as chemotherapy is a poison. Therefore, research focus has moved on to finding cancer-specific targets and pathways in the cells. Cancer cells often have receptors on the cell membrane or nucleus which can be targeted, or they have mutations causing activation of enzyme pathways influencing cell proliferation and growth. Examples included the EGFR mutations in lung cancer and HER2 receptors in breast cancer. The key principle is that the target is vital to the cancer cell, but is not present, or unimportant, in normal cells, giving a huge advantage to targeting it.

The HER2 receptor is on the breast cancer cell membrane in 20% of breast cancers. These HER2-positive tumours had a poor prognosis, having 50% shorter median survival for HER2- positive metastatic tumours. Trastuzumab (Herceptin) is a monoclonal antibody against the HER2 receptor, and it showed moderate activity in metastatic disease, improving response rates and survival, but not achieving cures. To test its value in early breast cancer, three large adjuvant trials, aiming to recruit 12,000 patients, were opened. Recruitment was rapid, including around 50 volunteers from Belfast, to whom we are very grateful. Patients received standard care of surgery, chemotherapy and radiation, and were then randomised to placebo or Herceptin treatment for 1 – 2 years.

I was at the annual meeting of the American Society of Clinical Oncology in Chicago in 2005 when the results of all three trials were released in a plenary session[14]. A massive lecture hall, packed with 5,000 Oncologists, heard the incredibly positive results (relapse rates halved and a 9% improvement in survival with Herceptin). The largely American audience were very excited, culminating in a standing ovation. When the session ended, there was rush to the phones to spread the news, and no doubt order Herceptin for their patients. The UK processes prevented us from using the drug for another year. Of note, one-year course of Herceptin cost about £30K per patient, or £3M for the cohort of 100 eligible patients. Our annual chemotherapy drug budget for Northern Ireland had crossed the landmark £1M only eight years previously. Our annual drug budget now exceeds £30M. Drug costs and value for money are a major issue, with the suggestions that some new therapies may cost over £1m per patient! HER2-positive breast cancer patients now have a better outlook than HER-negative. The role of targeted drugs has expanded exponentially, with many new agents against a multitude of target throughout Oncology.

Immunotherapy is also a promising "new" therapy. Basically, if the immune system recognises the cancer cells as foreign, then it will strive (usually unsuccessfully) to attack and kill the cancer cells. Immunotherapy aims to boost this reaction but with the risk that the patient may develop autoimmune disease causing potentially serious disease in organs such as pituitary, adrenal, liver, and colon. William Coley, a US Surgeon in the late 19th century, observed a patient with cancer who got infection, with a high fever. When he recovered from the infection the tumour had undergone "spontaneous" regression. Coley postulated that the infection stimulated the immune system which then cleared the cancer. He sought to recreate this in the clinic. He developed an infected potion, modified to reduce the sepsis risk and injected his cancer patients with this "Coley's toxin"[15] . He did achieve high pyrexia, but with no antibiotics available there were some fatal infections. It caused cancer remission in some patients, but the infections were a major issue, especially when others were making the toxin, as effective quality control was lacking. "Coley's toxin" was eventually abandoned, when more effective and safer options emerged.

Modern immunotherapy using interferon and interleukin-2 emerged in the 1990's. These gave a broad-based boost to immune activity, causing significant acute toxicity with vascular leak syndrome. Long term remissions were achieved in 5-10% of patients but the acute toxicity, often requiring Intensive Care Unit input, was challenging. Current immunotherapy targets parts of the immune cascade and is more specifically geared towards cancer. It is less toxic and much more effective. Bulky metastatic malignant melanoma, which was almost universally fatal, now yields more than 50% long term complete remissions.

The buzz words now in Oncology are "personised medicine". This approach evaluates mutations in the patient's germline and tumour DNA and targets therapy accordingly. Not every tumour can have a biopsy and the use of "liquid biopsy" where tumour DNA is harvested from peripheral blood is likely to help these patients. Before giving a patient capecitabine

chemotherapy, we routinely test them for germline mutations in Dihydropyrimidine dehydrogenase (DPYD), as those mutations put patients at risk of severe toxicity from capecitabine[16]. At the higher level tumour DNA mutation burden can be analysed to determine the likelihood of benefit from chemotherapy. The OncotypeDX gene panel is widely used to assess the likelihood of benefit from adjuvant chemotherapy in breast cancer, often sparing the patient futile and toxic therapy if benefit is unlikely to accrue[17]. Many modern therapies are designed to be effective against specific mutations, and mutation screening can identify those most likely to benefit. The developmental challenge for molecular oncology is to identify, from all the mutations found in a tumour, those critical mutations to target for cure.

A word of caution is that patients can currently avail of commercial mutation testing of a panel of over 200 genes[18], costing up to £3,000. The interpretation of the results is particularly challenging, as a mutation which is important in one cancer site may have little importance in another. This is a major area for research. I see the future as involving mutation analysis of the patient and their tumour, thereby getting the personalised specific best and least toxic treatment cocktail for them, with the drug chosen based on mutational status, and not on the organ of origin of the cancer. If you want to delve deeper into the history of cancer, I strongly recommend "The Emperor of all maladies" by Siddhartha Mukherjee which gave me inspiration for this address[19].

When I entered Oncology in 1985, the 10-year survival rate for cancer in the United Kingdom was 25% and Oncology was not a "trendy" specialty. As a Medical Trainee in Altnagelvin Hospital, I stated my intention to enter Clinical Oncology training. A senior Consultant counselled "You have done well in postgraduate examinations, and you could change to a more interesting specialty". To me my chosen specialty was the most interesting, given its exciting potential and I hoped to see a big boost in cancer outcomes in my career. Indeed, 10-year cancer survival has doubled to reach over 50% by 2020. Early diagnosis and screening played a large part in that as, by the time cancer has metastasised, options for cure are still somewhat limited.

I believe that the next generation will make huge strides through the molecular maze and, by the time they are getting back to their bicycle in 30 years, they will see the 10-year survival rate push above 85%. People with cancer will expect to be diagnosed early and cured unless they cannot have treatment due to other major medical illnesses or to frailty.

Clinical Oncology has been an exciting and rewarding career for me and there is much more excitement to come. I trust that the next generation will have as much satisfaction from Oncology as I have had, and that they will gain as much reward from changing the outlook for people with cancer.

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Figure 3 Patient has given verbal consent to use anonymised and slightly modified case history and images for teaching and academic purposes.
Written consent requested.

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Clinical Paper

Watch and wait for Rectal Cancer: A 9 year Experience

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ABSTRACT:

Background: Neoadjuvant long course chemoradiotherapy has become the standard treatment for locally advanced rectal cancer. It can reduce tumour bulk, downstage, reduce the risk of local recurrence, and increase the possibility of clear resection margins. The aim of our study is to evaluate all patients over a 9 year period who underwent neoadjuvant chemoradiotherapy for rectal cancer and entered our watch and wait programme.

Methods: Data were analysed from a prospective database for all patients diagnosed with rectal cancer over a 9 year period (2011-2019 inclusive).

Findings: Over a 9 year period, 532 patients were treated for rectal cancer, with 180 patients receiving long course chemoradiotherapy. 61 (11%) patients entered a watch and programme as they had a complete clinical and radiological response following chemoradiotherapy. Within this programme, 40 patients (65%) remain disease free over the follow-up period (mean 38 months); 12 (20%) patients had regrowth and proceeded to surgery; and 9 (15%) proceeded to palliation due to being unfit for surgery or had distant metastatic disease. Overall (all cause) mortality was 18% during follow-up period in the watch and wait group.

Conclusions: Neoadjuvant long course chemoradiotherapy is the standard treatment for locally advanced rectal cancer. 34% of our patient group who received long course chemoradiotherapy entered a watch and wait programme with the majority avoiding major rectal surgery.

KEY WORDS: Rectal cancer, watch and wait, long course chemoradiotherapy

INTRODUCTION:

Colorectal cancer treatment and surveillance has undergone changes in the past decade which have resulted in improved outcomes.[1] However, it remains the third most common cancer and the fourth most common cause of cancer death worldwide, accounting for roughly 42,000 new cases and 16,000 deaths in the U.K. per year.[2] Of these new cases, 32% of male patients and 23% of female patients will have presented with rectal cancer.[2]

Total mesorectal excision (TME) is the standard surgical procedure for the treatment of rectal cancer. It is the removal *en bloc* of the rectum, mesorectum, and surrounding mesorectal fascia – through either an abdominal or abdominoperineal approach.[1] TME surgery has significant potential complications – with a 2% risk of peri-operative mortality and a 5% risk of reoperation. Patient reported quality of life is also impacted – those having undergone an abdominoperineal resection will live with a permanent colostomy, and even those who were candidates for sphincter preservation surgery report experiencing bowel dysfunction and low anterior resection syndrome.[3]

The benefit of TME decreases when the mesorectal fascia surrounding the resected specimen (the circumferential resection margin (CRM)) is threatened or involved by tumour.[4,5] To combat this, long course neo-adjuvant chemoradiotherapy (LCCRT) was introduced in an attempt to downstage patients whose tumour was radiologically encroaching on the CRM. A sub-group of these patients developed a complete pathologic response to LCCRT, namely that there was no residual tumour in the resected specimen. From this finding, a Brazilian team recognised these patients could potentially avoid surgery.[6] Their 2004 study (mainly T3 or N1 patients) showed that these complete responders could be recognised clinically, and subsequently radiologically. It was determined with these complete clinical responders, a 'Watch and Wait' strategy could be employed. This involved intensive follow up with frequent clinical examination, endoscopy, and MRI imaging of rectum to ensure there was no regrowth of tumour. The outcomes from this watch and wait strategy demonstrated the majority of patients did not have regrowth, allowing them to avoid a TME resection with the associated morbidity and mortality. It was shown that the patients who did have tumour regrowth did not have any decreased disease specific survival compared to standard operative treatment.

Watch and wait has generated significant debate between colorectal surgeons and oncologists. There is now a trend towards organ saving strategies in surgical oncology. Management of anal and several ENT cancers have lead the way with impressive patient outcomes.[7,8]

Subsequent studies by the Brazilian group continue to display impressive results. However, they have not been consistently replicated by the surgical community. [9–11] Due to uncertainty of safety of this watch and wait strategy, there

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is a paucity of guidance currently published. To attempt to reduce this uncertainty, surgical units have been publishing their results (albeit all with small numbers), cumulating in a meta-analysis.[12] The authors wish contribute their data towards building a consensus within the surgical-oncological community on the validity of watch and wait strategy for complete responders following LCCRT.

Aim

The aim of this study is to add to the evidence of the role of watch and wait in rectal cancer following neoadjuvant long course chemoradiotherapy.

METHODS AND MATERIALS:

Methods

Prospective data collection was performed using the regional "Northern Ireland Electronic Healthcare Record" system. All patients diagnosed with rectal cancer between 2011 and 2019 within the South Eastern Trust were included. Cancers proximal to the rectum were excluded.

ANALYSIS and RESULTS:

Statistics

Categorical and numerical variables were compared by the use of χ^2 and one-way ANOVA and independent t-test respectively. Survival estimations were determined by the use of Kaplan-Meier curves. Comparison was performed with the log rank test. Kruskall-Wallis and Mann Whitney U was used to compare median follow up periods between groups. Differences were considered statistically significant for P values <0.05. IBM SPSS Version 24 was used for statistical analysis.

Comparisons between groups were analysed on an intention to treat basis. Therefore, those patients who were commenced on a definitive treatment plan were analysed within that group regardless of whether their treatment subsequently changed.

Results

Five hundred and thirty-two patients with rectal cancer were treated in the unit between January 2011 and December 2019. Treatment modality information was missing in 5 patients (0.9%). All subjects had a minimum of 12 months follow up data available at the time of analysis.

Overall, the mean age of patients was 67.8 years and 62.4% (n=332) patients were male. During the course of the study, 189 (35.5%) patients died from all causes. Median follow-up was 28 months (IQR 15-45 months). The characteristics of patients in each treatment group are summarised in *Table 1*.

Patients in the palliative care group tended to be older and included a lower proportion of male patients compared to other groups.

Preoperative staging data was available for 54 patients in the watch and wait group, 116 in the straight to surgery group, 34 in the short course radiotherapy group, 164 patients in the long course chemo-radiotherapy group, and 39 patients receiving palliative care from the time of diagnosis.

Survival curves for patients treated by each modality are presented in Figure 1. Mean survival differed significantly between groups ($p < 0.001$). Following exclusion of the patients treated with palliative intent, the only differences in median survival was between the watch and wait group (76 months) and those patients undergoing long course chemoradiotherapy followed by surgery (53 months, p=0.006) on pairwise comparison.

Among all of patients who received long course chemoradiotherapy (n=241), 134 (56%) proceeded to surgery, 46 (19%) patients did not undergo surgical excision on account of disease progression during this treatment or because they had been considered fit for surgical treatment initially, became unfit for surgery throughout the course of their treatment. 61 (18%) patients entered the watch and wait programme.

Of the 61 patients involved in the watch and wait programme, 40 are free from disease at median follow up of 38.2 months. Of the 21 patients who developed regrowth, median time to regrowth was 15 months. No rectal cancer regrowth was identified in patients after 34 months of follow-up (See *Figure 2*). Nine regrowth patients proceeded to palliative treatment, four underwent surgery including an APER or anterior resection. One patient had an onward referral to specialist pelvic clearance unit and one underwent a TEMS.

DISCUSSION:

This study demonstrates that for patients with complete clinical response following LCCRT, organ preservation is an option by embarking the watch-and-wait strategy for the well counselled patient. It has shown that a substantial number (40 out of 61) of patients undergoing a watch-and-wait strategy have avoided major rectal surgery with its inherent morbidity and potential permanent stoma, without loss of oncological safety at a median of 28 months follow-up.

After analysis of all subgroups of patients, with removal of those being treated with palliative intent from the outset, there was no significant difference found in all-cause mortality. There was a singular exception – the watch-and-wait group at 70.8 months compared those who had undergone LCCRT, as a pooled group, at a follow-up of 52.6 months showed significantly difference in survival. The wait-and-wait group having greater all-cause survival displayed at this point, but this result wasn't repeated at any other time point. The OnCoRe study and the 2017 meta-analysis also reported non-significance between wait-and-wait and intervention groups.[12,13]

A recurrence rate of 34% in the watch-and-wait group echo the results of the OnCoRe study (34%) at a similar median follow-up time point (28 vs. 33 months respectively). This falls short of the crude rate of intraluminal regrowth reported after meta-analysis (15.7%), but this crude rate does not take into account variations in follow-up periods in this meta-analysis and has not adjusted for these.

		Watch & Wait n=61 (11.5%)	Straight to Surgery n=160 (30.1%)	Short Course n=37 (7.0%)	Long Course n=180 (33.8%)	Palliative Care n=89 (16.7%)	Overall (n=532)	Test of significance
Age [a] mean		69.79	66.89	65.64	65.67	73.52	67.88	F = 7.86 4, 522 d.f p = <0.001
Gender [b] n (%)		M = 43 (70.5) F = 18 (29.5)	M = 96 (60.0) F = 64 (40.0)	M = 28 (75.7) F = 9 (24.3)	M = 117 (65.0) F = 63 (35.0)	M = 41 (46.1) F = 48 (53.9)	M = 330 (62.0) F = 202 (38.0)	x^2 = 15.28 4 d.f p = 0.004
T Stage[b] n (%)	1	1 (1.6)	18 (11.3)	0 (0.0)	2 (1.1)	0 (0.0)	21 (3.9)	x^2 = 79.44 12 d.f p = <0.001
	2	21 (34.4)	56 (35.0)	11 (29.7)	38 (21.1)	9 (10.1)	135 (25.4)	
	3	20 (32.8)	35 (21.9)	21 (56.8)	97 (53.9)	20 (22.5)	195 (36.7)	
	4	12 (19.7)	7 (4.4)	2 (5.4)	31 (17.2)	11 (12.4)	64 (12.0)	
	Missing	7 (11.5)	44 (27.5)	3 (8.1)	12 (6.7)	49 (55.1)	117 (22.0)	
N Stage[b] n (%)	0	28 (45.9)	68 (42.5)	18 (48.6)	59 (32.8)	18 (20.2)	191 (35.9)	x^2 = 31.65 12 d.f p = 0.002
	1	16 (26.2)	21 (13.1)	11 (29.7)	50 (27.8)	9 (10.1)	107 (20.1)	
	2	9 (14.8)	13 (8.1)	5 (13.5)	55 (30.6)	12 (13.5)	95 (17.9)	
	Missing	8 (13.1)	58 (36.3)	3 (8.1)	16 (8.9)	50 (56.2)	139 (26.2)	
All cause mortality [b] n (%)		11 (18.0)	33 (20.6)	9 (24.3)	69 (38.3)	32 (86.5)	171 (32.1)	x^2 = 35.17 4 d.f p = <0.001
Follow-Up [c] median (IQR)		38.26 (23.50, 46.50)	30.0 (19.00, 44.00)	40.0 (17.5, 63.5)	31.0 (19.00, 50.75)	9.0 (3.50, 20.00)	28.0 (15.00, 45.00)	H = 108.53 4 d.f p = <0.001

Table 1: Characteristics of patients included in each treatment group.

a. One-way ANOVA b. Chi-squared test c. Kruskall-Wallis test

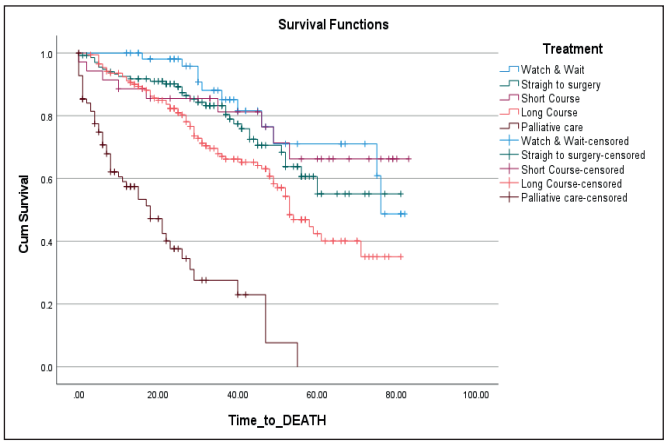

Figure 1: Kaplein-Meier survival curves for patients with rectal cancer treated with watch and wait (blue), straight to surgery (green), short course radiotherapy (purple), long course chemo-radiotherapy (orange) and palliative care (brown). Log rank $\chi 2 = 135.13$, 4 df, p = <0.001.

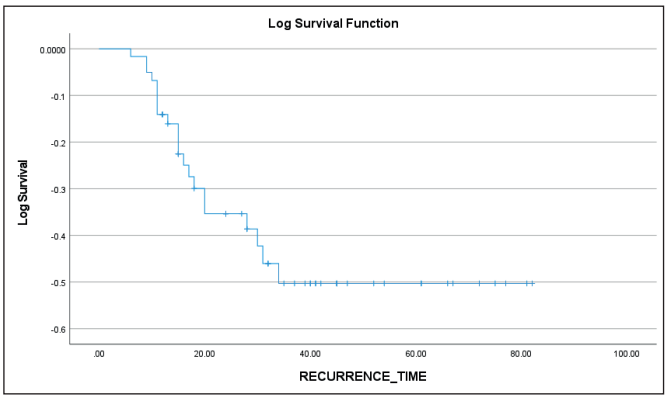

Figure 2: Kaplein-Meier Curve illustrating time to diagnosis of rectal cancer regrowth in patients undergoing "Watch & Wait" management.

Patient characteristics (*Table. 1*) of the included cohort, when compared to the patient characteristics of studies included in a 2017 meta-analysis and the largest cohort study to date (OnCoRe), appear generally homogenous.[12,13] Four studies (out of twenty-four) in the meta-analysis presented median ages higher than this cohort and 62% of patients meta-analysed were male, mirroring the 67% in this study. Median follow-up of this study was 28 months – similar comparing to the meta-analysis and the 2015 OnCoRe study (33 months).[13] The groups which responded to LCCRT, and those who didn't, did not differ in sex, age or tumour characteristics – echoing the results of the OnCoRe study.

The tumours represented in this study were characterised by similar T-stage to in both the OnCoRe study and the meta-analysis, with all having a majority of T3 tumours. Nodal stage differed – 45.9% of those in the watch-and-wait group in this study were N0, compared to 35% in the OnCoRe study, and 48% in the meta-analysis.

Clinical implication and future research

These findings arm the both clinician and patient in deciding the optimum treatment strategy for the patient with rectal cancer who has had a complete clinical response following LCCRT. This allows for full informed consent for a patient entering the watch-and-wait programme. To date, studies suggest upwards of one third of patients will unfortunately require surgery for local regrowth even after LCCRT. Despite this Habr-Gama et al in 2013 showed promising results when watch-and-wait plus salvage strategies were paired together in the setting of local recurrence post LCCRT. They demonstrated a 5 year local recurrence-free survival rate of 94%. Recurrences as a whole were infrequent, with the majority of those who did recur being amenable to salvage surgery. This may help provide reassurance to both patients and clinicians that a watch-and-wait approach with rigorous follow up is a safe and less invasive initial step in the treatment of rectal cancer.[14]

Nasir and colleagues in 2018 have suggested local regrowth surgery still has comparable R0 resections to original non-deferred surgical options. It has been shown that the majority of regrowth surgery can still be carried out via a minimally invasive technique (laparoscopic, robotic) without an increase in post-operative morbidity (anastomotic leak, post-op ileus, bleeding) and mortality along with favourable overall oncological outcomes.[15]

It is important to emphasise that watch-and-wait requires a strict follow up process, patients must be well informed and be willing to take part. Any institution introducing this method into their clinical practice requires a strong multidisciplinary team commitment to help identify appropriate candidates and have in place a robust follow-up protocol.

There remains no randomised controlled trial (RCT) for watch-and-watch for the complete clinical responder post LCCRT. Recruitment for this may be challenging, with often both clinicians and patients having firm ideas on the optimum treatment strategy, with the outcomes being vastly different, namely rectal surgery with its morbidity or simply close observation.

Future research may rely on meta-analysis of good quality data and should demonstrate that results are repeatable in all centres, not just highly specialised units.

Limitations

The small number of patients who undergo TME after complete pathological response prevented the authors from using a propensity-score matching method to compare those who chose TME surgery and those who chose watch-and-wait. This method attempts to address the confounding effect of selection bias between patients who choose differing management plans by statistically matching their co-variates. To address this issue, the authors intend to re-examine this data once the sample size grows.

CONCLUSION:

Neoadjuvant long course chemoradiotherapy is the standard treatment for locally advanced rectal cancer. Over a quarter of our cohort who received long course entered the watch and wait programme with the majority of these patients avoiding major rectal surgery.

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Clinical Paper

Could the Emergency Department Facilitate the Start of a Holistic Follow-Up Pathway for Patients Recovering from COVID-19?

Patrick Cook [1], Emma Allde [1], Flynn Griffith [1], Reza Khorasanee [2], Calum Luke[1], Benjamin Ridley[1], Thomas Simpson[2]

Abstract

Background:
For many patients suffering from COVID-19, Emergency Departments (ED) facilitate the first contact with clinicians. There is a high rate of psychiatric symptoms in COVID-19 survivors, including anxiety, depression, fatigue and sleep disturbance, which persist months after the acute phase.

Aims:
To investigate if COVID-19 patients discharged from ED have a higher prevalence of mental health symptoms than those admitted.

In addition, this study will investigate if discharged ED patients who now require COVID-19 follow-up with the respiratory team had a higher prevalence of mental health symptoms than admitted patients requiring follow-up.

Methods:
This was a retrospective cohort study (n = 472) with the PHQ-2 and GAD-2 scoring systems to quantify current anxiety and depression symptoms via a telephone consultation.

Results:

The PHQ-2 and GAD-2 scores were significantly higher for discharged ED patients than the admitted patients. There was a higher proportion of females with a positive PHQ-2 or GAD-2 score. Of the patients requiring respiratory follow-up, discharged ED patients were more likely to have a positive PHQ-2 or GAD-2 score than those admitted.

Conclusions:
Clinicians should maintain a low threshold for referring patients with psychiatric complaints post-COVID alongside respiratory symptoms irrespective of admission. It is imperative that available psychological services, crisis lines and other avenues of support post-COVID-19 are signposted to patients before discharge to facilitate earlier intervention.

Introduction

As the gatekeepers of the hospital, Emergency Physicians must quickly determine which patients require admission. Although patients may not require immediate admission, they may require further clinical input. As healthcare systems begin to understand the importance of early clinical intervention, ED is primly positioned to aid in this transition. The novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), causing the disease Coronavirus 2019 (COVID-19) was first identified in December 2019 in Wuhan, China and has since spread across the world. Following the SARS epidemic, caused by another coronavirus, 25.6% of survivors had Post Traumatic Stress Disorder (PTSD), and 15.6% had depressive disorders.[1] As the first and second wave of COVID-19 recedes, it is imperative to anticipate an increase in mental illness related to the infection and the nationwide lockdown measures and prepare mental health services for the added burden they will face.

Early research has indicated that those with a milder form of COVID-19 had a greater frequency of depressive symptoms than those with a critical form of the disease[2,3]. Furthermore, there is an inverse correlation between the length of stay amongst admitted patients and symptoms of depression at three months post-discharge[4]. Discharged COVID-19 patients, by definition, should have a milder form of the disease, and it is, therefore possible that these patients have a more significant psychiatric burden than those admitted. Specialist funding has been allocated for COVID-19 survivors, with patients describing persisting symptoms and high rates of anxiety, depression, fatigue, and sleep disturbance[3]. Guidelines are beginning to emerge for the management of these patients, with General Practitioners expected to make many of the referrals[5].

The ED is often the first clinical contact for COVID-19 patients and can, therefore, start a holistic COVID-19 pathway facilitating early clinical intervention. The British Thoracic Society (BTS) released a guideline in May 2020 recommending that clinicians undertake a 'Post-COVID-19 holistic assessment' of patient needs[6]. Following the

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publication of the BTS guidelines, we rapidly established a follow-up pathway that included screening for psychological issues. In this study, we will explore whether those attending ED and being discharged had higher rates of mental health symptoms than patients admitted. In addition, this study will investigate if discharged ED patients who now require COVID-19 follow-up with the respiratory team had a higher prevalence of mental health symptoms than admitted patients.

Methods

This retrospective cohort study investigated the proportion of patients suffering from anxiety and depressive symptoms in patients with confirmed or suspected COVID-19 infection presenting to our London ED during March, April and May 2020. Our study compared the proportion of patients with anxiety or depressive symptoms between those admitted and those discharged without admission from ED.

Participants

During the early stages of COVID-19 in the United Kingdom, many patients were not tested, and false negatives were commonplace. Therefore, in agreement with the literature, a positive COVID-19 test was not a prerequisite for diagnosis[7]. Criteria for inclusion were therefore as follows: all patients with proven or suspected COVID-19 managed in the Intensive Care Unit (ICU) or with Non-Invasive Ventilation (NIV), any patient coded as "COVID-19" in the hospital's patient record system and all patients with a chest X-ray that identified COVID-19.

Screening

Sixteen doctors of similar grade telephoned patients and screened patients per BTS guidance to determine if a respiratory review was required. The criteria are detailed in Table 1. In addition, clinicians screened for mental health symptoms. Staff were told to keep broadly to a defined script so that this screening programme could be performed by non-clinical staff in the future whilst simultaneously minimising variability. We used the Patient Health Questionnaire-2 (PHQ-2) score as a screening tool for depression and the Generalised Anxiety Disorder-2 (GAD-2) tool to assess anxiety symptoms. Although these tools cannot be used for diagnostic purposes, their high specificity and sensitivity could permit use in the Emergency Department to identify at-risk patients who can be signposted to appropriate avenues of support[8].

Patients for immediate follow up: Chest X-ray and inflammatory markers to influence further action.	Patients for non-urgent follow up: Chest X-ray within 12 weeks of discharge.
• Critical care input or non-invasive ventilation required (Irrespective of current symptoms) • MRC breathlessness score decrease ≥2 • Ongoing pneumonitis symptoms concerning clinician	• All patients with changes on CXR raising suspicion of covid-19 • All patients that required oxygen therapy ≥4L • Patients that had high clinical suspicion of COVID infection, now recovering **WITH** mild ongoing symptoms of pneumonitis

Follow-up

All patients with a positive PHQ-2 or GAD-2 were directed to IAPT (Improving Access to

Psychological Therapies); however, at present, no local, trust, regional or national clinical guidance exists on managing new or worsening mental health symptoms under COVID-19. Patients were discussed on a case-by-case basis when IAPT was insufficient or appropriate.

Table 1: Criteria for follow-up divided into urgent and non-urgent pathways.

Statistics

A chi-square test of independence was used to compare our patient outcome groups with the p-value set to <0.05 for a result to be considered significant.

Ethics

The telephone screening discussed in this report is part of an ongoing post-COVID-19 follow-up pathway. This pathway aims to identify, screen and refer patients with confirmed or suspected COVID-19 infection for appropriate follow-up. All data was routinely collected as part of that process, and ethical approval was not required. All patients consented verbally to undertake the screening questionnaire.

Results

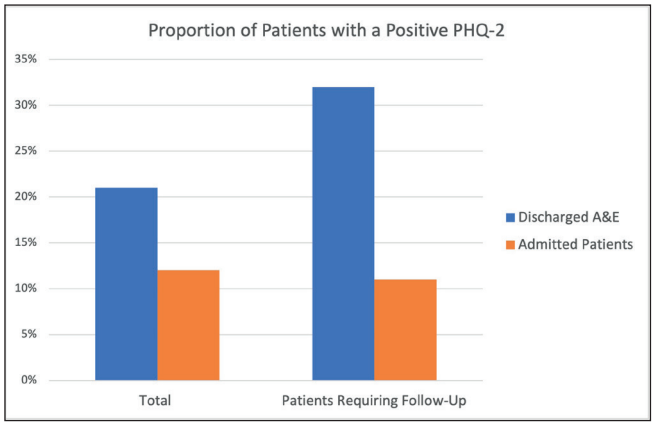
Age and Sex

The Mean age of those admitted was sixty-three, whilst the mean age of those discharged was forty-six. Of the discharged patients, 52% were female, and 48% were male, whilst the admitted had a higher proportion of males (57%) than females (43%).

PHQ-2

Four hundred seventy-two patients answered the PHQ-2 screening questions correctly, of which 15% were positive. A significantly greater number of positive PHQ-2 scores was observed in discharged ED patients at 21% compared to admitted patients at 12% (p=.0177). In addition, 32% of the discharged ED patients who required respiratory follow-up had a positive PHQ-2 compared to 11% of the admitted patients. In the discharged patient group with a positive PHQ-2 score, 63% were female and 37% were male, whilst in the admitted group, 58% were female and 42% were male.

GRAPH 1

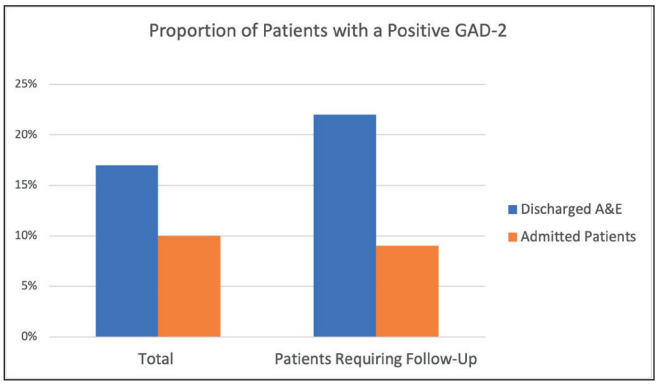


GAD-2

Similarly, we determined the GAD-2 score of 465 patients, of which 13% were positive. A significantly greater number of positive GAD-2 scores were observed in discharged ED patients at 17% compared to admitted patients at 10% (p = .0295). In addition, 22% of the discharged ED patients who required respiratory follow-up had a positive GAD-2

compared to 9% of the admitted patients. In the discharged patient group with a positive GAD-2 score, 61% were female and 39% male, while 60% were female and 40% male in the admitted group.

GRAPH 2



Discussion

To our knowledge, this is the first comparison of post-COVID-19 GAD-2 and PHQ-2 scores between discharged ED patients and those admitted. Although unique to COVID-19, it has been previously established that ED attendance is higher for patients with pre-existing mental health conditions[9]. Our study will likely further support the idea that mental health continues to be a significant challenge for ED clinicians.

However, it surprised the team that patients requiring a respiratory review following COVID-19 infection had higher PHQ-2 and GAD-2 scores, which is significantly greater amongst the discharged ED patients. It is uncertain why discharged ED patients requiring follow-up were significantly more likely to have positive PHQ-2 and GAD-2 scores than the admitted patients. However, this study may simply identify the "worried well", and this uncertainty remains without baseline PHQ-2 and GAD-2 scores before infection.

Although the severity of COVID-19 infection doesn't correlate with the development of psychiatric symptoms, the literature suggests sex and previous psychiatric history as the principal risk factors with a possible influence by age [3]an increasing proportion of individuals have reported the persistence and/or new onset of symptoms which collectively have been identified as post-COVID-19 syndrome by the National Institute for Health and Care Excellence. Although depressive symptoms in the acute phase of COVID-19 have been well characterized, the frequency of depression following recovery of the acute phase remains unknown. Herein, we sought to determine the frequency of depressive symptoms and clinically-significant depression more than 12 weeks following SARS-CoV-2 infection. A systematic search of PubMed, Ovid Medline and Google Scholar for studies published between January 1, 2020 and June 5, 2021 was conducted. Frequency and factors associated with depression in post-COVID-19 syndrome were recorded and qualitatively assessed through narrative synthesis. Methodological quality and risk of bias was assessed using a modified version of the Newcastle-Ottawa Scale (NOS. Unfortunately, our study did not include data on previous psychiatric history. Although 52% of discharged patients were female, 65% of those with a positive PHQ-2 score and 60% with a positive GAD-2 were female. Therefore, our data supports the literature on the female gender being a risk factor for developing psychiatric symptoms post Covid-19 infection. ED physicians should be mindful of these risk factors when considering the need for onward referral. However, literature investigating outcomes after COVID-19 infection continues to be limited by difficulty comparing data against non-COVID-19 patients[3] and as a retrospective cohort study this work is no different. It remains imperative that further research includes or investigates this and reduces the risk of confounding factors. Longitudinal, prospective studies are required before firmer conclusions can be drawn.

Our team has now integrated mental health screening into our COVID-19 follow-up, as those with mental health symptomatology may be at greater risk in light of this surprising data. We were fortunate enough to have the capacity to phone all our COVID-19 patients as part of our follow-up. Available services and other avenues of support must be appropriately signposted to patients before discharge. Increasingly clinicians and politicians alike are beginning to understand how early intervention, or better yet, preventative medicine can decelerate the rise in ED attendance. COVID-19 is not independent of this; however, ED can now dovetail with this earlier interventional strategy by providing a holistic COVID-19 follow-up and referrals where indicated or signposting available avenues of support.

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Clinical Paper

Straight to test reduces time to investigation and treatment

R S Wilson [1], D B Johnston [2], D McKay [3], D Mark [3]

Abstract

Straight to test (STT) is a recognised pathway for improving the waiting time for red flag referrals. Electronic patient care records (ECR) provide clinicians with a greater volume of clinical information allowing virtual triage and STT. We aimed to assess if using ECR and STT can reduce delays in diagnosis and treatment.

A review of 300 colorectal referrals between 2018-2019 was performed. Patients awaiting an appointment were reviewed electronically, by a single colorectal surgeon and re-triaged STT if appropriate. The delay in time from referral to initial review was removed, creating a second group for statistical comparison to demonstrate time saved if the strategy was adopted at the point of original triage.

91.3% (n= 274) were red flag referrals. 94% (n=282) were sent STT. Patients processed via traditional referral and clinic had a median time to scope of 36 days compared with 22.5 days, $p < 0.001$ if triaged STT via virtual clinic. Median time to management was 59 days for traditional and 35 days for STT, $p < 0.001$.

Introduction

Colorectal cancer remains the fourth most common cancer in the United Kingdom (UK) accounting for 11% of new cancer cases.[1] To improve access to hospital services, and time to diagnosis, target times with a maximum of two weeks wait (2WW) for red flag suspected cancer referrals and two months (62 days) from time of GP referral to cancer treatment, were introduced within the UK.[2] Despite these measures, the growing burden of red flag referrals has placed increasing strain on outpatient services, resulting in significant delays. Northern Ireland currently has one in five people awaiting a first appointment for elective care, highlighting the pressing need for modernisation and change.[3]

Within this climate, straight to test (STT) is being utilised as a means of reducing time to diagnosis by effectively removing the initial clinic review as a cause for delay.[4-7] STT provides additional capacity in outpatients by reducing the number of clinic attendances that each patient requires. However, the STT model has not been universally adopted in all colorectal centres with many existing STT models relying on telephone assessment clinics (TAC) by specialist nurse practitioners, which smaller units are often unable to fund. Such TACs are deemed necessary when determining the suitability of referred patients for invasive or non-invasive testing such as colonoscopy or CT colonography.[4-7] We present a novel approach to STT, incorporating technological advances, in the form of an electronic patient care record (ECR), allowing for greater assessment of referrals at the point of initial triage without the need for TACs.

Methods

A retrospective review of 300 colorectal referrals was performed between February 5th 2018 and July 22nd 2019 by a single consultant. Referral sources included General practitioner (GP) and hospital clinicians via electronic or paper referral format. Time from GP referral to hospital triage, first colorectal clinic, investigation and subsequent follow up or discharge was reviewed. All patients within the study had their initial GP referral triaged by a general surgeon, to a colorectal outpatient clinic. However, due to the waiting time delay for first outpatient assessments, patients on the red flag waiting list were reviewed by a single colorectal surgeon as part of a waiting list initiative. These clinics were provided virtually, and patients managed direct to test.

The patient referral details were verified using an Electronic Care Record (ECR) from which the consultant could access blood results, previous outpatient attendances, radiology reports and current patient medication to supplement and better triage the patient to an appropriate investigation route. Referrals were vetted in accordance with the Northern Ireland Referral Guidance for Suspected Cancer (NICaN) red flag indicators and patients down or upgraded accordingly. Patients were contacted by letter to inform them of the plan and received additional information regarding the investigation requested. Patients were not telephoned as part of this process. Patient investigations were decided based upon the referring complaint, recommendations from NICaN guidelines, patient frailty and renal function. Patients deemed fit for primary endoscopy were sent for colonoscopy +/- OGD. Those unfit for colonoscopy were sent for CT Colonography or CT scan with delayed oral contrast +/- OGD.

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Reports of any investigation results were then reviewed electronically and a decision regarding follow up was made. A retrospective review of outcomes and results of this patient cohort was then performed with demographics, referral times, referral indications, investigation results and timings, time to diagnosis and treatment recorded. Once data collection was completed the time delay from initial referral to Virtual clinic was removed to create a second group for comparison, that would act as an outcome measure, had virtual clinics and STT been adopted at initial point of triage. (Figure 1)

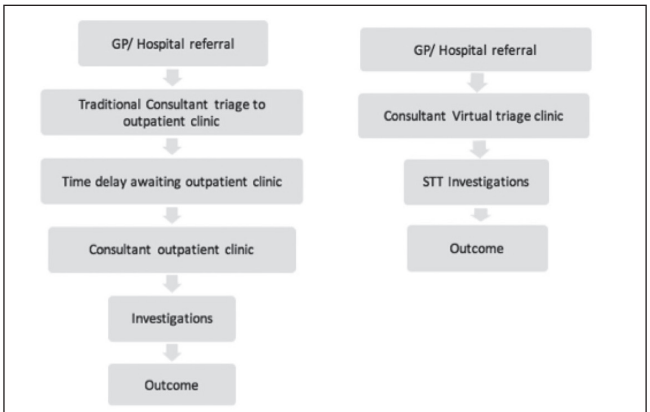

Figure 1: Change from traditional pathway to virtual straight to test clinic at point of initial triage demonstrating a streamlined service

Data was not normally distributed; therefore, an exact sign test analysis was conducted comparing the groups. Values were considered statistically significant if $p < 0.05$. Data was analysed using SPSS version 26 for Windows (SPSS, Inc., Chicago, IL, USA).

Results

300 colorectal referrals were reviewed between February 5th 2018 and July 22nd 2019 in a virtual clinic by a single colorectal surgeon. 91.3% (n= 274) were red flag, 7% (n= 21) urgent and 1.7% (n= five) routine. Eleven referrals were upgraded to red flag (4 routine and 7 urgent) and 12 red flag referrals were downgraded to urgent for failing to meet the red flag criteria for referral. Altered bowel habit, PR bleeding, anaemia, abdominal pain and weight loss made up the majority of indications for initial referral to the service. The median number of days to triage was 1 day (IQR = 2). Median number of days to initial colorectal clinic (virtual clinic in this case) was 13 days (IQR = 41).

The average age was 61.79 years (minimum 16, maximum 88). 135 (45%) were male and 165 (55%) were female. 85% had blood tests performed by the GP that were within three months of the referral. Only seven patients had an eGFR <40 mL/min/1.73m^2.

94% (n=282) were sent direct to test, however five did not attend their scope procedure. 6% (n=17) declined their direct to test and were reviewed in clinic.

As expected, the main investigation method for colorectal referrals involved a colonoscopy. However, some patients had more than one investigation and others were deemed more suitable for cross sectional imaging (Figure 2).

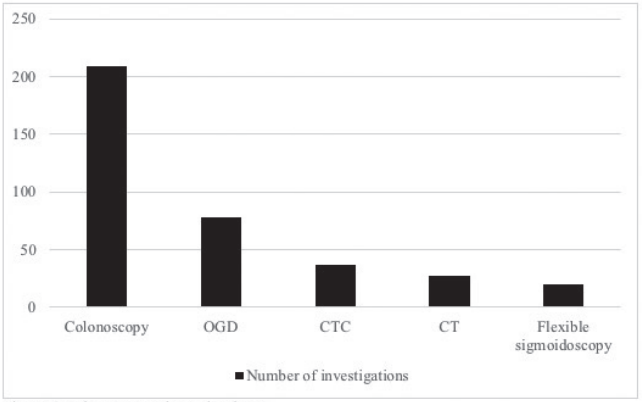

Figure 2: Direct to test investigations

No complications after endoscopic procedures or other investigative modalities were reported.

The median time to vetting of the initial GP referral, by a general surgeon was 1 day, IQR 2 days. Due to waiting list delays, the time from GP referral to first appointment by colorectal surgeon was a median of 13 days, IQR 41 days. Incorporating STT at point of initial triage would enable 100% of all referrals receiving their primary review within the 14-day referral target, with 75% of patients receiving review within two days.

Red flag patients median time to scope was 36 days, IQR 55 days. If triaged straight to test by virtual clinic the median time was 22.5 days, IQR 19.75 days. Exact sign test analysis of these two groups found a statistically significant median decrease in time in the STT group, $p < 0.001$.

Benign		Malignant	
Diverticulosis	60	Rectal adenocarcinoma	5
Tubular adenoma	29	Caecal adenocarcinoma	3
Haemorrhoids	24	Rectosigmoid adenocarcinoma	2
Hiatus hernia	9	Sigmoid Adenocarcinoma	2
Gastritis	9	Colonic adenocarcinoma	1
Hyperplastic polyp	8	Gastric adenocarcinoma	1
Colitis	8	Peritoneal carcinomatosis	1
Tubulovillous adenoma	5	Total	15
Constipation	3		
Coeliac	2		
Oesophagitis	1		
Oesophageal ulcer	1		
Barret's	1		
Peptic ulcer	1		
Duodenitis	1		
Irritable bowel syndrome	1		
Leiomyoma	1		
Colonic lipoma	1		
Radiation proctitis	1		
Rectal Ulcer	1		
Total	167		

Table 1: Diagnosis

Diagnosis was identified as date of radiological diagnosis or date of pathology report released from specimens sent at time of endoscopy (Table 1).

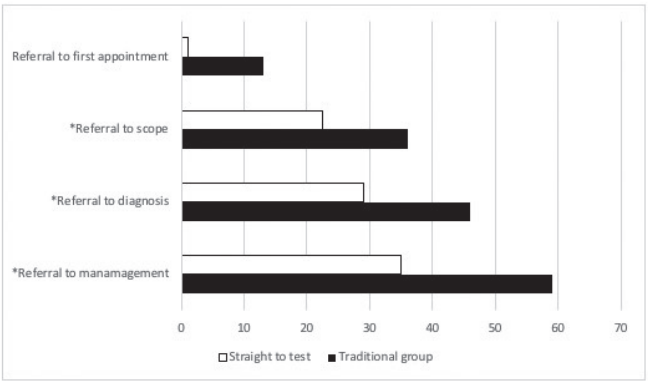

Figure 3: A comparison of times for patients from referral to first appointment, scope, diagnosis and management. * P <0.0001

Median time to diagnosis for red flag patients was 46 days (IQR = 53 days). For the virtual clinic group, median 29 days (IQR = 24 days). (Figure 3) Exact sign test analysis of these two groups found a statistically significant median decrease in time in the STT group, $p < 0.001$. 19.6% (n= 59) had normal investigations and were therefore discharged. 16.6% (n=50) needed a clinic appointment to guide further investigation.

All patients diagnosed with malignancy went on to multidisciplinary discussion. The remaining patients were informed by letter or face to face appointment, depending on the nature of their initial referral, and the findings of investigations and diagnosis given. Advice, treatment or follow up was determined on a case-by-case basis. For example, those with diverticulosis were given dietary advice, haemorrhoids were banded, those with tubular adenomas were listed for a repeat scope as per British Society of Gastroenterology (BSG) guidelines.

Management was defined as the date when medical therapy was commenced, the date of first intervention e.g. surgery, chemotherapy, banding of haemorrhoids, or when surveillance investigations were planned, or referral on to another specialty. Median time to management for red flag patients was 59 days (IQR = 63.5 days). For the virtual clinic group, median time was 35 days (IQR = 51.5 days). Exact sign test analysis of these 2 groups found a statistically significant median decrease in time in the STT group, $p < 0.001$.

Follow up was required for 85 patients after initial investigations. 20% of patients on a traditional referral pathway, with confirmed cancer, received treatment within 62 days of red flag referral. This improved to 53.3% if STT at the point of initial triage was used.

Discussion

Waiting times for first outpatient appointment are increasing across the UK, with patients in Northern Ireland waiting the longest. Regional reviews have highlighted the need to adopt new technologies, such as patient electronic care records as part of strategic planning, to address the issue.[3,8-9] However, the COVID pandemic is likely to place an even greater burden on healthcare systems, highlighting the need to rapidly adopt new practices, to improve patient flow from referral to investigation, discharge or treatment.[3, 10-11]

An ECR provides clinicians with greater access to information, enabling virtual clinics to decide on suitability of STT, thus ensuring safe assessment of the patient and triage to the appropriate investigation, without a face to face clinic appointment. Virtual clinics, without direct patient contact, have been an established aspect of many medical disciplines over the last decade with surgical specialties only recently incorporating them into their practice [12]. Utilising this route to diagnostics frees up much needed capacity in outpatients for those that require direct face to face attendance. Moreover, by utilising virtual ECR clinics, at the point in which the initial GP letter is triaged, considerable time is saved for the patient on their red flag pathway. Of the 300 patients treated by a virtual STT route in this study 92.7% (n=278) were managed without complication or cancellation highlighting that this route is both safe and acceptable. Moving to an ECR triage model rather than triage to telephone clinic, not only reduces cost but allows units with less resources such as clinical nurse specialists to effectively and safely manage STT without initial review.

The ECR triage and STT model would improve compliance with NHS cancer targets, of 2 weeks from referral to first appointment, to 100%. They would also significantly improve time to investigation, discharge or treatment. Virtual clinics and organising STT investigations, allows for timelier diagnosis of each patient and, if required, multidisciplinary team meeting discussion and treatment for confirmed cancer. Doing so, not only improves patient satisfaction but may also lead to improved outcomes as it correlates with a significantly shorter time to oncological treatments and surgery. Current targets for cancer care in Northern Ireland state that 95% of patients should begin their first treatment for cancer within 62 days from initial referral for suspected cancer and that 98% of patients diagnosed with cancer should receive their first treatment within 31 days of a decision to treat[10]. In our study, we found that 20% of patients with confirmed cancer received treatment within 62 days of red flag referral, this would have improved to 53.3% if STT was initially used. We recognise that, despite this significant improvement in service efficiency, further work is needed to ensure that targets for cancer care are met. The imbalance between waiting list times for endoscopy or cross-sectional imaging can make it difficult to meet a rising demand, with further resource allocation for necessary diagnostic access a requirement for the future.

The STT approach can be limited by the quality of information from the primary care referral. However, utilisation of an ECR in this study has shown it to be robust with only 2.3% of referrals having insufficient information to enable appropriate STT. Incorporating STT at point of triage as a standard referral pathway also allows for further education and communication to GP's, to enhance the quality of referrals further and ensure all appropriate bloods are updated before

referral. With only five patients not attending for requested investigations we have demonstrated STT using an ECR as safe and acceptable to patients within our local population. We recognise that other parts of the UK, with greater migrant populations, may require additional safeguards to ensure the safe dissemination of information to them from clinicians. In some cases, the need for an interpreter may prohibit the use of STT by the method described in this study[6].

In conclusion, this study has shown significantly improved times to investigation, diagnosis and management when a straight to test approach is utilised. This cost effective and efficient route could help manage the growing service demand in the post COVID-19 environment.

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Medical History

Pestilence, Plague and Pandemics: A Troubled History

Wren MWD, Petts D, Guthrie G, Clarke S, Nation BR, Peters L, Mortlock S, Sturdgess I, Wright M, Burt C.

ABSTRACT

Humankind has lived with the danger of endemic, epidemic and pandemic disease for thousands of years. The effects of these outbreaks have often devastated human populations. Sixteen pandemic events causing an estimated 147 million deaths have occurred since the eighth century, the black death and the influenza pandemic of 1918-1920 probably having the greatest impact.

Animal populations, both wild and domestic, have similarly suffered devastating outbreaks of disease which, on occasions, have translated into serious effects on human health. The deliberate or accidental introduction of animals into virgin areas has given rise to unforeseen disease events occasionally leading to extinction. Similarly, human intent or negligence and the vagaries of nature itself has resulted in ill health and loss of life. This paper describes the history of pandemics, epidemics and disasters and the attempts to bring them under control.

INTRODUCTION

Major outbreaks of disease have blighted humankind ever since the establishment of sedentary villages and small towns and by the introduction of domesticated farm and work animals. Spread of disease was enhanced by the close proximity of housing and their inhabitants and livestock, and accentuated by the establishment of national and international trade.[1]

It is now generally accepted that there is a significant chance of the occurrence of future pandemics and of health systems collapse, especially in poorer countries. It is estimated that any pandemic arising from natural or animal causes could lead to as many as 10 million deaths worldwide, a figure already surpassed by the current SARS-CoV-2 pandemic.

It is also expected that climate change and global warming will increase the exposure of populations to vectors and pathogens previously not encountered before in certain countries.[2] Identifying the origins of zoonotic pathogens and their transmission will be crucial for early detection and prevention.[3]

Many diseases have a devastating impact on wild and economically important animals. Deliberate or accidental introduction of animals such as cats, mice, rabbits and rats into new habitats has led them to become the origin of plagues in their own right as predators or as sources of disease. The use of animals for biological control has also produced unforeseen adverse effects.

Examples of events caused by human intent or negligence have led to damage to the habitat and property. These have resulted in ill health and loss of life owing to the release of biological agents, toxic chemicals or radiation into the environment.

HUMAN PANDEMICS AND EPIDEMICS

There are five stages through which pathogens from animals evolve into pathogens in humans.[4] Pathogens that occur in animals only then undergo the transfer of the pathogen to humans. Limited outbreaks may then occur in the human population followed by a prolonged human outbreak. Pandemics may then occur as a result of this exclusive outbreak amongst humans becoming country and worldwide.

Eight of the 15 temperate diseases possibly reached humans from domestic animals, three from apes or rodents, the remaining four still of unknown origin. Eighteen of the 25 major human pathogens originated in the Old World and possibly one-third of all emerging diseases have originated from changes in land use thereby increasing animal-human interaction.

Fig 1. Ancient mass grave in China.

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Table 1. Spread of pandemics through trade and travel.

Route of spread	Examples
Overland trade routes	The Silk Road: far East to Middle East Overland routes between Constantinople and Western Europe Siberia and Russia to Europe (via Vienna)
Oceanic and sea routes	Trade: China to India Trade: India to Africa via Indian ocean then to Egypt and Europe via The Red and Mediterranean seas Trade: Europe to The Americas via The Atlantic Ocean including the transport of slaves Cruise ships: Country to country; continent to continent
Air travel	Global air travel

The first probable epidemic occurred in China around 3000 BCE as evidenced by the presence of mass graves (Fig 1). Three pandemics of The Plague have occurred in history. The Plague of Justinian occurred from 541 to 747 CE, The Black Death from 1346 to 1844 and during the year 1894 originating in the canton province of China. Major trade routes decided the major hot spots of Plague, with navigable rivers determining the geographical pattern of sporadic cases. Further studies by Yue *et al*.[5] reveal that Plague penetrated further into Europe through local trade route networks. Table 1 lists the routes by which pandemics are spread.

Throughout history there have been a number of other notable epidemics. Medieval leprosy is an example of relationships that developed between disease, social stigma and various theological interpretations. Between 1500 and 1600, syphilis, an apparently new disease, appeared among the army of Charles VIII during the siege of Naples and reached as far as China in the early part of the 16th century. Debate continues as to whether the disease first appeared in Europe or was brought into Europe from The Americas with the return of Christopher Columbus and his crews.

Yellow fever, originating in Africa, was transmitted to the Western Hemisphere via the slave trade with notable outbreaks occurring in the Yucatan (1648), Hispaniola (1793-1804), Philadelphia (1793) and Swansea in South Wales (1865). The Swansea outbreak was brought from Cuba on the barque Helca. A total of 28 passengers contracted the disease and 16 died. Several crew members were taken ill and died, and at least 27 inhabitants of Swansea contracted the infection and 15 of them died.[6]

Smallpox occurred in The Americas, Iceland, The Balkans and 18th and 19th century Europe, during which some half a million people died.

Carrion's disease occurs in Peru and was studied by Daniel Carrion (Fig 2) who was appalled by the death rate (over 10,000 deaths between 1870 and 1871). He observed that Verruga Peruana and Oroya fever were transmitted by

Fig 2. Daniel Carrion
Demonstrated that verrugua peruana and Oriya Fever were manifestations of the same diseases. Wellcome Images

a sandfly vector and, by injecting himself with verruca material, subsequently died of Oroya fever demonstrating they were different manifestations of the same disease.

Contemporary 20th century disease epidemics have consisted of poliomyelitis, malaria, tuberculosis, Eastern Equine Encephalitis, Dengue fever, Chikungunya fever, Zika virus and the Human Immunodeficiency Virus causing AIDS, all leading to significant morbidity and mortality.

For those diseases that are mosquito-borne the vector is often an invasive species of mosquito that is spread by international trade and whose common breeding ground is stagnant water, including in old stored tyres. Affected countries include those in Europe, the United States, Latin America and South Africa.

Twenty million cases of tuberculosis with 1.5 to two million

deaths each year and approximately 10,000 deaths occurred each year from poliomyelitis between 1945 and 1955 before vaccination was introduced.

PANDEMICS: PREPAREDNESS AND PREVENTION

It is now generally accepted that there is a significant chance of future pandemics and of possible health system collapse, especially in poorer countries.[7] It has been estimated that any pandemic arising from natural or animal causes could lead to significant mortality worldwide.

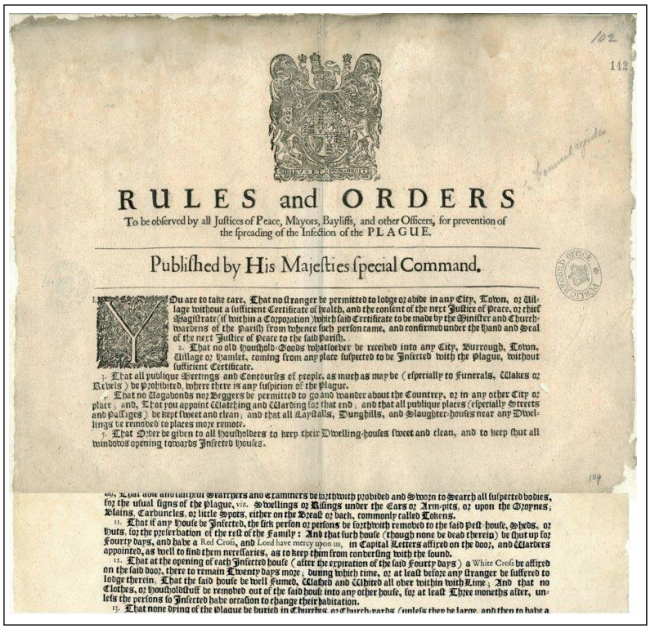
HISTORICAL CAUSES OF EPIDEMICS

Throughout history the causes of epidemics have been attributed to a number factors. The anger of a vengeful or unforgiving Gods is typified in the Iliad where Homer describes Apollo raining down plague on the Greek army. Similarly, The Holy Bible describes the "ten plagues" of Egypt as reflecting the wrath of God punishing the Egyptian people in the book of Exodus.

Astrological movements have been assumed to be the source of pandemics. For example, on 20th February 1345 the alignment of Saturn, Jupiter and Mars in the constellation of Aquarius was blamed for the outbreak of the Black Death. Expectation of such astrological events could help to place prevention steps in place.

The presence of bad or poisoned air, known as Miasma, was to be avoided[8] such as associated with marshes (for example in ancient Rome) and human waste dumps. Overcrowded or slum areas were also included in areas to be avoided. In 1518 King Henry VIII ordered slaughter houses to be placed outside of city walls, banned kissing and introduced social distancing[9] in plague orders issued by decree (Fig 3).

Religion has played a part in apportioning blame to the rise of epidemics. Accusing Jewish people of poisoning wells was commonplace in the Middle Ages. On 14th February 1349, 2000 Jews were burned to death in Strasbourg.



RULES and ORDERS

To be observed by all Justices of Peace, Mayors, Bayliffs, and other Officers, for prevention of the spreading of the Infection of the PLAGUE.

Published by His Majesties special Command.

YOu are to take care, That no Stranger be permitted to lodge or abide in any City, Town, or Village without a sufficient Certificate of health, and the consent of the next Justice of Peace, or chief Magistrate; if within a Corporation (which said Certificate to be made by the Minister and Churchwardens of the Parish from whence such person came, and confirmed under the hand and Seal of the next Justice of Peace to the said Parish.

2. That no old Houshold-Stuffe whatsoever be received into any City, Burrough, Town, Village or Hamlet, coming from any place suspected to be Infected with the Plague, without sufficient Certificate.

3. That all publique Meetings and Conventions of people, as much as may be (especially to Funerals, Wakes or Revels) be prohibited, where there is any suspition of the Plague.

4. That no Rogabonds nor Beggers be permitted to go and wander about the Country, or in any other City or place, and, That you appoint Watching and Warding for that end, and that all publique places (especially Streets and Pallages) be kept sweet and clean, and that all Laystalls, Dunghills, and Slaughter-houses near any Dwellings be removed to places more remote.

5. That Order be given to all Householders to keep their Dwelling-houses sweet and clean, and to keep shut all windows opening towards Infected houses.

6. That due and diligent Searchers and Examiners be forthwith provided and Sworn to Search all suspected bodies, for the usual Signs of the Plague, viz. Swellings or Risings under the Ears or Arm-pits, or upon the Groynes, Blains, Carbuncles, or little Spots, either on the Breast or back, commonly called Tokens.

11. That if any House be Infected, the sick person or persons be forthwith removed to the said Pest-house, Sheds, or Huts, for the preservation of the rest of the Family: And that such house (though none be dead therein) be shut up for fourty days, and bade a Red Cross, and Lord have mercy upon us, in Capital Letters affixed on the door, and Watchers appointed, as well to find them necessaries, as to keep them from conversing with the sound.

12. That at the opening of each Infected house (after the expiration of the said fourty days) a White Cross be affixed on the said door, there to remain Twenty days more, during which time, or at least before any Stranger be suffered to lodge therein. That the said house be well Fumed, Washed and Cleansed all over within with Lime. And that no Clothes, or Houshold-stuff be removed out of the said house into any other house, for at least Three moneths after, unless the persons so Infected bade occasion to change their habitation.

13. That none dying of the Plague be buried in Churches or Church-yards (unless they be large, and then to bade a

Fig 3. Henry VIII Plague rules and orders.
National Archives

In the early modern era vermin were apportioned the blame for disease such that in 1647 Aberdeen council ordered the poisoning of rats and mice to prevent the spread of diseases.

In the modern era particularly, changes in land use have led to deforestation and the change of the use of land to farming, mining and oil extraction. Such changes have resulted in closer contact between humans and wild animal and rodent reservoirs – so-called "spill over events".

HISTORY OF PREVENTION

To the end of the 17th century diseases were assumed to be the sign of a poor moral and spiritual condition. The public effort to control disease included isolation of the sick and the quarantine of travellers. In 1665 houses in London were placed under quarantine in an attempt to stop the plague.

In the 18th century isolation and quarantine became more common across Europe especially in sea ports around the Mediterranean. Lady Mary Montagu, (Fig 4), having recovered from smallpox in 1715, reported on the use of "variolation" against smallpox on her visit to the Ottoman Empire in 1717. Her six-year-old son was variolated in 1718 and her two-year-old daughter in 1721. Lady Mary Wortley Montagu was, it is thought, responsible for importing variolation into England in 1721.[10]

Fig 4. Lady Mary Wortley Montagu.
Thought to have imported variolation into England in 1721.

Benjamin Jesty, a Dorset farmer, used cowpox to "vaccinate" his family against smallpox in 1774, noticing that milkmaids with cowpox lesions on their hands were "resistant" to suffering from smallpox. Edward Jenner improved the outcome and safety of patients by using smallpox vaccine in 1796.

The 19th Century

In 1853 vaccination against smallpox was made compulsory. Louis Pasteur and Robert Koch developed the Germ Theory of disease and suggest that disease is caused by bacteria and "unfilterable agents". Koch, together with Freidrich Loeffler, formulated Koch's postulates in 1884 as a result. Identification of filth as a cause and vehicle of transmission is termed "The Great Sanitary Awakening" and changed perceptions about health.

Disease was recognised as an indication of poor social and environmental conditions and increasing urbanisation led to an increase in the number of diseased individuals with London experiencing unprecedented numbers of cholera, typhoid and tuberculosis (consumption). As a result isolation and quarantine became difficult to establish.

The 20th Century

Sir Arthur Newsholme ,[11] (Fig 5) a Local Government Board physician, advised people to stay at home if they were sick and to avoid large gatherings during the 1917-1918 influenza pandemic. Unfortunately, his advice was not published by the Government of the day. He argued that many lives could have been saved if his suggestions were followed. There were no imposed lockdowns until it was too late and the attempt to limit crowds at large sporting events was delayed. Vaccination against influenza was introduced in the 1930s with large-scale availability in the 1940s. Development of vaccines then became a priority for many countries.

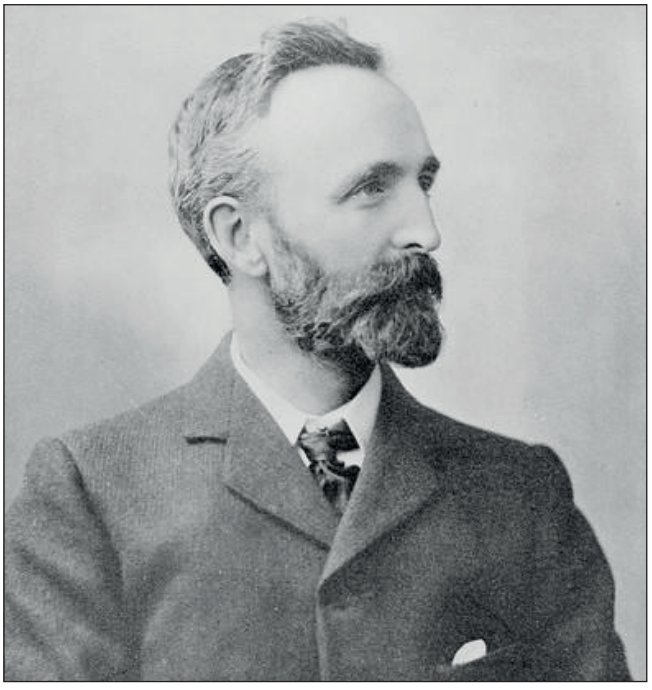


Fig 5. Sir Arthur Newsholme.
Local Government Board Physician during the 1917-1918 Influenza pandemic

Epidemics and pandemics of infectious diseases have devastated civilisations and over the centuries mankind has developed effective tools to deal with such outbreaks. A clearer understanding of quarantine and hygiene together with improved science has led to better hygiene and infection control together with the development of antibiotics, antiviral agents, vaccines, diagnostics and better reporting and surveillance.

WHAT HAVE WE LEARNED? [12]

Early warning detection, preparedness and laboratory facility

It has been demonstrated that international collaboration is essential for dealing with pandemics.

The need for early warning has led to improved local, national and international epidemiological surveillance. This has resulted in the development of a network of bodies that monitor, report and give advice. Organisations such as Public Health England (PHE), the US Centers for Disease Control and Prevention (CDC), the European Centre for Disease Prevention and the World Health Organization Global Outbreak Alert and Response Network. History has shown that lack of training, poor engagement of clinical staff, politicians and the general population, together with poor surveillance, isolation and the response capacity leads to poor control of outbreaks.

It has also been recognised that a resilient network of special and routine laboratory services has become essential for the detection and diagnosis of infectious diseases, especially when the disease is novel.

Development of novel diagnostics and effective vaccines

It has been demonstrated that international collaboration is essential for the dissemination of information necessary for the identification, detection and epidemiological typing of outbreak and pandemic strains to enable a clearer understanding of their epidemiology.

Development of vaccines, antimicrobial agents and vector control greatly impacts on the progress of an epidemic as demonstrated by earlier epidemics and pandemics.

WORLDWIDE PANDEMICS: COMPARISON OF EFFECTS

Between 1347 and 2019 there have been 16 pandemics causing at least 141 million deaths.

Table 2 lists these pandemic events with their estimated global death tolls.

Effects on healthcare systems

In Mediaeval Europe science, technology and medical

Pandemic	Estimated death toll
The Black Death 1347-1352	75 million
The Great Plague of Seville 1647-1652	2 million
The Russian Cholera Pandemic 1852-1860	1 million
Global Influenza Pandemic 1889-1890	1 million
"Spanish Flu" Influenza Pandemic 1918-1920	50 million
"Asian Flu" Influenza Pandemic 1957-1958	2 million
"Hong Kong Flu" Influenza Pandemic 1968-1969	1 million
SARS-CoV-2 2019-????	15 million (WHO estimate)

Table 2. Pandemic events from 14th to 21st centuries.

practice lagged behind the Islamic world. A combination of local knowledge of healing herbs and the use of town-based practitioners such as apothecaries and barber surgeons and university trained physicians were consulted but these groups did not share helpful information. Early hospitals in Europe, established mainly in response to the injured from the Crusades, were primitive. Sanitation and hygiene were poor and disease transmission poorly understood. Earliest attempts at disease control is believed to have occurred in Venice with other major ports adopting a detention period of 40 days (quarantine).

The influenza pandemic beginning in 1918, thought to be caused by the bacterium *Haemophilus influenzae* (no laboratory methods were available to detect viruses), had no treatment and the only protection in use at the time were face masks (Fig 6). The healthcare systems were seriously understaffed owing to losses caused by the First World War together with the high death rates from influenza. Medical school graduates, retired medical personnel, student nurses and dentists were drafted to make up for the losses. Healthcare was fragmented, social distancing measures were introduced but often too late.[10,13]

The introduction of socialised medicine in the late 1920s began to provide healthcare free at the point of access, first introduced in Russia followed by Germany, France and the United Kingdom.

The opening, in Vienna, of an international bureau for fighting epidemics was established in 1919 and was recognised as the forerunner of the World Health Organization.[14]

Economic effects

The Black Death ended population growth with one-third to a half of the population of Europe dying. The relationship between land-owning lords and the peasants working their land deteriorated significantly. Workforce reduction occurred owing to high levels of mortality resulting in demands for higher wages and greater competitive marketing particularly trading in wool, textiles and silk resulting, paradoxically, in increased economic welfare of the surviving population. Little coordination of sanitary efforts occurred, medical efforts failed since the profession was unprepared for such

Fig 6. Page appearing in Time magazine encouraging the wearing of masks during the influenza pandemic.

large-scale outbreaks resulting in many doctors and priests either dying or fleeing.

The influenza pandemic of 1918-1920 had short-lived negative effects with recovery of per capita income and economic recovery before the downturn experienced in the 1930s.

The retail grocery sector declined and an increased demand for beds, mattresses and bedpans occurred owing to massive increases in patient numbers. Labour supply temporarily declined owing to losses of men resulting from the First World War.

ANIMAL PLAGUES, PESTILENCE AND PANDEMICS

As with humans many diseases have had a devastating impact on wild and economically important animals. Deliberate or accidental introduction of animals such as cats, mice, rabbits and rats into new habitats has led them to become plagues in their own right; as predators or sources of disease. The use of animals for biological control has also produced important unforeseen effects. Important animal epidemics are listed below.

African swine fever became endemic to sub-Saharan Africa in wild pigs and warthogs and has now spread worldwide leading two massive losses of farmed pigs. In 1957 it became established on the Iberian Peninsula with concomitant outbreaks in France and Belgium which led to spread among

Outbreak	Detail
United States of America Nine major outbreaks between 1870 and 1929	Two detailed major outbreaks. 1914-1929; resulting in slaughter of cattle, sheep, swine and deer. 1929; outbreak originating in hogs that had eaten infected Argentinian meat from a tourist ship.
United Kingdom	1967; Infected lambs from Argentina and Chile led to the slaughter of 442,000 animals Stan estimated cost of £370 million. 2001; 2000 cases identified; six million animals culled. 2007; Outbreak in Surrey caused by the 01 BFS67 strain (a vaccine-like strain) which was used at the Institute of Animal Health four Km from the outbreak. Outbreaks occurred in nearby farms, all at-risk animals culled. Windsor Great park closed to protect the deer population.
China, Taiwan, Japan and Korea	Experienced major outbreaks

Table 3. Major outbreaks of Foot and Mouth disease.

wild boar across the Caucasus, Eastern Europe, Greece, Russia, Iran and Azerbaijan. The disease reached China in August of 2018 and India in 2020 and continues to spread.[15]

Bat White Nose Syndrome was first detected in New York and subsequently spread across North America in 2006 killing nearly six million bats with some species declining by 99% Caused by *Pseudogymnoascus destructans,* bat hibernation is disrupted leading to depletion of fat reserves and subsequent starvation. Paradoxically, it is not yet been found in Europe.[16]

Chlamydia infection in Koala bears is sexually transmitted, caused by *Chlamydia pecorum,* and leads to infertility, urinary and respiratory infections, blindness and death. Combined with drought and concurrent retrovirus infection, it has massively reduced Koala populations.[17]

Chytridiomycosis, an infection by the chytrid fungi *Batrachochytrium dentrobatis* and *B. salamandivorans*, has been linked to dramatic population decline and extinctions of amphibians in the Americas, Australia, East Africa and the Caribbean. Over 200 species have been affected and in Panama 30 species have been lost. American bullfrogs and African clawed toads seem to be resistant to infection and trade in these two species is blamed for the spread of the disease [18].

B. dendrobatids was first reported in Europe in the early 2000s and in the UK in 2005. As in the rest of the world, infection with this fungus is having a devastating effect on native amphibians. As an example, it has been associated with mass die-off of wild European fire salamanders, leading to a 99% decline in the national population of this species in the Netherlands.

Ebola infection in Great Apes has become a recent and serious problem. It is known that infection with Ebola virus will kill 95% of great Apes. The chimpanzee population in Cote d'Ivoire was decimated in the early 1990s and repeated outbreaks in the Democratic Republic of Congo have taken a heavy toll on the Gorilla population. Approximately 5000 Western Gorillas died in the period 2002-2003.[19]

Foot and Mouth disease is a debilitating and sometimes fatal viral infection of cloven-hoofed animals, including domestic and wild bovids, sheep, goats and wild animals including elephants and hedgehogs. Highly contagious, it has severe implications for the farming industry as control is achieved by the culling of affected herds and requires scrupulous decontamination of equipment, vehicles, clothing and feed. Table 3 outlines the major outbreaks of Foot and Mouth disease since the 1870s

Rinderpest is a viral disease of cattle and even-toed ungulates and has a mortality approaching 100% in immunologically naive populations. After a global eradication programme (Fig 7) the last case was recorded in 2001.[20] It is thought that measles and canine distemper, similarly causing devastating disease in naive populations, possibly emerged from rinderpest around 600 BCE.

West Nile Encephalitis was originally found causing disease in birds. This mosquito-transmitted virus was isolated in 1999 from patients with encephalitis in New York. At the same time several crows in the city and birds at the Bronx zoo were found to have died of this infection. Millions of birds in the United States of America have died of this disease and the virus has been detected in 48 species of mosquito and in 250 bird species and in horses.[21]

Sarcoptic mange (caused by *Sarcoptes scabei*) affects over 100 animal species as well as humans. It infests wombats, red foxes, lynx, wolves and domestic dogs and is thought to have rendered foxes on Bornholm extinct.[22]

Fig 7. Rinderpest campaign stamp.
Only the second global viral disease to have been eradicated.

Sylvatic plague arrived in North America around 1900 on ships from Europe carrying rats. Entire colonies of Prairie Dogs have been destroyed and 90% of black-footed ferrets, predators of prairie dogs, have subsequently been lost. Transmission to humans occasionally occurs, particularly among hunters.[23]

MAN-MADE THREATS AND DISASTERS

Human intent or negligence has led to great damage to human life, habitat and property. These have resulted in ill health and loss of life due to the release of microbiological agents, toxic chemicals or radiation into the environment.

Laboratory accidents

Accidents in the laboratory have led to exposure to chemical toxicity, radiation and biological agents.

Table 4 lists the most important events that have led to death, potential serious harm or injury.

Biological and chemical warfare

The use of biological agents, chemical toxins and radiological agents has occurred as a deterrent or for offensive purposes.[27-29] Possibly most infamously was the use of chlorine and mustard gas in the First World War in 1917 resulting in 6000 fatalities and 185,000 injuries. Preparation of sugar lumps containing tiny vials of anthrax spores [30] and the preparation of glanders and cholera as weapons was also documented. Experimental use of anthrax and plague on Japanese prisoners of war was recorded and subsequent preparation of biological weapons was developed by Israel, Iraq, Soviet Union, Libya, the USA and the UK. In 1972 The Biological Weapons Convention introduced regulations to control development and stockpiling of such weapons. However, in 1979 the accidental release of anthrax from a military unit near Moscow resulted in 64 deaths. Anthrax, used as a bio-terror weapon sent through the national post in the USA resulted in five deaths. Chemical poisoning using

Year	Site	Event
1958	Los Alamos National Laboratory, United States of America	Accidental exposure of scientist to a fatal dose of radiation
1967	Marburg Laboratory, Germany	Seven fatalities, work with monkeys infected with Marburg virus
1978	Birmingham, United Kingdom	Medical photographer fatally exposed to smallpox virus via unfiltered air duct [24]
1997	United States	Chemistry Professor, death due to skin absorption of dimethyl mercury[25]
2007	Pirbright Institute, Surrey, UK	Culpable in Foot and Mouth disease via drainage leak.
2009	CDC, Atlanta, USA	Viable anthrax spores sent via postal system.
2011	Yale University, USA	Student dies via hair entrapment in lathe while working alone out of hours.
2012	Animal Health and Veterinary Laboratory, Surrey UK	Viable anthrax spores sent other laboratories
2015	Tsinghua University, China	Researcher dies in explosion and fire[26]
2016	University of Hawaii, Honolulu, USA	Researcher lost arm as a result of hydrogen/oxygen explosion.
2018	Science Institute, Bengaluru, India	Cylinder gas explosion. One death and three seriously injured

Table 4. Laboratory accidents leading to death or potential serious injury.

a polonium-210 isotope poisoned Alexander Litvinenko, and Novochock nerve agent has been responsible for the poisoning of three people in England and the political activist Alexei Navalny.

Chemical accidents

In 1952 groundwater, soil and nearby water wells were contaminated by hexavalent chromium produced by a cooling tower leakage from a compressor station in Hinkley, California, USA. It was responsible for a number of cancer cases including of the lung and nasal sinuses. In the same year the great "smog" of London, smoke containing pollutants, resulted in at least 6000 people dying from respiratory complications with many more suffering prematurely from long-term respiratory disease.[31]

In Japan, in 1956 (Minamata)[32, 33] and 1960 (Yokkaichi), two serious chemical releases occurred involving toxic methylmercury discharged into Minamata bay which accumulated in the local fish and was subsequently eaten by the local population. Over 2265 victims were documented many suffering coma and death. Airborne sulphur dioxide released from the petrochemical refinery in Yokkaichi gave rise to severe respiratory symptoms in the population leading to a 10- to 20-fold higher mortality rate above the national average.

Perhaps the most well-known chemical accident occurred in Bhopal, India where at least 40 tons of highly toxic methyl isocyanate gas leaked from the Union Carbide pesticide company owing to equipment failures including safety devices.[34] At least 3800 died immediately with an estimated 20,000 premature deaths over the next two decades from associated complications.

Radiation

The Three Mile Island nuclear power plant in Pennsylvania, USA suffered a partial reactor meltdown in 1979 due to mechanical and human error involving the cooling system. Radioactive gases were released including iodine-131 leading to the mass evacuation of 200,000 people. Similarly, in 1986 in Chernobyl, Ukraine a powerful explosion in the nuclear reactor occurred followed by a core fire and second explosion resulted in the release of around 70 tons of nuclear fuel containing iodine-131 and caesium-137 during a nine-day period (Fig 8).[35] The radioactive cloud spread across Europe as far as the United Kingdom. Over 200,000 people were evacuated from the nearby surroundings. Two reactor staff died, 237 staff and fire fighters suffered acute radiation sickness and approximately 4000-5000 other cancer types were recorded.

Fig 8. The destroyed reactor at the Chernobyl nuclear plant.

In 2011 a large earthquake followed by a large tsunami resulted in three nuclear core meltdowns with three hydrogen air explosions and flooding of the lower reactors in the nuclear plant at Fukushima in Japan resulting in the evacuation of 154,000 people.

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Medical History

The Launch of William Whitla's Medical Institute: Concept and Commissioning

Alun Evans

Introduction

For the first 23 years of its existence, The Ulster Medical Society (UMS) met in the General (Royal) Hospital in Frederick Street (see Figure 1), Belfast,[1] according to Joseph Nelson, "For several years…in the cold underground storey".[2] Alternatively, to John Fagan, the President in 1884-85, it was a "...congenial place, we must admit, for prosecuting its (the UMS's) operations."[3] However, it had become apparent that a change of venue was necessary, but it would prove to be just one step in the quest for a permanent home for the UMS.

Figure 1:
The General (Royal) Hospital. Frederick Street, Belfast, c. 1900 (Courtesy of Archiseek)

The Belfast Museum

At a special meeting of the UMS on 23rd December 1884 a Report from its Council was:[4]

> …desirous of increasing the interest of the members in the meetings of the Society, & feeling that your place of meeting is very far from being comfortable or attractive, with a view of bringing the members into closer fellowship one with the other.

It recommended a change of venue from the General Hospital to the Belfast Museum, and a change of day (from Tuesday to Thursday), and that tea should be served at 7.30 pm. The Museum, run by The Belfast Natural History and Philosophical Society (BNH&PS), at No 7 College Square North, had been established by public subscription, the first of its kind in Ireland (see Figure 2).[5]

Figure 2:
The Museum, College Square North, Belfast, c. 1865 (Courtesy of the National Library of Ireland, Dublin)

The Report continued:[4]

> Some of the junior members of the Society have felt that the meetings were very lukewarm and and that there is a want of sympathy displayed one with the other: & in order to bring about a closer acquaintanceship & cause a firmer bond of union to exist amongst the members of the Society – your Council recommend the "Social Cup of Tea." Your Council express [sic] the hope that the members will throw more zeal & energy into the working of the Society, by attending the meetings in greater numbers and assisting the Society in procuring

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pabulum [intellectual sustenance].

This was passed and signed by John Fagan[6] on 8th January 1885, when the first meeting in the Belfast Museum took place, although the UMS continued to hold its Annual General Meetings in the General Hospital.[7] Fagan congratulated the members on the change of meeting place and expressed the hope that, "…the members would join more heartily in the working of the Society". The move, however, may have been triggered by external influences, because a piece in The Northern Whig reported[8] the move, and continued:

> This change has been rendered necessary by a decision come to that the meetings of the Society shall embrace the social element, and thus be conformed to the practice observed by similar scientific bodies in London, Dublin, and other large towns. The business of the meeting commenced at eight o'clock, but members assembled for tea half an hour earlier.

Some outside pressure may have been exerted by the British Medical Association which had held its Annual Meeting in Belfast the previous summer.[9] In his Introductory Remarks,[3] Fagan noted the change in venue, and hoped their work would be carried on with increasing energy under the somewhat altered conditions, adding:[3]

Figure 3:
Address to Sir William Whitla, June 1902, 'Illuminated by McCaw, Stevenson & Orr Ltd, in succession to Marcus Ward & Co., Belfast'
(Courtesy of Special Collections, QUB Library)

> I entertain the hope that the meetings of this Society will be honoured as well as benefited by a larger attendance of its senior members than it has been heretofore…. We have, representing the various branches of the profession in this town, men of high culture and vast and varied experience, whose opinions in discussions on the subjects with which they have specially identified themselves would form valuable contributions to medical science….With a rich vein of material at its command, and as I hope, the active co-operation of all its members, both young and old, I see no reason, gentlemen, why the Ulster Medical Society should not hold a prominent place among similar institutions throughout the kingdom.

Indeed, the choice of the Museum as the new venue was an obvious one, as Fagan himself had joined the BNH&PS in 1875, as had a fair proportion of Belfast's senior doctors,[10] including the doyens of early Victorian Medicine in Belfast.[11] Moreover, the Museum, as a cultural and social hub, was "A home of Science, Literature and Art," and, "…several of the other societies of the town…[had]… made it their home."[12]

Very probably, William Whitla (see Figure 3) had a hand in the UMS's choice of venue because he had moved into No 8, College Square North, next door to the Museum, in 1884,[13] joining the BNH&PS in 1887.[9] He and his Salvationist wife, Ada, resided there, until they moved into Lennoxvale in 1906, which was later to become the Vice-Chancellor's Lodge.[13]

The Museum became the UMS's home, almost continuously, for the next 17 years, after which, Dr Nelson recalled that the meetings were held, "…amidst stuffed birds, jars of snakes, and Egyptian mummies. (Laughter)".[2] Clearly, the UMS had come into close contact with the Museum's 'Cabinets of Curiosities'.[5]

The Excursion to Lombard Street

Almost a decade later the UMS moved into new premises at 13 Lombard Street and held its Annual General Meeting there on 20th July 1894.[14] But things did not go well, because on 16th April 1896 a Council Report stated:[15]

> Owing to the rapid growth of the Society and the inconvenience of the present rooms, the Council recommend that the owners be noticed [sic] of our intention to leave on 1st November next.

William Whitla later described the move as a "…dreary experience,"[16] and Joseph Nelson thought the rooms were "…almost attic."[2] In November 1896, meetings resumed[17] in The Museum, except for an occasional one held in Queen's College,[18] until dedicated accommodation became available late in 1902.

A Permanent Home for the Society

William Whitla had been President from 1886-87 and was asked to stay on for another year but "...circumstances beyond my control prevented my accepting the position then".[16] He became President again in 1901, when, in his Opening

Address in November, he gave a potted history of the 'greats' of Ulster Medicine, and intimated that the time was ripe that "…this flourishing Society should aspire to a local habitation of its own." The Annual Dinner for 1901-02 took place on 21st November 1901, in the Princes' Restaurant, Donegall Square North.[19] It was attended by 84 persons.

Whitla was in great voice at the Dinner:[19]

> As regards the length of the talking period to-night, when I sit down I suspect that none of you will suspect that I abridged the toast list in order to give rein to my own poor chatter, or that any one will feel like the Irish sailor after his first visit to church – "that there is too much singing with too little drinking, and one man engrossed the whole conversation."

He insisted that he would not be delivering a speech, but he wished to make a simple statement regarding the future of the UMS, adding:[19]

> When it gets very 'dry' I know you have the antidote at your elbows in the form of moisture. (I have taken the precaution to send the waiters round with the 'minerals.') At our opening meeting I ventured to voice what I believe is the universal feeling of the Society - that we should have a local habitation of our own, in which we could hold our meetings, and enjoy the privileges of a first-class library and reading-rooms in a place of which we might not be ashamed.

He ruled out the "dreary idea" of renting a series of rooms in a large public building and dismissed the possibility of re-appointing a large derelict house:[19]

> It would not even be a white elephant, but a dead leaden-coloured beast, whose maw we could never fill, and it would not even be a joy to look upon.

The only hope he held out was a "building of our own" – a "Medical Institute" –but, "let us confine our attention entirely to the question of its upkeep." Various projections and estimates ensued as to how the upkeep might be assured, as it was up to the UMS to take over the building's upkeep. He continued:[19]

Since I have been your President fifteen years ago, it has been the dream of my life that one day I should be able to leave behind me when that day came enough money to build for you a suitable Institute.

Whitla's dream was now realisable, thanks to the prodigious success of his medical publications, especially his *Dictionary of Medical Treatment*, which was translated into many languages, including Chinese.[20] Whitla went on to describe the new Institute:[19]

> It will have a frontage of 45 feet…Upon the first floor will be one large room, or small hall, 45 by 33, outside measurement. It will be quite as large as the large room in the Museum… I trust this is the last dinner the UMS will ever have in a Restaurant. I should expect that this hall will dine 120 people with comfort. …members can smoke in the billiard room …I should hope that, whilst the billiard room will be fully enjoyed by the members, that no spirituous liquors shall ever be supplied in the building, save at times like the annual dinner…a plot of ground within 100 yards from where we now meet, in College Square North, is available.

Doctors and Drink

The report of the Dinner in the News-Letter drew a lively correspondence under the heading 'Doctors and Drink.' It was sparked by a letter[21] from a Dr AHH M'Murtry, of the Crumlin Road, who was a strong advocate of temperance.[22] His polemical letter included lines such as the "'fearful pit and miry clay' of drunkenness," and described the Prince's Restaurant as a "Fashionable wine-shop," commenting:[21]

> It is surely possible for sensible men, especially for the members of the noble, learned, and honoured profession like the medical, to dine together, to perform every social function and fulfil every hospitable duty, to cultivate every virtue of fellowship and gratify every longing of brotherhood, without drinking intoxicating liquors. What possible affinity can such demoralising drinks have with those pure and lofty sentiments?

This drew a short, restrained reply from 'MEDICO,' which concluded:[23]

> If Dr. M'Murtry joins the new institute I am sure all will be glad of his mature advice and co-operation. His enthusiasm for the temperance cause is well known, and perhaps some overflow might be directed to elevate the profession in other ways.

'M.D.' also weighed in,[24] regretting, "…for the sake of the doctor's reputation and consistency" that Dr M'Murtry had failed to quote his own words he delivered in a paper two years before:[24]

> Twenty years ago I had a severe attack of pneumonia, accompanied by extreme prostration. Two esteemed and trusted medical friends…. believing that I was in danger of sinking, ordered me a small and carefully regulated dose of whisky, which I took, and began to amend the self-same hour.

M.D. maintained that the whisky had not only saved "Dr. M'Murtry's valuable life," but under similar circumstances, had saved thousands of lives.

M'Murtry responded[25] with yet more temperance rhetoric, attacking M.D. for cloaking himself in anonymity, and ended:

> To every word of the foregoing I firmly adhere today, though I am sorry that some of my brethren have somewhat disappointed the hope expressed in it. I am consoled, however, by the belief that my previous letter has won the approval, and I the spoken or unspoken thanks, of thousands of your readers. I thank you for

> your courtesy, and decline to take any further notice of anonymous assailants.

M.D. replied,[26] observing that, "Dr. M'Murtry hath waxed wroth once more." He accused M'Murtry of trying to pose as a victim, and fired this Parthian shot:

> An indulgence in intemperate language is as baneful to a man's reputation as is an indulgence in strong drink, and it greatly mars his power for good.

This very public spat cannot have done the local profession any good and rather took the gloss off Whitla's magnanimous gesture. Indeed, it is tempting to suspect that M.D. was none other than Whitla himself, but in his Materia Medica of 1903, although he recommends[27] alcohol, particularly whiskey, as a narcotic in a range of conditions, and, "… occasionally by the use of alcohol life may be saved which would otherwise be lost", he doesn't claim that it had saved thousands of lives.

The provision of alcohol at UMS functions was a perennial, vexed problem: in 1886, the question as to whether wine should be provided at a Conversazione was debated, but on the result of a motion, it was agreed that "…there should not be any wine".[28] The following year a motion that the wine bill for the dinner would be paid out of the UMS's funds was initially passed, and then voted down.[29] In 1901, the ticket for the Annual Dinner of 10s – 6d included aerated waters & cigars, but the wine bill was divided among those taking wine.[30]

The Smoking Concerts

All this may explain why the UMS elected for Smoking Concerts: the first, "most successful." in 1900, hosted by the UMS President, James Graham, for the members on a vile February evening,[31] and another to entertain those attending the British Association Meeting in September 1902. It was held in the Botanic Exhibition Hall and was attended by about 200 "principal professional gentlemen." They were treated to "…an attractive and varied literary and musical programme…assisted by Mr Whitworth Mitten, the accomplished London tenor, who charmed the audience with his several contributions,"[32] with light refreshments being served. The Smoking Concerts seem to have been Conversaziones with smoking substituted for wine. According to the Irish-American journalist, Frank Harris,[33] "…sobriety became the custom" in just a decade towards the end of the Victorian era, and it was, "The cigarette introduced by the Prince of Wales which made London Society sober."

The source of the Smoking materials for the Concerts is not recorded.

The Medical Institute's Foundation Stone

The foundation stone was laid on April 12th 1902, by Professor Peter Redfern.[34] It was to be sited from land acquired from 'Inst' on the other side and end of College Square North. The work contractors were M'Laughlin & Harvey, and the architect, William J. Fennell. The estimated cost was about £6,500, and the building was due for completion by the end of the year. The Chairman, the Reverend Dr Hamilton, President of Queen's College:[34]

> ... understood there would also be rooms for recreation for such members of the medical profession, if there is any such, as ever condescended to such a light method of spending their time. (Laughter and Applause.)

The recently knighted Sir William Whitla then presented a solid silver trowel to Professor Redfern, who laid the stone amid loud applause, and declared it well and truly laid. In the cavity of the stone was placed a sealed bottle, containing records of the UMS. The silver trowel bore the Irish hallmark, an inscription, and a beautiful engraving of the new building, drawn to scale from the architect's plans.

The New Medical Institute's Opening

The Opening Ceremony on 26th November 1902[35] was a gala event with many guests invited (see Figures 4 & 5). It was performed by Lord Dudley, the Lord Lieutenant, accompanied by his wife, The Countess of Dudley. The three-storey building was perpendicular in the Gothic style,

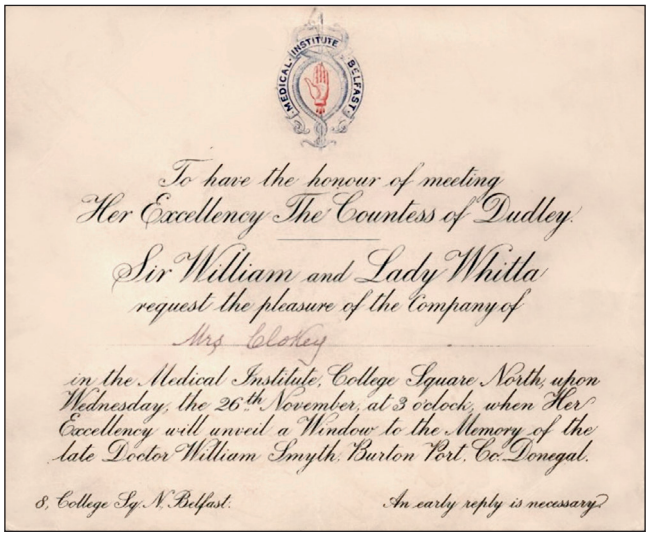

Figure 4:
Invitation to the Unveiling of the Dr Smyth Memorial Window (Obverse side – Author's Collection), sent to a 'Miss Clokey,' probably the Principal of Glencraig Infant School, and a friend of Ada, please see: https://streetdirectories.proni.gov.uk/media/05PPtPE-sOd8ROtnTB5ugw..a?ts=xUFJvQJaGZFORucuqBSmO5VrzQOQcRxaN77Ed2694q0.a (Last visited: May 2022)

in ashlar with red Dumfries sandstone worked in moulded dressings, which included stone 'bosses' carved with the heads of four great local physicians: Andrews, Gordon, MacCormac (elder), and Redfern. The total cost of the new Institute was about £8,000 [£800,000 today].

The Chair was again taken by Dr Hamilton, President, who observed:[35]

> The hour of enfranchisement of the Ulster Medical Society, struck upon the clock of time, and with that hour

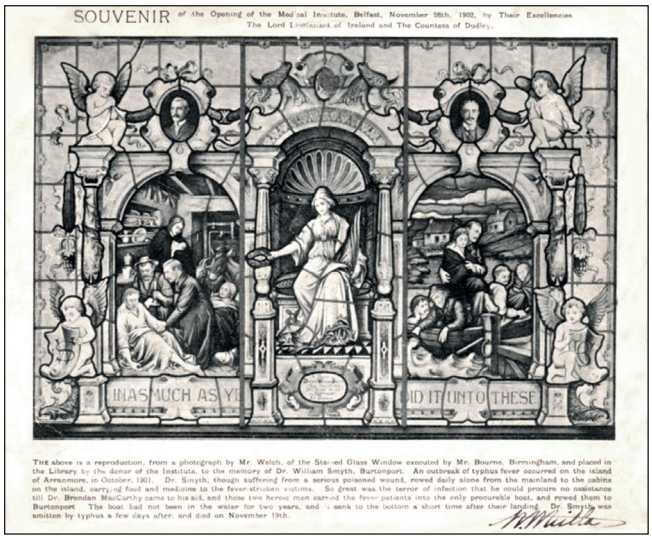

Figure 5:
Invitation to the Unveiling of the
Dr Smyth Memorial Window (Reverse side)

came the man in the person of my friend, your friend, Sir William Whitla."

Sir William then spoke, and having handed the deeds to Dr Campbell, the incoming UMS President, amid great cheering, he presented the key to the Lord Lieutenant. The key had its head in the form of an open shamrock. It is joined to a fluted and tapered stem by richly carved mouldings; the former was encircled by sprays of shamrock. The obverse of

Figure 6:
The Whitla Medical Institute, College Square North, Belfast, in 1986 (Courtesy of Dr Paul Larmour)

the key bore an enamel replica of the seal of the new Medical Institute, with the Red Hand of Ulster in the centre. The Institute finally became 'The Whitla Medical Institute' after Sir William's death in 1933.[36]

The Lord Lieutenant then declared the new Institute open (see Figure 6) and lavished praise on Sir William's generosity. Speeches followed from Dr Hamilton, Professor Redfern and Dr Nelson.

The Lord Lieutenant and Countess of Dudley next drove to the Harbour Office (stopping on the way at Mr W Kilpatrick's establishment in Donegall Place to get their photographs taken). It was a tight schedule for the Dudleys, as only two days before, he had laid the foundation stone of the Municipal Technical College[37] which, once built, was to spoil the Museum's outlook and blight its setting.

The Dr Smyth Memorial Window

That afternoon, Her Excellency The Countess of Dudley returned to unveil the Dr Smyth Memorial Window.[38]

Sir William, who took the chair, reported that The Duke of Abercorn had "…a long-standing engagement in England… [but]…I rejoice to know that Sir Thomas Myles, as one of the Smyth Fund trustees, will not be absent." The window, by the artist Swaine Bourne of Birmingham, was placed above the fireplace in the reading-room.

It was uplifting stuff from The Countess:[38]

> The few and striking facts connected with the life and death of Dr. William Smyth are well known to all of you – the years in which he attended the sick, the outbreak of typhus on Arranmore, when he nursed the fever-stricken islanders and rowed them in an open boat to the mainland; finally, his death from the infectious fever. The profession to which he belonged is one with which is associated a lengthy chronicle of noble deeds, many of them unostentatiously performed in the ordinary course of duty, often unrecorded and unacquainted with fame. Of this profession he was a true and worthy representative. (Applause.) … His life teaches many lessons, and his memory distils a pleasant fragrance. Upon it rests forever the dignity of service and sacrifice.

The window was then unveiled: "It was greatly admired by the Countess, as well as by all present." Sir William then read the poem, "Amid the wastes and wilds of Arranmore." A souvenir album was presented to Lady Dudley. Dr Joseph Nelson, senior trustee of the Institute, proposed a vote of thanks. This was seconded by Sir Thomas Myles, President of The Royal College of Surgeons in Dublin, who had been a college mate of William Smyth.[2]

Annual Dinner

At the Annual Dinner that evening, Sir William, responding to a toast to him and his wife, referred to Dr Nelson's description of the Museum, and, betraying his interest in Biblical prophecy,[13] added:[38]

> …their sojourn among the snakes, stuffed birds, bottle specimens and mummies. They had now come up from the land of Egypt, and if he was to judge from the oratory they had listened to that night, they had come into a land flowing with milk and honey. They had placed at the top of their roof the fiery serpent as a memento of their journey in the wilderness.

Introducing a note of levity, he was comparing the serpent on the Staff of Aesculapius, gracing the crest of the new Institute, with the snakes that the UMS had encountered during its time in the Museum.

Conclusion

The UMS's first meeting took place in the new Institute on 11th December,[39] its first in its dedicated home since its formation 40 years before. It also severed its links with the BNH&PS, which it had enjoyed almost continuously for the past 17 years. These may have been 'wilderness' years, but during that time the membership of the UMS had almost tripled, doubtless driven by the introduction of UMS Fellowships in 1885. This, after all, was the reason for moving to the Museum in the first place.

Acknowledgements

Thanks are due to Dr Michael Trimble who arranged access on my behalf to the UMS records. Special thanks are due to Kathy Clarke and Colin Mathews for making me feel do at home in the UMS's Rooms in The Whitla Medical Building, The Centre for Biomedical Sciences and Education, QUB. I am grateful to Dr Paul Larmour for his valuable advice and for granting me access to Figure 6. Lastly, as ever, I wish to record my gratitude to Deva Evans (Graphics) and Beth Evans (Proofreading).

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Medical History

Higgs Boson: Chapel Hill, CERN, QUB

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Key Words: Geordies, Nobel Prizes

INTRODUCTION

Professor Sir Peter W. Higgs was born in Elswick, Newcastle-upon-Tyne in 1929. I[1] was born nearby in Jesmond, near Newcastle University, a few years later.

For schooling, Higgs with his parents, was moved to Bristol. His father was employed as a BBC engineer[1,2]. At Bristol, Higgs's left arm was broken by a fall into a crater left by a German bomb[1,2]. Higgs read Physics at Imperial College, London, where he progressed to a Ph.D. in Physics with Distinction. This led to Higgs's appointment at Edinburgh University in the Physics Faculty[1,2]. From its Tait Institute of Mathematical Physics, in October 1964, Higgs published a brief communication, "Broken Symmetries and the Masses of Gauge Bosons"[3].

In 1965-1966 Higgs spent a sabbatical year at the University of North Carolina, Chapel Hill[1,2,4]. Higgs expanded upon his 1964 publication[3], and in November 1965 from Chapel Hill submitted his paper, "Spontaneous Symmetry Breakdown without Massless Bosons" to *Physical Review*[5]. Higgs sent simultaneous copies to colleagues he thought would be interested in a pre-publication reading[1,4].

CERN: HIGGS FIELD AND THE HIGGS BOSON:

The Conseil Européen pour la Recherche Nucléaire, European Organization for Nuclear Research, known as CERN, was established with an initial Resolution at a December 1951 meeting of the United Nations Educational, Scientific and Cultural Organization (UNESCO) in Paris. In June 1953 the CERN Convention was signed by twelve Member States, and in 1955 construction of CERN's Geneva Research Facility began[6]. At present membership has grown to twenty-three Member States along with Associate Members and Observers[7].

The Higgs field causes elementary particles to attain mass[8]. CERN originally defined the Higgs boson as "a particle predicted by theory. It is linked with the mechanism by which physicists think particles acquire mass[9]". Proof of the predicted particle, it was thought, would complete the Standard Model of Particle Physics developed during the second half of the last century[8,9,10,11,12]. Higgs' 1966 paper[5] and what followed was a crucial turning point in understanding this model for all matter[1,4, 8,10,11,12].

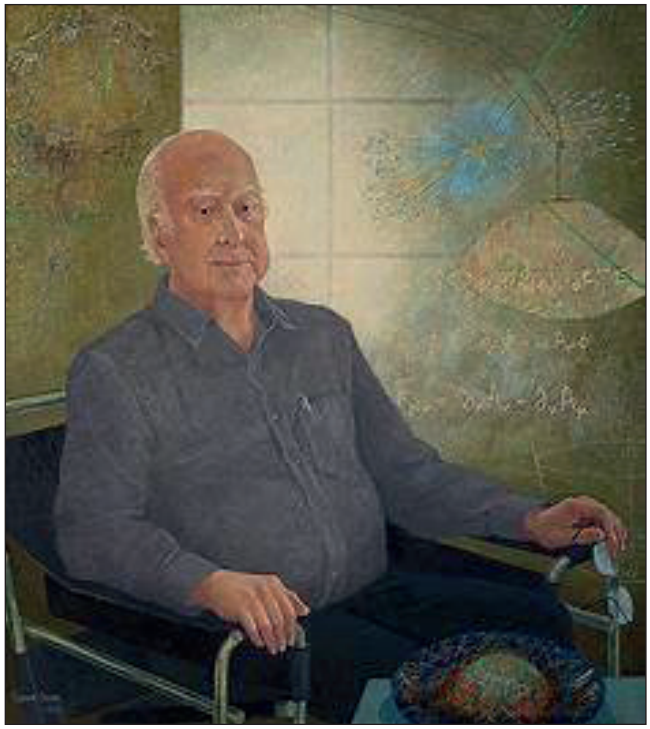

Figure 1. Sir Peter Higgs (1929-) by Victoria Crowe, OBE, DHC, FRESE, MA (RCA), RSA, RSW (1945-). Oil on canvas, 2014, 127 x 140.5 cm. Reproduced by permission of the Royal Society of Edinburgh.

Forty-seven years after publication of his 1966 paper, submitted from Chapel Hill, Peter Higgs (Fig. 1) was awarded the 2013 Nobel Prize in Physics, shared with

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Professor François Englert of the Free University of Brussels. The Nobel Citation states: "For the theoretical discovery of a mechanism that contributes to our understanding of the origin of mass of subatomic particles, and which recently was confirmed through the discovery of the predicted fundamental particle, by the ATLAS [A Toroidal LHC Apparatus] and CMS [Compact Muon Solenoid] experiments at CERN's Large Hadron Collider"[13,14,15].

GEORDIES VISIT UNIVERSITY OF NORTH CAROLINA, CHAPEL HILL

In March 1966, while a Clinical Associate in Anaesthesia at Harvard University, I was invited to the University of North Carolina, Chapel Hill to advise changes needed in the leadership of Surgical Departments. Welcomed with Southern hospitality, I was introduced to my "fellow Geordie", Peter Higgs. Our dinner host told me that 'Wykehamist' Professor Freeman J. Dyson[16,17,18] at the Institute for Advanced Study (IAS) in Princeton, New Jersey had insisted that the following week, on March 15, 1966[1,4], there should be a Higgs lecture at IAS on the acquisition of mass by subatomic particles.

FREEMAN J. DYSON: IAS, PRINCETON

Freeman J. Dyson was born at Crowthorne, Berkshire, in 1923, the son of Sir George Dyson, Composer, and Director of Music at Winchester College from 1924, and his lawyer wife, the former Mildred Atkey[16,17,18,19,20]. He was elected a "Scholar" at Winchester College. These select seventy boys lived within the College[18]. Freeman Dyson was awarded prizes in Mathematics and Science. He also distinguished himself in Athletics and became a Shakespearean Scholar[18].

In 1941, Dyson proceeded as Scholar to Trinity, Cambridge[16,18,19,20]. Paul Dirac was Dyson's Physics Professor[21], as was Arthur Eddington[22]. Dirac was a Fellow of St. John's College and winner of the 1933 Nobel Prize in Physics for "the discovery of new productive forms of atomic theory"[21]. He was also Lucasian Professor of Mathematics (1932-1967), the chair held by Newton (1663-1696), and Stephen Hawking (1979-2009)[23]. Dyson studied Mathematics with the legendary G.H. Hardy[24]. World War II interrupted Dyson's Cambridge education and from 1943-45 he was Civilian Scientist for the R.A.F.[17,19,20,25]. He later elucidated his rationale for civilian scientific work in critiques of nuclear and other warfare[26]. He returned to Cambridge to complete his B.A. in the Mathematics Tripos in 1945. Dyson entered Cornell University's Physics Department under future 1967 Physics Nobelist Hans Bethe in 1946[27]. At Cornell Dyson developed a collegial friendship with Richard P. Feynman, Professor of Theoretical Physics, and 1965 Winner of the Nobel Prize in Physics[1,19,28,29]. While Dyson contributed to the mathematics of theories of quantum electrodynamics, he did not share Feynman's Nobel Prize[17,19].

While Dyson never received his Doctorate, he taught at Cornell from 1949-1952[17]. Professor Dyson accepted a Permanent Position offered by Director J. Robert Oppenheimer[30](Table 1), at the (IAS), Princeton, New Jersey, as a colleague of Einstein[19] (Fig. 2). Dyson was elected Fellow of the Royal Society in 1952[20]. Dyson held his Professorship at IAS for the remainder of J. Robert Oppenheimer's directorship (1947-1966) and throughout Dyson's career[17,19,25] (Table 1). Dyson's original contributions to mathematics, physics and

TABLE 1. DIRECTORS, INSTITUTE FOR ADVANCED STUDY, PRINCETON, NJ[30]

Director	In Office
Abraham Flexner	1930-1939
Frank Aydelotte	1939-1947
J. Robert Oppenheimer	1947-1966
Carl Kaysen	1966-1976
Harry Woolf	1976-1987
Marvin L. Goldberger	1987-1991
Phillip A. Griffiths	1991-2003
Peter Goddard	2004-2012
Robbert Dijkgraaf	2012-2022
David Nirenberg	2022-

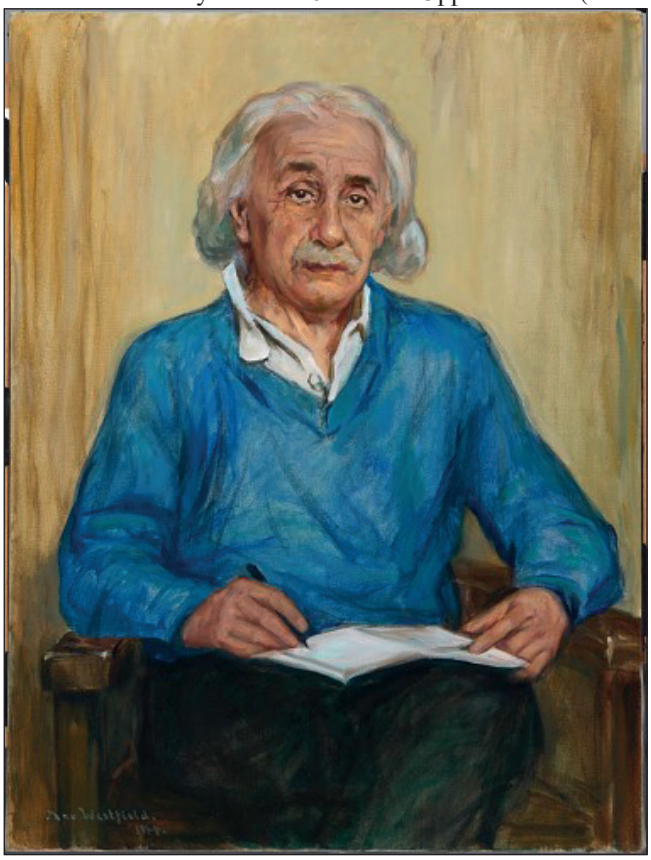

Figure. 2. Albert Einstein (1879-1955). Oil-on-canvas, 1944 by Max Westfield (1882-1971), 40.5 x 30.5 inches. Catalog no. NPG.67.16, National Portrait Gallery, Smithsonian Institution, Washington, DC. Gift of the artist; ©Estate of Max Westfield, and reproduced with permission.

cosmology led to a long list of publications[19,31,32,33]. While he was never awarded the Nobel Prize, he received many honours including the Max Planck Medal (1969), the Harvey Prize[34](1977), the Wolf Prize in Physics (1981), and twenty-one honorary doctorates[20].

FOUNDING AND DIRECTORSHIP OF IAS IN PRINCETON, NEW JERSEY

The IAS was founded in 1930 with an initial endowment of five million dollars (just over one million pounds, or 62.5 million pounds in 2019[35]), the gift of renowned Newark, New Jersey Department Store innovator and philanthropist, Baltimore-born Louis Bamberger and his sister, Mrs. Felix ("Carrie") Fuld[36]. Bamberger was acquainted with Harry Gordon Selfridge from Selfridge's early career at Chicago's Marshall Field's. They corresponded for many years[37]. After selling his sixteen-story department store to the owners of Macy's at peak before the October 1929 Stock Market Crash, Bamberger and his sister considered endowment of a medical school in Newark. They consulted their legal and financial advisors, Herbert Maass and Samuel Leidesdorf, to select the individual they considered most astute and knowledgeable: Dr. Abraham Flexner, author of the eponymous 1910 Report on Medical Education[36,37,38]. Dr. Abraham Flexner was a brother of Dr. Simon Flexner who served as the first Director of the Rockefeller Institute for Medical Research, later renamed Rockefeller University, from 1911-1935[39]. The Flexners were acquainted with and assisted by President Theodore Roosevelt[37,39]. Louis Bamberger and Carrie Fuld met with Dr. Abraham Flexner in New York City[37].

Abraham Flexner advised against establishing a medical school in Newark, New Jersey. Abraham Flexner advocated instead for the foundation of an independent educational institution to support and encourage creative scholarship in multiple disciplines. The Bamberger siblings were inspired by the potential of Abraham Flexner's proposal and agreed, with the stipulation that Flexner serve as the new Institute's first Director[30,37] Dr. Flexner served from 1930-1939 (Table 1). Bamberger and Flexner's appointees to the initial 1930 Board of Trustees included 1912 Nobel Prize Winner in Physiology and Medicine Alexis Carrel[40], Johns Hopkins Professor of Pathology and Bamberger cousin Florence R. Sabin, and former Johns Hopkins Medical School Dean Lewis Weed[37]. A suitable site was acquired in Princeton, New Jersey, and Fuld Hall, named for Bamberger's late business partner and brother-in-law Felix Fuld, was built[36,37,41] (Fig. 3). Louis Bamberger supported the lease of Princeton University space for the new Institute until separate facilities were available[37]. Abraham Flexner developed a close and collegial friendship with Louis Bamberger, who maintained an active role in the academic and administrative affairs of the (IAS), and continued his financial support. Upon Bamberger's death in 1944, IAS was the beneficiary of the greater part of his estate[37].

In October 1932 the Institute announced the appointment of its first two Professors of Mathematics, Oswald Veblen and

Figure 3. Cornerstone-laying ceremony, Fuld Hall, IAS, May 22, 1939; Photographer unknown.

Attendees shown left to right: Alanson B. Houghton (IAS Trustee), C. Lavinia Bamberger (sister of IAS founders and benefactors, Louis Bamberger and Caroline (Carrie) Bamberger Frank Fuld), Albert Einstein, Anne Crawford Flexner (wife of Abraham Flexner), Abraham Flexner (IAS Director), John R. Hardin (IAS Trustee), Herbert Maass (IAS Trustee), Harold W. Dodds (President, Princeton University). Louis Bamberger and Mrs. Fuld did not attend and were represented by their sister. From the collections of the Shelby White and Leon Levy Archives Center, Institute for Advanced Study, Princeton, NJ, USA, no. E-36, and reproduced with permission.

Albert Einstein[36] (Fig. 2). In 1933, Einstein surrendered his German passport at the German Consulate in Antwerp. He proceeded to England where he considered other offers of academic positions. In October 1933, while still a "Research Student" at Oxford[41] Einstein arrived in Princeton, New Jersey to begin what would become a lifetime tenure[36,42].

In February 1966, shortly before Peter Higgs' March 15, 1966 guest lecture at Professor Dyson's invitation, the IAS publicly announced the upcoming retirement of its director, J. Robert Oppenheimer who would be succeeded by Harvard's Littauer Professor of Economics, Carl Kaysen[43,44,45] (Table 1).

Professor Kaysen had been President J.F. Kennedy's Deputy Special Assistant for National Security Affairs from 1961-1963, including the Cuban Missile Crisis, before his appointment to the Economics Faculty at Harvard. During World War II, Kaysen had served the U.S. Air Force as an Intelligence Officer at High Wycombe, where officers were quartered in Wycombe Abbey, a school for young ladies. At IAS, Kaysen and Dyson became close colleagues and friends who shared reminiscences of their wartime experiences[17,45,46]. J. Robert Oppenheimer died of throat cancer on February 18, 1967[19,43]. Kaysen continued as Director of IAS until 1976, when he returned to Cambridge, Massachusetts to accept a Professorship at the Massachusetts Institute of Technology. Here he served as David F. Skinner Professor of Political Economy[46].

PETER HIGGS AT HARVARD

Early in the morning after being dined with Peter Higgs at Chapel Hill, I phoned Prof. Fred Mosteller[47,48,49,50,51,52] with whom my Harvard boss Henry K. Beecher[53,54] (Fig. 4) had me working on non-parametric statistical problems[47,51]. I recounted my meeting with Peter Higgs. I learned that Fred Mosteller, who had received his Ph.D. from Princeton in 1946 and maintained strong academic ties throughout his career, was acquainted with Professor Dyson, as well as with Harvard's Professor Kaysen (Table 1). After my telephone call to Professor Mosteller, Peter Higgs was invited to speak

Figure 4. Henry K. Beecher (1904-1976), Henry Isaiah Dorr Professor of Anaesthesia Research, Harvard University. Oil on canvas, 1962, 48 x 31 inches, by Jean-Pierre Alaux (1925-2020). From the collections of the Massachusetts General Hospital, No. 81. Beecher was mentored by Harvard Professor of Surgery Edward Delos Churchill and Danish Nobel Laureate August Krogh of the University of Copenhagen. Henrik Bendixen and I continued the research of Professor Lorraine Smith, Musgrave Professor of Pathology at QUB.

at Harvard on March 16, 1966, the day after his visit to the IAS[1,2,4]. Peter Higgs gave his lecture and then by request was asked to continue in symposium mode. The reported attendees included future 1979 Nobel Prize Winner Sheldon Glashow of Harvard and later University Professor at Boston University[55], long-time distinguished Harvard Professor of Physics Sidney Coleman[56], Harvard Associate Professor of Biophysics Walter Gilbert, later Winner of the 1980 Nobel Prize in Chemistry[57], and Professor Fred Mosteller of Harvard, best known at that time for establishing the authorship of the *Federalist* Papers[58]. In his 2013 Nobel Prize Acceptance Lecture, Higgs credited his 1966 Harvard invitation to Stanley Deser of nearby Brandeis University, who became Ancell Professor of Physics and later Visiting Professor at the California Institute of Technology, Pasadena[59,60].

CERN

The proofs for validation of Higgs' work came from two parallel experiments of CMS and ATLAS at CERN's Large Hadron Collider (LHC) beneath Geneva, Switzerland[2,10,12,61,62,63]. Geordie Peter Higgs' 2013 Nobel Prize was shared with Professor François Englert of the Free University of Brussels[13,64]. Higgs' brief communication to *Physical Review Letters,* received on 31 August 1964 and published on 19 October 1964[3] had, at the request of the Editor[4,59] referenced Englert and Brout's similar communication to the same journal published on 31 August 1964[64]. Englert's colleague, Robert Brout, had predeceased[65].

At the July 4, 2012 CERN press conference honouring Peter Higgs, Queen's University Belfast-educated Director of Accelerators and Technology, Stephen Myers was among the CERN leadership[62]. Also present were Professors Gerald Guralnik of Brown University, Providence, RI[66,67], and Carl R. Hagen[66,67]of the University of Rochester, New York State, whose parallel efforts[4], along with those of Thomas Kibble, FRS 1980, Knighted 2014[68,69], had contributed to understanding of the Higgs mechanism and boson characteristics. After the CERN Press conference, Peter Higgs took the next flight back to Edinburgh with colleague Alan Walker[2].

STEPHEN MYERS: BELFAST AND GENEVA

Physics Review published Peter Higgs' landmark paper submitted from Chapel Hill on May 27,1966[5]. Higgs returned from Chapel Hill to Edinburgh in the autumn of 1966[1,2,4]. Belfast-born Stephen Myers was then a student at QUB. He received his BSc Degree in Electrical and Electronics Engineering with First Class Honours in 1968 and his PhD in 1972[70]. Late in 1972, he began his career at CERN as Engineer-in-Charge for the operation of the Intersecting Storage Rings (ISR)[70]. In 1983 he coauthored preliminary performance predictions for a Large Electron-Positron Collider (LEP)[70]. Myers was given responsibility for commissioning the LEP, and oversaw its preparation. During the 1990s Myers was appointed Project Leader of the LEP upgrade. QUB awarded Myers an Honourary DSc (Eng) in 2003[70,71].

CERN released the details of the September 19, 2008 incident which disabled the LHC. Reports state that "…a fault occurred in the electrical bus connection in the region between a dipole and a quadrupole, resulting in mechanical damage and release of helium from the magnet and cold mass into the tunnel. Proper safety measures were in force, the safety systems performed as expected and no-one was put at risk"[72,73].

In October 2008, Myers was nominated CERN's Director of Accelerators and Technology. In the aftermath of the

Figure 5. CERN, July 4, 2012; Announcement of the proof of the Higgs boson. Co-Nobel Prize winners in Physics 2013, Englert and Higgs are shown.

The central physicists, CERN management and officers: Front row, left to right: Physicist Francois Englert, Physicist Peter Higgs, ATLAS spokeswoman Fabiola Gianotti, CERN Director Steve Myers. Second row, left to right: CERN Director Sergio Bertolucci, CERN Director- General Rolf Heuer, CMS spokesman Joe Incandela, Physicist Carl Hagen, Physicist Gerald Guralnik. From the Photograph Collection of CERN, Geneva, Switzerland, and reproduced with permission.

September 19, 2008 incident, Myers organized the repair of the LHC and directed its continued operation from 2010 through 2012. Under his direction, in 2012, the LHC received approval for two large experiments, ATLAS and CMS, to confirm the Higgs boson[74,75]. Myers was named Head of CERN's Office of Medical Applications from January 1, 2014[74,76].

On April 2, 2014, Myers returned to QUB to lecture on "The Large Hadron Collider and the Discovery of the Higgs Boson"[77,78].

Work continues at QUB with the development of new particle accelerators. Dr. Gianlucca Sarri, who received his Ph.D. from QUB in 2010, has reported on proposals to build a powerful yet compact particle accelerator at QUB as part of ongoing work by the European Strategy Forum on Research Infrastructures[79,80]. Plasma, ionised gas broken down to its basic components, can provide much higher accelerating power than a solid-state accelerator. The proposed accelerator is designed to use lasers to move the plasma particles in waves. Dr. Sarri reports that the space required for a plasma-based particle accelerator will be reduced ten-fold from 400 by 400 meters to 40 by 40 meters. Potential medical applications include enhanced images of biological samples and early detection of tiny cracks or defects in medical instrumentation[79].

The proposed accelerator at QUB would be used to produce accelerated particles used for radiotherapy and nuclear medicine. The European Strategy Forum on Research Infrastructures is expected to shortly reach their decision on the report[79,80,81].

CERN AND MEDICAL PROGRESS

The history of subatomic particle therapy goes back at least a century[82,83,84,85]. In recent years, investigators at CERN and with affiliations to many universities and hospitals worldwide have investigated a broad array of technologies and applications. CERN's medical endeavors continue[76,86,87].

EPILOGUE

Shortly after my return from Chapel Hill to Harvard, on March 17, 1966, Fred Mosteller told me that, "Peter Higgs' lecture-cum-symposium was convincing and well-received. A Nobel Prize will follow." That award, and others, did follow. On November 15, 2013, the City of Edinburgh, granted its Freedom of the City to Professor Peter Higgs[88]. Geordie Higgs' birthplace, as well as mine, granted Freedom of Newcastle-upon-Tyne on April 2, 2014[89].

On April 17, 2014, Higgs' Nobel Prize co-winner, Professor François Englert, delivered the David M. Lee Historical Lecture in Physics at Harvard. He recounted the formulation of the theory known as the Brout-Englert-Higgs mechanism[3,64]. Professor Englert discussed the role of the ATLAS and CMS detectors at CERN, and "the implications for unknown universal structures that might be revealed at even higher energies"[90].

ACKNOWLEDGEMENTS

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Letters

HAART, THE HEART AND THE POTENTIAL FOR INTERACTION

Editor,

Approximately 103,800 people in the UK are living with human immunodeficiency virus (HIV) as a chronic disease, reflecting the major impact of highly active antiretroviral therapy (HAART). Physicians will be familiar with links between HIV and acute coronary events[1, 2] but may be less familiar with potential interactions between HAART and cardiovascular medication.We describe a patient living with HIV who underwent primary percutaneous coronary intervention (PPCI) with stent implantation for acute myocardial infarction, along with some important therapeutic considerations that were required to optimise his cardiovascular prognosis.

A 47-year old man presented with acute chest pain for 4 hours and was diagnosed with ST-elevation myocardial infarction. He underwent PPCI with stenting of an acutely occluded proximal left anterior descending coronary artery. An echocardiogram showed impaired left ventricular systolic function with an ejection fraction of 30%. Standard therapy with aspirin and ticagrelor were commenced along with eplerenone, atorvastatin, ramipril and bisoprolol.

The patient was HIV-positive, well controlled on HAART comprising a combination of emtricitabine/tenofovir and efavirenz. Since 1999 the University of Liverpool has maintained a free HIV drug interaction resource which enables healthcare professionals to check HAART against any new medication being initiated. It provides a traffic light system demonstrating the strength of any potential interaction, a summary of the evidence and the specific effect expected. The Table summarises its comments relating to interactions with antiplatelet therapy.

	Clopidogrel	Ticagrelor	Prasugrel
Emtricitabine	Unlikely to affect	Unlikely to affect	Unlikely to affect
Tenofovir	Unlikely to affect	Unlikely to affect	Unlikely to affect
Efavirenz	**May diminish efficacy**	**May diminish efficacy**	Unlikely to affect
Etravirine	May diminish efficacy	May diminish efficacy	
Abacavir	May diminish efficacy	Unlikely to affect	Unlikely to affect
Nevirapine	May enhance efficacy	May diminish efficacy	
Darunavir/Ritonavir	Likely to diminish efficacy	Likely to enhance efficacy	Unlikely to affect
Darunavir/Cobicistat	Likely to diminish efficacy	Likely to enhance efficacy	Unlikely to affect
Atazanavir	Likely to diminish efficacy	Likely to enhance efficacy	Unlikely to affect
Fosamprenavir	Likely to diminish efficacy	Likely to enhance efficacy	Unlikely to affect
Indinavir	Likely to diminish efficacy	Likely to enhance efficacy	Unlikely to affect
Lopinavir	Likely to diminish efficacy	Likely to enhance efficacy	Unlikely to affect
Saquinavir	Likely to diminish efficacy	Likely to enhance efficacy	Unlikely to affect
Tipranavir	Likely to diminish efficacy	Likely to enhance efficacy	Unlikely to affect
Dolutegravir	Unlikely to affect	Unlikely to affect	Unlikely to affect

Table. Potentially important effects of antiretroviral drugs on the efficacy of antiplatelet agents[3]. Those relevant to this patient are highlighted in bold

Because efavirenz could potentially decrease ticagrelor efficacy due to induction of cytochrome P450 3A4, we switched from ticagrelor to prasugrel. Additionally, because of potential interactions between efavirenz, atorvastatin and eplerenone, we switched the latter two to rosuvastatin and spironolactone.

HAART has been a key development in modern medicine, achieving a life expectancy for people living with HIV close to that of the HIV-negative population[4]. Primary PCI is another major advance, but relies on effective dual antiplatelet therapy to prevent stent thrombosis, a highly-lethal early complication[5].

Clinical teams should be aware of potential overlaps between HAART and cardiovascular medicines, as well as a valuable resource that guides the selection of agents least likely to be compromised by co-prescription with HAART.

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REACTIVE NON-REGIONAL LYMPHADENOPATHY FROM THE COVID-19 mRNA VACCINE: A NOVEL SIDE-EFFECT

Editor,

A 42-year-old South-Asian male presented with multiple new painful lumps in his right groin, 1 week after receiving his 2nd dose of the Pfizer vaccine in the left arm.Systematic questioning did not reveal any history of temperatures, night sweats, or weight loss. There was no history of injury to the right leg or any signs of local infection. There also was no history of genital discharge or ulceration. No past medical history of tuberculosis or family history of cancer was noted.

Recent travel history was unremarkable.

On examination two lumps were palpable in the distribution of the vertical chain of inguinal lymph nodes.

These were tender, firm in consistency and had a smooth surface. Systemic examination revealed no significant lymphadenopathy in the other regions. Abdominal and urogenital examination was also unremarkable.

Biochemical investigations revealed normal inflammatory markers including white cell count of 5.49 cells10^9 /L, C-Reactive protein 0.7 mg/L and ESR2 mm/hour on 2 consecutive samples thereby making the suspicion of an infectious aetiology like tuberculosis less likely. Lactate dehydrogenase was 180 U/L and full blood count was normal (Haemoglobin 150 g/L, Platelet count 265 cells 10^9/L) ruling out the possibility of haematological malignancy. Other biochemical tests including urea and electrolytes, liver enzymes, ferritin, vitamin B12 and folate levels, corrected calcium, and alkaline phosphatase levels were all found to be within normal range. An ultrasound scan (USS) confirmed two inguinal lymph nodes (Figure 1 images a, b) with the largest lymph node measuring 3cm in diameter and described as homogenous with preserved hila in keeping with reactive lymphadenopathy. A follow up USS in 4 weeks revealed a significant reduction in size (6mm) (Figure 1 images c, d) and their appearance was also reported to be normal. Further clinical follow-up in 3 months revealed absence of any ongoing or new symptoms and complete resolution of inguinal lymphadenopathy.

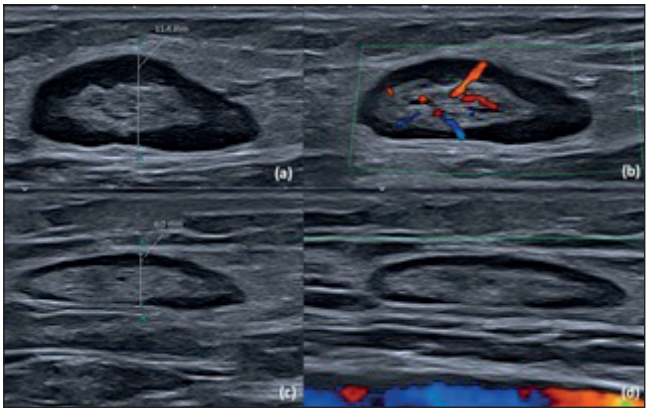

Fig. 1: Grey scale (a) and Colour Doppler (b) ultrasound images of the right groin 10 days after the COVID vaccine demonstrated a mildly enlarged superficial femoral lymph node (vertical group) measuring 11.4 mm in short axis diameter with preserved fatty hilum and minimally increased hilar vascularity, in keeping with a reactive lymphadenitis, corresponding to clinically palpable mildly tender lump.

Follow up grey scale (c) and Colour Doppler (d) ultrasound images of the right groin showed complete regression of the reactive lymphadenitis to normal, appearing right superficial femoral lymph node measuring 6 mm in short axis diameter with negligible vascularity on colour Doppler correlation.

At the time of writing this report non-regional reactive lymphadenopathy had not been reported as a possible transient side-effect to anyvaccine[1, 2, 3]. This is hence the first reported case in literature highlighting this novel side-effect.The authors acknowledge the absence of a definitive investigation that could confirm direct causation between the vaccine and our case's presentation. However, the absence of any other plausible explanation, the timing of development of the symptoms after the vaccine administration, and complete clinical and radiological resolution of inguinal lymphadenopathy with conservative management supports the hypothesis that this was an adverse reaction to the novel vaccine. Furthermore, the initial radiological appearance of a reactive lymphadenopathy also reinforces our suspicion.

This case emphasizes the importance of obtaining recent immunization history in people presenting with unexplained lymphadenopathy, thereby possibly avoiding the need for further CT imaging and invasive lymph node biopsy tests. There has also been a lot of interest in investigating the migratory function of dendritic immune cells as a cause of local lymphadenopathy following inflammation[4, 5]. This case also highlights the need for further research to fully understand the pathophysiology of distant site lymph node activation following vaccine administration.

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ALLERGIC CONTACT DERMATITIS TO A COMMON TOPICAL ACNE TREATMENT – AN UNFAMILIAR MIMIC OF ANGIOEDEMA.

Editor,

A previously healthy, non-atopic 12-year-old girl presented to the Emergency Department with a pruritic, facial skin eruption. Examination revealed localised facial swelling, tenderness and erythema limited to periorbital, malar, and nasal areas (Figure 1). The patient was commenced on intravenous antibiotics and admitted for inpatient observation.

Concern was heightened six hours later, with urgent review demonstrating rapid progression in symptom severity.

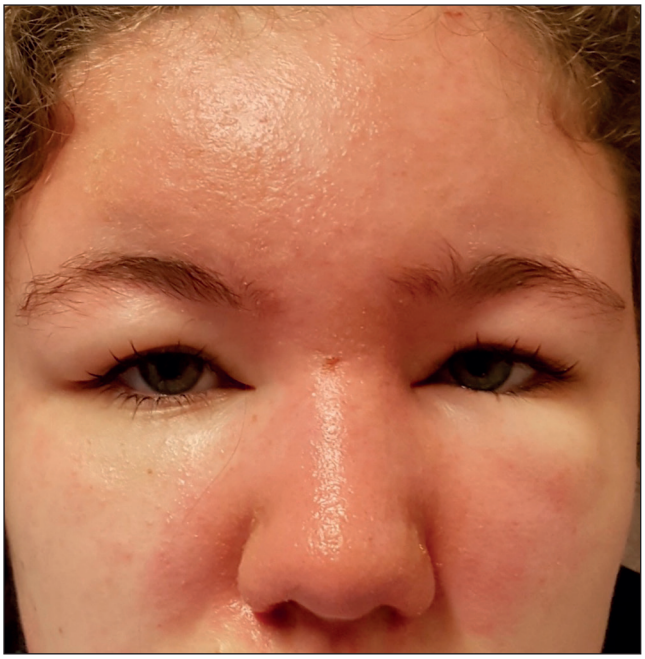

Figure 1. Photograph upon initial presentation of mild/moderate facial erythema, crusting and swelling.

Examination revealed marked periorbital oedema resulting in almost complete palpebral fissure closure, with skin thickening, coalescing papules and honey-coloured crusts (Figure 2). Reassuringly, there were no signs of airway, respiratory, cardiovascular, or gastrointestinal compromise, and normal vital signs made anaphylaxis unlikely. Likewise, without visual disturbance or restriction in eye movement, concerns of periorbital cellulitis were lowered.

Upon revisiting the history, the exacerbation coincided with the continued use of topical Benzoyl Peroxide (BPO) gel which had been prescribed by her general practitioner two weeks earlier as a common first line agent used in mild papulopustular acne.

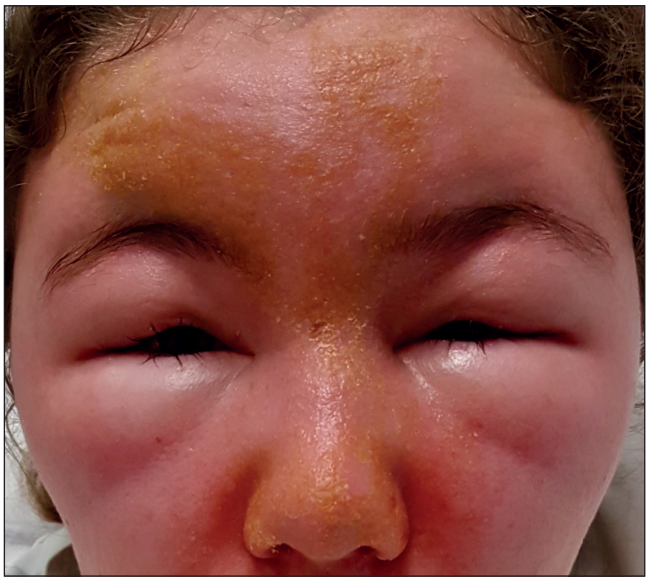

Figure 2. Photograph six hours later of florid/marked facial swelling, erythema and coalescing papules with honey-coloured crusts associated with allergic contact dermatitis.

Treatment with oral corticosteroids and topical corticosteroid/antibiotic therapy was commenced. Marked improvement was seen within twenty-four hours of treatment with complete resolution achieved at two weeks. While a patch test was not performed to confirm sensitization, the clinical presentation and timing of symptoms were deemed pathognomonic for Allergic Contact Dermatitis (ACD), as recognised instantaneously upon consultation by dermatology colleagues. While practice has moved away from patch testing in paediatric populations, avoidance measures were successfully undertaken for products containing topical BPO and alternative topical acne treatments commenced without symptom reoccurrence.

ACD is an inflammatory skin response induced by contact with an allergen, causing a type four hypersensitivity reaction. When it manifests on the face, it is often misdiagnosed as angioedema due to the marked periorbital swelling[1]. It can be differentiated from angioedema by demonstration of associated superficial erythema, dermatitis, pruritus, tenderness and, most importantly, a history of allergen contact. Later, as the swelling resolves, desquamation is a distinguishing feature of ACD, in contrast to patients with angioedema.

BPO is a common first line topical treatment for acne vulgaris in children and young people[2]. While common side effects of skin irritation are recognised and reflect BPO's irritant properties, little is known of its allergenicity[3]. ACD to BPO as described, is felt to be underreported due to its similarity in clinical presentation to irritant contact dermatitis[4]. Symptom onset and exposure history can be helpful in establishing the diagnosis which is ultimately verified upon patch testing[5].

While there are few reported cases of contact sensitisation to BPO, risk factors for ACD have been identified. These include a compromised epidermal barrier, allergen contact at multiple sites and prolonged, frequent exposure. Multiple risk factors result in a more severe reaction, as in our case.

This case highlights ACD as a cause of pseudoangioedema - knowledge of which will help paediatricians and General Practioners target the correct underlying pathophysiology when assessing children and adolescents using this agent for treatment of acne vulgaris. With improved awareness of its allergenicity, adolescents can be safely counselled regarding its application and side effect profile.

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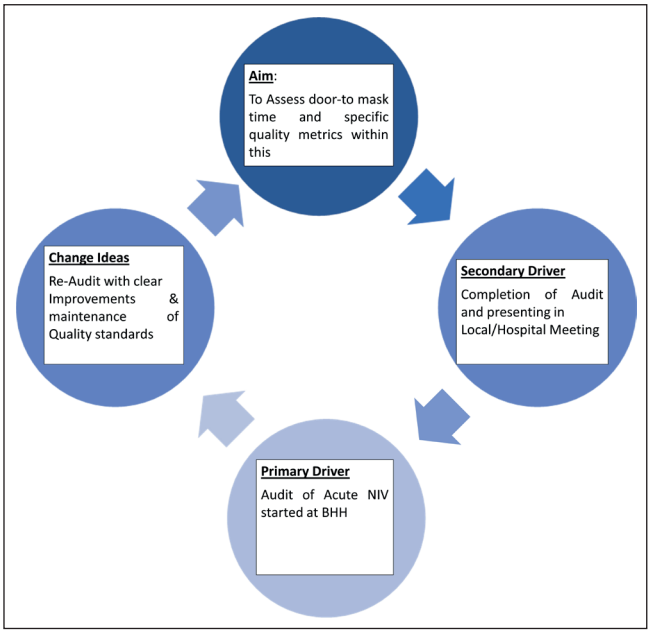
RESPONSE TIMES FOR ACUTE NON-INVASIVE VENTILATION SET-UPS

Dear Editor,

NIV is a lifesaving treatment in chronic obstructive pulmonary disease (COPD). Prompt NIV treatment in hypercapnic COPD exacerbations allows for improved physiological outcomes, reduced intubation rates and shortened hospital stay in (1, 2). Therefore, consensus expert opinion is that prompt application of acute NIV substantially reduces the risk of death and should be started without delay in appropriately selected patients with acute hypercapnic respiratory failure (AHRF).The 'door-to-mask' time (hospital arrival to NIV commencement: target ≤120 minutes) has been widely used to measure the quality of acute NIV services as per the 2018



BTS Quality Standards (3, 4). In setting a 120 min target from arrival to mask application, this statement intends to establish that recognition and treatment of AHRF are time-critical events for patients admitted acutely. We previously reported a median 'door-to-mask' time at the emergency department at Heartlands Hospital in 2014 of 115 min, meeting the 2018 BTS quality standard of ≤120 minutes(5). As part of an important quality improvement initiative, we have subsequently developed internal guidelines and monthly NIV training sessions to try to improve acute NIV service quality.We aimed to look at response times within the door-to-mask time using standards derived from the British Thoracic Society/Intensive Care Society Guideline for the ventilatory management of acute hypercapnic respiratory failure and 2019 BTS NIV Audit Report to generate insights for future quality improvement (6) (Figure 1).

Data on metrics were recorded for all acute NIV recipients in the Emergency Department (ED) at Heart of England Foundation NHS Trust and stored in our acute NIV quality database for subsequent extraction and calculation of median (interquartile ranges (IQR)). Between 27/03/19 and 26/09/19, 89 patients received NIV with 46 starting on acute NIV in ED, 38 developed acidosis later and 5 had incomplete data(7). The total door to mask time in ED was 163 (197) mins. Within this, the door-to-first-ABG time was 29 (55) minutes, the first-ABG-to-Decision making/call time was 72 (77)minutes and decision making-to-mask time was 40 (20) minutes. We saw an increase in door-to-mask time from 2014 to 2019, likely reflecting the national increase in ED wait times. However, the decision-making to mask time was 40 min which has decreased from 55 since 2014, reflecting the improved response times of physiotherapists potentially due to feedback on performance and monthly NIV training sessions for allied health professionals, as well as internal guideline development (8). This audit is part of a continual quality improvement project and will serve as a foundation to monitor specific response times and quality with iterative interventions. With the ongoing COVID-19 pandemic and stringent infection control measures around aerosol generating procedures, it is now essential to determine the impact this has had on NIV service quality and excess deaths with a view for continual quality improvement.

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UNUSUAL CASES OF ACUTE PANCREATITIS IN PATIENTS WITH COVID-19

Editor,

COVID-19 commonly presents as cough, shortness of breath, and fever, but extrapulmonary manifestations are being reported in recent times[1]. This is consistent with the fact that the ACE2 receptors through which the coronavirus SARS-CoV-2 enters cells are present in many organs beside the lung[2]. Gastrointestinal involvement in COVID-19 has become more common with many patients presenting with pain abdomen, diarrhoea, nausea and vomiting[3]. Here we outline 2 cases of COVID-19 associated acute pancreatitis.

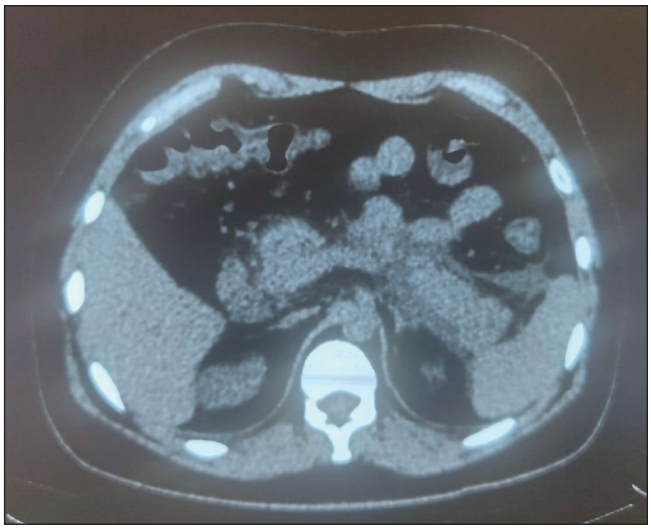

Figure 1: Axial plain CT images showing enlarged pancreas with peripancreatic fat stranding

A 33 year-old male diagnosed with COVID-19 presented with loose non foul-smelling and non blood-tinged stools, vomiting and pain abdomen. The patient had stable vitals and denied consumption of alcohol over the last 4 months. The epigastric and left hypochondriac region were tender on palpation. Lab investigations revealed grossly elevated serum lipase (5257 IU/L) and amylase (3269 IU/L). CT scan of the abdomen and pelvis revealed perinephric fat stranding in the head, body and part of the tail of the pancreas- suggestive of acute oedematous pancreatitis. Minimal peripancreatic fluid was also seen extending to the anterior perinephric fascia (Figure 1). A diagnosis of acute pancreatitis secondary to COVID-19 infection was made. The patient was given IV fluids, broad spectrum IV antibiotics, analgesics and other supportive treatment. A CT guided fluid aspiration was done for the peripancreatic fluid which was sterile. Patient recovered completely following treatment and was discharged.

In another instance, 76-year-old woman tested positive for COVID-19 after developing low grade intermittent fever over 10 days. Over the course of her home isolation, she developed generalised weakness and myalgia, productive cough MMRC grade 3 breathlessness. She did not consume alcohol.

Respiratory rate was 32 cpm and on auscultation bilateral crepitations were heard in the infrascapular areas. A high resolution CT scan of the chest showed features suggestive of COVID-19 pneumonia with a CT score of 17 out of 25.

Two days after admission, she started developing pain in the epigastric and left hypochondriac area which was tender on palpation and was associated with nausea and vomiting. Repeat investigations revealed grossly elevated amylase (1955 IU/L) and lipase (4895 IU/L). Abdominal ultrasound detected the presence of minimal ascites, prominent pancreatic duct and fluid collection near the tail of the

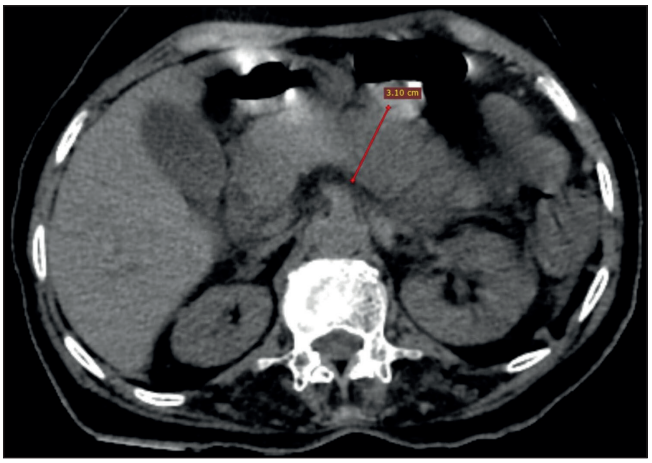

Figure 2: Plain CT axial view showing enlarged pancreas with fluid in the tail region with peripancreatic fat stranding.

pancreas. NECT of abdomen revealed a bulky pancreas, with inflammatory fat stranding present at the tail end of the pancreas and some enlarged peripancreatic lymph nodes present near the pancreatic tail (Figure 2). The patient was given IV fluids, broad spectrum IV antibiotics, analgesics and other supportive treatment. Despite resolution of the pancreatitis with treatment, the patient developed worsening lung complications and succumbed to the disease.

COVID-19 infection has been linked to pancreatitis in the absence of traditional risk factors like alcohol consumption or gallstones[4], as in the case of our patients, both of whom had neither a significant history of alcohol consumption or any evidence of gallstones on imaging. Other causes of pancreatitis include trauma and steroid use, and a history of neither was present in our patients. Both patients had no history of pain or swelling in the parotid region- which would rule out mumps as a potential cause of pancreatitis. Furthermore, neither patient had a history of scorpion stings, which is a rare cause of cause pancreatitis. In both patients serum calcium and triglycerides were within normal limits. Considering all the above, a diagnosis of COVID-19 related pancreatitis was made. As more cases of acute pancreatitis in patients with COVID-19 are being reported, it becomes pertinent to screen patients with COVID-19 presenting with gastrointestinal complaints for pancreatitis with serum amylase, lipase and abdominal CT scan.

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Book Case

BOOK REVIEW:

Drife J O. *This Medical Life*. Clinical Press Ltd. Bristol. U.K., 2020.

James Owen Drife is a man of many parts. As Professor of Obstetrics in Leeds he had a distinguished academic career. For many mere mortals that would be a sufficient life-time achievement. He has, however, many more strings to his bow. Author of academic articles, teacher, wit, raconteur, stage performer and after-dinner speaker, to name just a few. "This Medical Life" is a compilation of published articles written by Drife over a period of more than 40 years. Drife , in his author's note says that he "resisted the temptation to tweak the wording or add footnotes." A consequence of that decision is that some of the topics are no longer topical, but the writing is still engaging.

When he was a medical student in Edinburgh Drife participated in student reviews, and later as a postgraduate student, that experience led him, with a group of friends, to participate in the Edinburgh Fringe Festival in the 1970's. As a complete coincidence, one of his fellow performers was a trainee in neurology in London at the same time as me. (We worked on the same ward.) The book contains an account of their escapades on the Edinburgh Fringe published in the BMJ in 1974 - "Louder and Funnier".

This led to a sequence of humorous short articles, published in "World Medicine" in 1977-8 and then in the "BMJ" in a regular column as "Opinion" from 1988-1990. He was recruited by Stephen Lock who felt that the pages of medical journals lacked humour. The relationship with the BMJ continued when Richard Smith took over as editor. Richard Smith has written an entertaining foreword lauding Drife's injections of humorous wit and wisdom to the pages of his journal. Richard Smith, brother of the comedian Arthur Smith (frequently heard on Radoi 4) is fond of self-deprecating humour.

In about 200 short articles the subject matter varies widely and ranges from his experiences as a medical student, his shared love of the "Beano" with his wife, interactions with his students, an appreciation of James Robertson Justice's portrayal of Sir Lancelot Spratt, the need for a new section of the House of Lords - "The Lords Medical", "How to Party" and "Seven Guidelines of Wisdom". In this latter article he opines, and I quote - "Today's NHS is constantly seeking novelty. Its jargon has a six-week shelf life. In this context it takes nerve to point out the obvious. Wisdom is old fashioned, but it can be repackaged under a snappy title like Clinical Governance..." He also says "who ever heard of a wise person reading numbered guidelines? Or writing them?" He also has pithy comments on medical educators' attempts to teach wisdom.

My feeling is that information, knowledge and wisdom are concepts entirely different from each other. We live in an age overflowing with information. Many now feel the information available in fractions of a second using an electronic device makes knowledge redundant. (Guidelines are also available on such devices.) Wisdom is a scarce commodity. This little book is overflowing with wisdom, delivered in a fashion that frequently made me, like Richard Smith, laugh out loud.

Stanley Hawkins
Retired Neurologist

Ulster Med J 2022;**91(3):**173-177

Abstracts

Scrubs (QUB Surgical Society) Medical Students' Academic Medicine Conference & Research Symposium

30th April 2022, Queen's University, Belfast

ENDOSCOPIC BALLOON DILATATION FOR PAEDIATRIC SUBGLOTTIC STENOSIS: SYSTEMATIC REVIEW AND META-ANALYSIS

Author: Gopika Sreejith

Aim: Subglottic stenosis (SGS) is a rare life-threatening condition that involves a narrowing of the airway. It may be congenital or acquired affecting children predominantly. Traditionally, it has been treated by surgical interventions, but in recent times a shift towards minimally invasive Endoscopic Balloon Dilatation (EBD) has been observed. This review aims to identify whether EBD is a safe approach as the primary mode of treatment of SGS in the paediatric population.

Methods: A systematic review was performed on EBD for paediatric SGS in compliance with the PRISMA guidelines. Studies published from 2000 onwards, with sample size greater than 5 and described EBD without adjuvant procedures were included. A meta-analysis of proportions was performed using the R software.

Results: 21 studies were included, with a total of 922 patients, of which 753 underwent EBD. The mean sample size of the studies is 43.90 ± 40.25, and the grand mean age is 2.91 ± 4.08 years. Primary outcome assessed was technical success. A high overall technical success rate (avoidance of tracheostomy/laryngotracheal reconstruction) was observed (84.30%, 95% CI [76.62%, 89.80%]). Similarly, low levels of mortality (2.13%, 95% CI [1.09%, 4.13%]), high rates of symptom improvement (77.42%, 95% CI [62.62%, 87.52%]) and low rates of reintervention (30.43%, 95% CI [18.88%, 45.12%]) were also observed.

Conclusion: EBD is a successful procedure in majority patients, with low levels of adverse events and marked symptom improvement. It is therefore a safe alternative to current procedures in the primary management of paediatric SGS.

A REVIEW OF LITERATURE ON ANATOMICAL VARIATION OF THE EXTRA-HEPATIC BILIARY TREE

Author: Grace Kettyle

Introduction: Knowledge of the notoriously variable anatomy of the extrahepatic biliary tree is crucial, given the increased occurrence and complexity of hepatobiliary surgeries where failure to recognise the variant anatomy may lead to inadvertent iatrogenic injury.

Aim: This review aimed to examine world literature to establish the types and frequencies of anatomical variants within the extrahepatic biliary tree, identified using cadaveric techniques and imaging modalities.

Methods: A database search of MEDLINE, EMBASE and PubMed conducted in June 2021 returned 3440 articles, of which 29 were deemed eligible for inclusion.

Results: A rare malposition, the left-sided gallbladder, was observed in 0.04-0.60% across five studies. The medially inserted cystic duct into the common hepatic duct had a reported prevalence ranging from 10-24.3%. Variant cystic artery origin was noted from the left hepatic artery (1-1.9%), gastroduodenal artery (1-7.5%) and the aberrant right hepatic artery (3-12.1%). It was also observed that in 3.6-32% of subjects the course of the cystic artery lay extraneous to Calot's triangle. Michels' and Hiatt's classification systems were used to define the anatomical variations of the hepatic arteries: studies using Michels' Type III reported a prevalence from 6.4-15%, Michels' Type VI from 0.6-7% and Hiatt's Type III recorded an incidence of 9.7-14.8%.

Conclusion: The anatomy of the extrahepatic biliary tract is *indeed* widely variable, as is the conflicting reported data from the different imaging modalities used. Surgeons should therefore anticipate such complexities and adapt techniques to avoid biliary and arterial injuries and associated intra- and postoperative complications.

IMPACT OF THE COVID-19 PANDEMIC ON PATIENTS WITH PAEDIATRIC CANCER IN LOW-INCOME, MIDDLE-INCOME, AND HIGH-INCOME COUNTRIES: A MULTICENTRE, INTERNATIONAL, OBSERVATIONAL COHORT STUDY.

Author: Manasi Shirke

Aim: Paediatric cancer is a leading cause of death for children. Children in low-income and middle-income countries (LMICs) were four times more likely to die than children in high-income countries (HICs). This study aimed

to test the hypothesis that the COVID-19 pandemic had affected the delivery of healthcare services worldwide and exacerbated the disparity in paediatric cancer outcomes between LMICs and HICs.

Methods: A multicentre, international, collaborative cohort study. Patients recruited from 91 hospitals and cancer centres in 39 countries providing cancer treatment to paediatric patients between March and December 2020.

Results:1660 patients were recruited. 219 children had changes to their treatment due to the pandemic. Patients in LMICs were primarily affected (n=182/219, 83.1%). Relative to patients with paediatric cancer in HICs, patients with paediatric cancer in LMICs had 12.1 (95% CI 2.93 to 50.3) and 7.9 (95% CI 3.2 to 19.7) times the odds of death at 30 days and 90 days, respectively, after presentation during the COVID-19 pandemic ($p<0.001$). After adjusting for confounders, patients with paediatric cancer in LMICs had 15.6 (95% CI 3.7 to 65.8) times the odds of death at 30 days ($p<0.001$).

Conclusions: The COVID-19 pandemic has affected paediatric oncology service provision. It has disproportionately affected patients in LMICs, highlighting and compounding existing disparities in healthcare systems globally that need addressing urgently. However, many patients with paediatric cancer continued to receive their normal standard of care. This speaks to the adaptability and resilience of healthcare systems and healthcare workers globally.

PREOPERATIVE MEDIASTINAL STAGING IN RESECTABLE NON-SMALL CELL LUNG CANCER IN A SINGLE SURGICAL CENTRE

Author: Rachael Macaulay & Karolina Janus

Accurate preoperative staging of mediastinal lymph nodes in non-small cell lung cancer (NSCLC) aids selection of patients suitable for lung resection.

Guidelines released by the European Society of Thoracic Surgeons (ESTS) in 2014 outline that 100% patients with suspected cN1 or greater NSCLC require invasive mediastinal lymph node staging.

Aim: The aim of this audit was to collect and analyse data on the adherence to the ESTS guidelines for patients with TNM stage N1 or greater clinical lung cancer in a single surgical centre in Belfast.

Method: Data of all lung cancer resections between February 2019 and May 2021 were retrospectively reviewed using the Electronic Care record and the Dendrite operative database. 72 patients met the inclusion criteria.

Data collection included whether patient received EBUS and/or mediastinoscopy, along with pre-operative N stage (from PET) and post-operative N stage

Results: On analysis of the data:

- 34% of cN1 patients received staging
- 68% of cN2 patients received staging
- 4 patients were under staged (cN1 pre resection and pN2 post resection)

Conclusion: Our results fell short of the 100% standard set by ESTS.

It should be highlighted that our audit was during the height of the Covid-19 pandemic. During this time, system pressures in healthcare, particularly in Northern Ireland, were unprecedented. This is highly likely to have impacted these results, particularly in patients where confirmatory staging may not change the eventual treatment. Re-audit is recommended.

THORACOTOMY VS VIDEO-ASSISTED THORACOSCOPIC SURGERY IN THE TREATMENT OF VASCULAR RINGS

Author: Isabel Campbell

Aims: This review aims to investigate the surgical approach, post-operative complications, length of stay in hospital, symptom resolution, reoperation rates and mortality of both VATS procedures and thoracotomy procedures in the treatment of VRs. Then to assess the application of VATs in a modern surgical setting.

Methods: A literature search of the MEDLINE and SCOPUS databases were performed at the projects inception to present. From the 361 articles retrieved, 271 were excluded. After utilising the exclusion criteria and thorough manual screening, 14 studies were included in the review. 6 of these studies investigated the outcomes using thoracotomy, 3 case reports plus 2 studies that investigated the outcomes using VATS and 3 studies that directly compared the two procedures. Overall, 590 cases in this review focused on using thoracotomy operations and 190 cases used VATS.

Results: The main themes from the results demonstrated VATS had a reduced operating time, length of stay in hospital, reduced rates of post-operative complications in comparison to thoracotomy. Both procedures showed similar rates of reoperation, mortality and short-term symptom resolution.

Conclusion: This review provides insight into the encouraging outcomes in the use of VATS in comparison to thoracotomy in the treatment of VRs. VATs should be considered as an alternative to thoracotomy in the surgical treatment of vascular rings.

APPLICATION OF PHOTOGRAMMETRY IN MEDICAL EDUCATION

Author: Sofia Aliotta

Aims: It aims to offer the reader a better understanding of photogrammetry as a 3D reconstruction technique and to provide some guidance on how to choose the appropriate

photogrammetry approach for their research area (including single- versus multi-camera setups, structure-from-motion versus conventional photogrammetry and macro- versus microphotogrammetry) as well as guidance on how to obtain high-quality data.

Methods: This review introduces the photogrammetry approaches currently used for digital 3D reconstruction in anatomy teaching and discusses their suitability for different applications.

Results: This review highlights some key advantages of photogrammetry for a variety of applications in medical education, but it also discusses the limitations of this technique and the importance of taking steps to obtain high-quality images for accurate 3D reconstruction

Conclusion: Photogrammetry is an upcoming technology in medical education as it provides a non-invasive and cost-effective alternative to established 3D imaging techniques such as computed tomography.

PRIZE WINNERS

Ariana Axiaq (1st place, poster presentation)
Nidhruv Ravikumar (1st place, poster presentation)
Julia Slater (2nd place, poster presentation)
Michael Keenan (3rd place, poster presentation)

Gopika Sreejith (1st place, oral presentations)
Isabel Campbell (2nd place, oral presentation)
Sofia Aliotta (2nd place, oral presentation)
Manasi Mahesh Shirke (3rd place, oral presentation)

Defining the Rectosigmoid Junction in Clinical Practice.

Julia Slater, Department of Anatomy, Queens University Belfast

ABSTRACT

The differentiation between sigmoid and rectal cancers requires a precise, standardised definition of the rectosigmoid junction. This may maximise the benefits of adjuvant therapies and provide greater consistency between clinical trials, making the comparison and analysis of results more reliable. In current clinical practice, there is no single definition used to identify this point which may lead to the misclassification and suboptimal management of these patients.

Systematic reviews of Medline and Embase identified 19 articles defining the rectosigmoid junction; these descriptions were collated and categorised as endoscopic, radiological, and morphological, including both macroscopic and histological findings. Endoscopic and radiological markers are identified during preoperative investigations whilst morphological landmarks are useful in the intraoperative and postoperative analysis. A preoperative definition may be used to initially categorise a lesion as being rectal or sigmoid and if rectal, inform the decision as to whether neoadjuvant chemoradiotherapy may be required. From the endoscopic and radiological markers discussed, the visualisation of sigmoid take-off on MRI most consistently fulfils these criteria. A second postoperative definition may be used to definitively confirm the location of a lesion within the resected specimen. Currently, the coalescence of the taenia coli at the rectosigmoid junction appears to be an appropriate marker.

INTRODUCTION

The rectosigmoid junction (RSJ) represents the transition point between the distal sigmoid colon and proximal rectum, highlighted in Figure 1. This region may be identified by several anatomical landmarks. However, there is currently no single, universal definition used to accurately and consistently identify the RSJ, as evidenced in the most recent national guidelines (2,3). This can pose an issue when defining colorectal cancers as either sigmoid or rectal lesions. This decision is currently made by the individual clinician or multidisciplinary team which may lead to misclassification of cancers and possible suboptimal management. Furthermore, clinical trials comparing rectal and sigmoid tumours use a range of markers to define the RSJ, limiting the comparability and interpretation of these important studies. Therefore, a consistent definition of the RSJ is desirable to provide a universal method of classifying and treating colorectal cancers and to standardise study protocols of future clinical trials.

The aims of this report were to identify and appraise the various markers of the RSJ, and to determine which of these markers may be used to differentiate between sigmoid and rectal lesions in the clinical setting.

METHODOLOGY

Systematic reviews of the literature were performed using the databases Medline and Embase; the keywords used were 'rectosigmoid junction' or 'colorectal junction'.

Inclusion criterion: a description of the RSJ in the abstract or a reference to a description made in the full text.

Exclusion criteria: Case reports and conference abstracts.

A total of 21 articles were identified from Medline and Embase; two of these articles were later recognised as commentaries of another review paper and were therefore excluded, leaving 19 papers to analyse.

RESULTS

Table 1, Categorisation of anatomical markers identifying the rectosigmoid junction.

Category	Description
Morphological	
• Macroscopic	Coalescence of the taenia coli
	Loss of epiploic appendices
	Level of the sacral promontory
	Level of the third sacral vertebra
	Sudeck's critical point
	Relation to the anterior peritoneal reflection
• Histological	Muscular sphincter
	Mesenteric waist
Endoscopic	
	Distance from the anal verge
	Distance from the dentate line
Radiological	
	Sacral promontory
	Anterior peritoneal reflection
	Sigmoid take-off

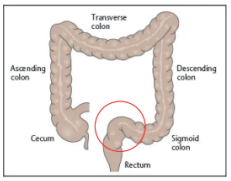


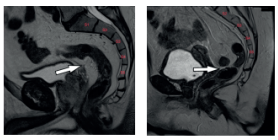
Figure 1, Anatomy of the Colon (1).

ANATOMICAL MARKERS

Histological / Macroscopic:
- Coalescence of taenia coli , shown as three distinct bands in Figure 2.
- May be disrupted by surrounding pathology.
- Does not inform preoperative diagnosis.

Endoscopic:
- RSJ typically measured from anal verge or dentate line.
- Variation in measurements possible between operators and instrumentation.

Radiological:
- Reproducible for preoperative diagnoses.
- Anterior peritoneal reflection, identified as 'definitively present' in 68% of MRI scans (5). Level varies between individuals as demonstrated in Figures 3 and 4.
- Sigmoid takeoff, demonstrated in Figure 5, describes the junction of mesorectum with mesosigmoid, level consistent in patients with and without colorectal cancer.



Figures 3 and 4, Sagittal MRI scans from a male and female respectively, white arrow indicates the levels of the anterior peritoneal reflection at S4 and below S5. Image courtesy of Radiology, Northumbria Healthcare Trust.

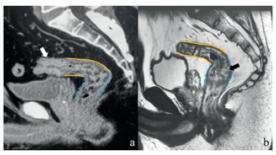


Figure 5, CT and MRI scans taken in the sagittal plane illustrating the rectosigmoid junction between the sigmoid colon, indicated by the solid yellow lines, and the rectum, indicated by the dashed blue line. White arrow - plane of the sigmoid take-off on CT. Black arrow – plane of the sigmoid take-off on MRI (6).

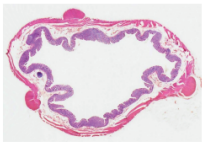


Figure 2, Histological specimen from the colon showing the three bands of the taenia coli (4).

CONCLUSION

The RSJ may be defined by a range of the morphological, endoscopic and radiological markers and it is of clinical importance in the characterisation of lesions as being rectal or sigmoid. The ideal preoperative marker for use in clinical practice would provide a consistent and reproducible means of distinguishing rectum from sigmoid, which also accounts for anatomical variations which may alter the length of the rectum. Of the endoscopic and radiological landmarks discussed, the sigmoid take-off appears to most accurately fulfils these criteria. The coalescence of the taenia coli is recommended as the postoperative definition of the RSJ, identified within a resected specimen. To further assess the suitability of these markers, a prospective study comparing the preoperative diagnoses of rectal and sigmoid lesions using the sigmoid take-off with postoperative identification of the taenia coli is recommended.

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The Impact of Ionising Radiation on Endothelial Cell Physiology

QUEEN'S UNIVERSITY BELFAST
THE PATRICK G JOHNSTON CENTRE FOR CANCER RESEARCH

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Research conducted as part of MSc project in Cancer Medicine

ScruOs

Introduction

Aim:
To investigate the pathophysiology induced in endothelial cells following exposure to ionising radiation (IR).
An estimated 50-60% of patients with cancer receive some form of radiotherapy, which may be curative, palliative or an adjunct to surgery[1]. **It works by killing cancer cells preferentially compared to normal cells.**

However, normal tissues are unavoidably exposed to IR, leading to adverse effects including a triphasic inflammatory response. In the acute phase, rapidly dividing tissues (e.g. mucosae) fail to proliferate leading to ulceration. In the months following, fibrotic changes take place. This can lead to a loss of organ functionality[2].

In addition, the endothelium has been shown to exhibit a **pro-inflammatory change in phenotype**[3]. IR may be responsible for prolonged endothelial activation, along with endothelial cell loss. The endothelium is responsible for the delivery of O_2 and nutrients to surrounding cells[4]. Endothelial dysfunction induced by IR may therefore play a role in the chronic adverse effects of IR[5]. Therefore it is important to understand the underlying pathophysiological changes leading to this dysfunction.

Methods

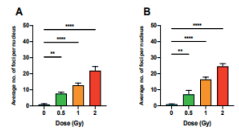
Cell culture:
Cardiac microvascular endothelial cells (CMEC) and bEnd.3 (Brain endothelial.3) cells were incubated at 37 in recommended media conditions.
Irradiation: Samples were irradiated with an X-RAD 225 (PRECISION X-RAY INC.)
Immunofluorescence: DNA damage was assessed using an antibody to 53BP1 (Table 2.1), a DNA damage repair protein which specifically localises to DNA double strand breaks (DSBs), described here as foci. Cells were fixed in paraformaldehyde 4%.

Calcium Imaging
Dishes were irradiated at 2 Gy and loaded with Fluo-4 AM/probenecid one hour post irradiation and compared to a non-irradiated control dish. Fluo-4AM is an indicator of Ca2+.
Cells were visualized using a 10X water dipping objective lens (CFI Plan Fluor 10X/0.30W).

Excitation of Fluo-4 AM was performed with a mercury lamp through the use of excitation/emission filters . WinFluor software (v4.1.6) was for acquisition and data analysis
Fluorescence intensity (F) was determined from 50 cells for each recording by placing a ROI on a randomly selected individual cell. The change (Δ) in fluorescence ΔF/F0 was plotted against time (s) for each recording where ΔF/F0 = F(t)-F0/F0, where F(t) is the fluorescent value at a given time. Data was exported to Microsoft excel where maximum fluorescence values were calculated
Cell Proliferation
2 x 96 well plates were seeded per timepoint. A control plate was compared to a treatment (2 Gy) plate.
Plates were read at 24, 48 and 72 hour timepoints. (FLUOstar Omega Plate Reader). 10 µl cell proliferation reagent PrestoBlue™ Cell Viability reagent was added to each well. Absorbance values were read 1.5 hourspost-addition (Excitation/emission: 560/590nm).

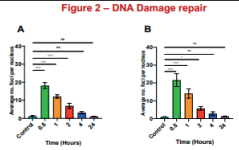
Results

Figure 1 – Dose response relationship



Dose response relationship indicating a linear increase in the number of DNA Double Strand Breaks (DSBs) with dose up to 2 Gy compared to unirradiated control. DSBs were labelled with anti-53BP1 with the average foci per nucleus found across 50 EC nuclei per cell line.
1A - CMEC
1B - bEnd.3
Key for statistical significance:
One star (*) P<0.05, two stars (**) P<0.01, three stars (***) P<0.001, four stars P<0.0001(****)

Figure 2 – DNA Damage repair

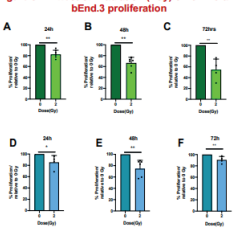


2A – CMEC
The number of DSBs significantly increased at T=0.5h (P<0.0001) The number of DSBs then gradually decreased back to non-significant levels (P>0.05) by T=4h, continuing this decline up to 24 hrs post-irradiation. One-way ANOVA was performed to test for statistical significance where P<0.0001(****).

2B – bEnd.3
The increase in DSBs is statistically significant at T=0.5h, the timepoint at which the maximum number of DNA DSBs were counted (P(0.0001). The number of DSBs decreased back to non-significant levels (P>0.05) by T=4h, continuing this decline up to 24 hrs post-irradiation. One-way ANOVA was performed to test for statistical significance where P<0.0001(****).

Results

Figure 3 – Effect of irradiation (2Gy) on CMEC and bEnd.3 proliferation

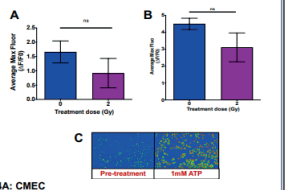


3A - Relative reduction in CMEC proliferation post-irradiation (2Gy) compared to non-irradiated controls at 24 hours. Proliferation was reduced by 17.83% following 2Gy irradiation, relative to 0Gy. (p<0.01, N=5).
3B - At 48 hours, the mean percentage proliferation of irradiated cells was 66.66%. The reduction was statistically significant (P<0.01, N=5).
3C - At 72 hours, the percentage proliferation was reduced to 54.59% in irradiated (2Gy) CMEC cells, relative to 0Gy.The percentage difference was statistically significant (P<0.01, N=4).
3D - Relative reduction in bEnd.3 proliferation to a mean of 85.5% relative to 0 Gy following exposure to 2 Gy at 24 hours. This was found to be a statistically significant reduction (P<0.005, N=4).
3E - Further reduction compared to control observed, where proliferation fell by 25.38%. The reduction was also found to be statistically significant (P<0.01, N=5).
3F - Recovery in % proliferation relative to 0Gy. Mean percentage proliferation relative to 0 Gy rose to 90.51%. The reduction in proliferation was still found to be was found to be statistically significant (P<0.05, N=4).

Statistical data was analysed using a Mann-Whitney U test

Results

Figure 4 - The effect of radiation on cell physiology as assessed by Ca^{2+} transients evoked by ATP bEnd.3 and CMEC cells



4A: CMEC
Bar graph shows the average maximum fluorescence (Ca^{2+} influx). The 2 Gy treatment plate demonstrated a reduction in mean average maximum fluorescence (0.9174 DF/F0) compared to 0 Gy control (1.659 DF/F0) – however this difference was not statistically significant following analysis with unpaired t-test (P>0.05).

4B: bEnd.3
Bar graph shows the average maximum fluorescence. The 2 Gy treatment plate demonstrated a reduction in mean average maximum fluorescence (3.106 DF/F0) compared to 0 Gy control (4.494 DF/F0) – however this difference was not statistically significant following analysis with unpaired t-test (P>0.05, N=5).
4C: Live cell Ca^{2+} imaging

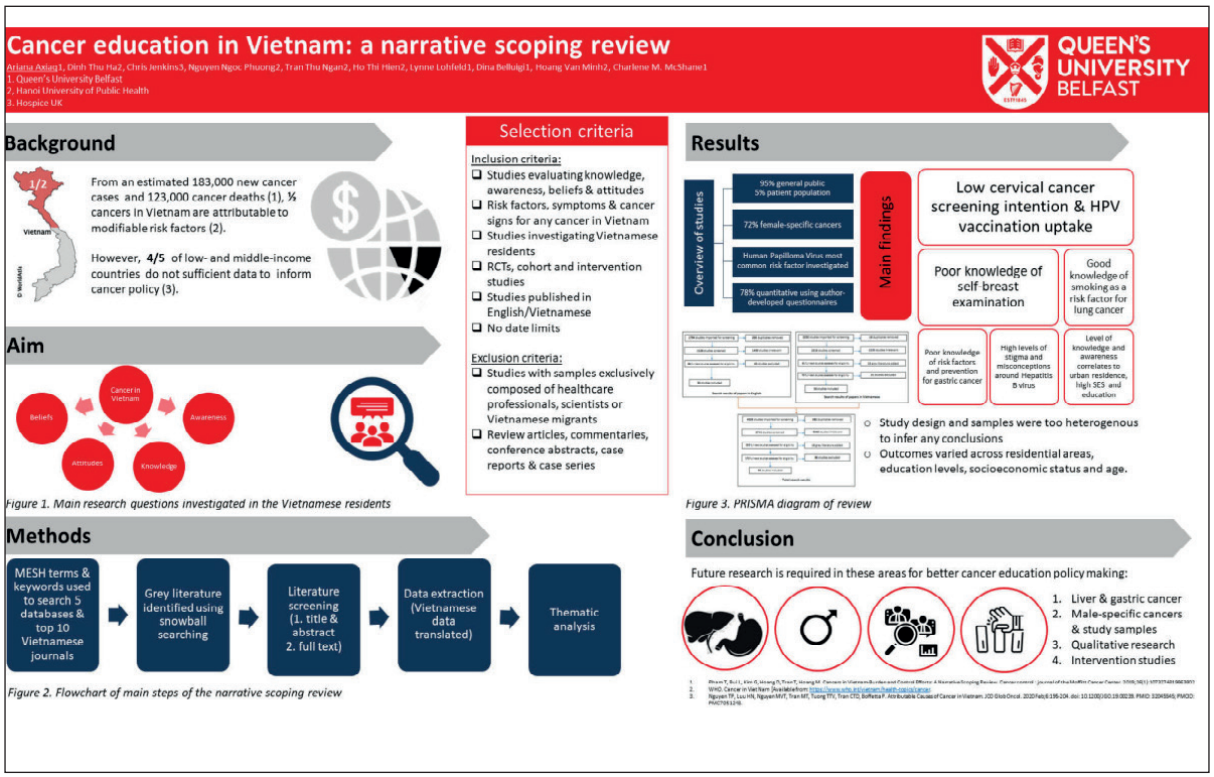
Conclusions

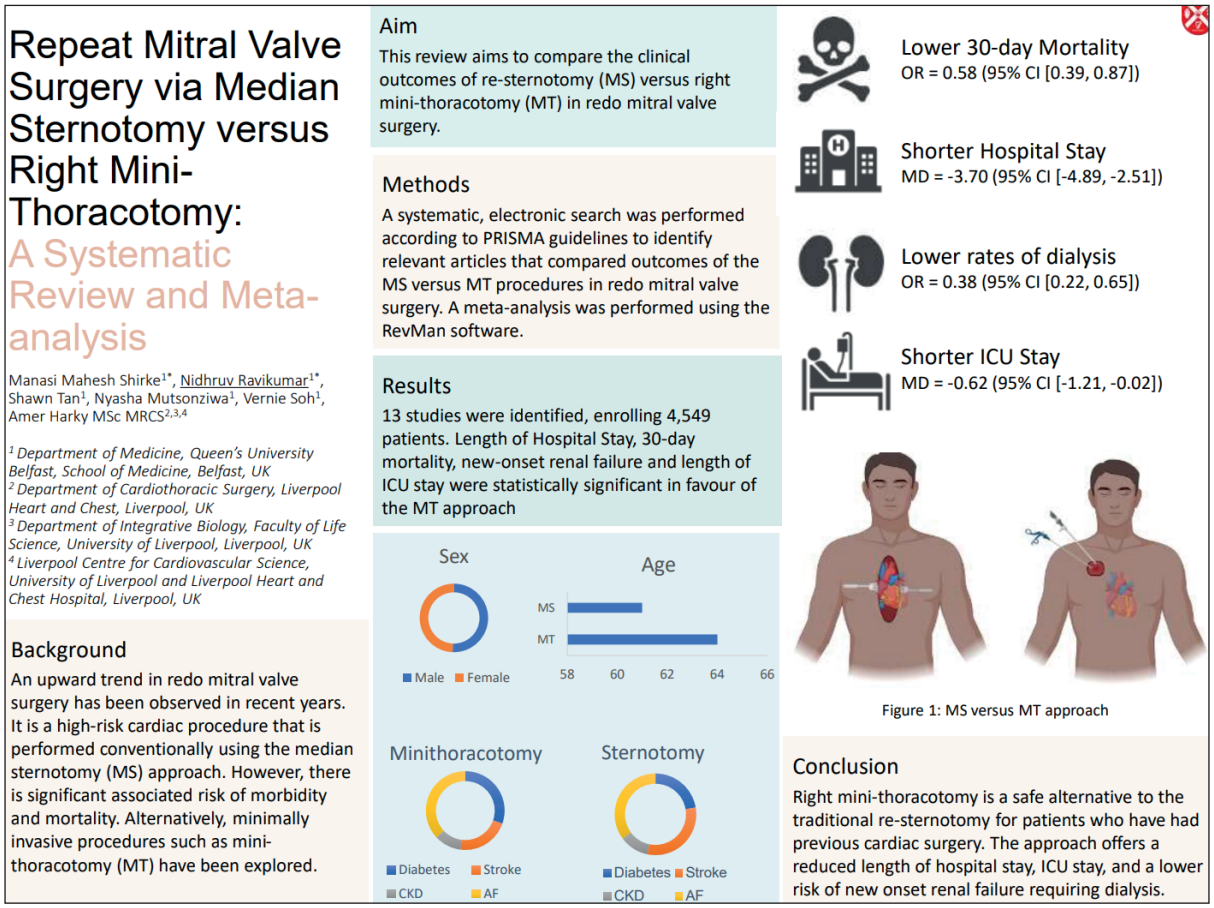
- The data obtained indicate that IR is capable of inflicting significant pathophysiological damage to ECs.
- ECs are capable of fixing DNA damage as shown and preserve physiological Ca^{2+} signalling is at clinical doses of radiation (2 Gy).
- However, EC proliferative capabilities are reduced following exposure to IR. Their inability to fully recover in 2 cell lines warrant further investigation into disrupted underlying cell signalling mechanisms.

Further research and future work

- Further work (not shown) completed as part of this MSc project investigated the impact of the endothelial inflammatory activators **Nigericin** and **lipopolysaccharide** on EC proliferation. An analysis of the **fibrotic changes** induced in mouse bladders at 20 Gy was also conducted.
- Future work would harness **western blot** analysis to understand the cell signalling pathways involved in EC inflammatory activation, and **ex vivo Ca2+ imaging**

References 1. Baskar, R., Lee, K. A., Yeo, R. & Yeoh, K.-W. Cancer and Radiation Therapy: Current Advances and Future Directions. *Int J. Med. Sci.* 9, 193 (2012). 2. Rubin, P. & Casarett, G. Clinical radiation pathology as applied to curative radiotherapy. *Cancer* 767–778 (1968). 3. Baselet, B. *et al.* Functional gene reveals cell cycle changes and inflammation in endothelial cells irradiated with a single X-ray dose. *Front. Pharmacol.* 8, (2017). 4. Galley, H. F. & Webster, N. R. Physiology of the endothelium. *Br. J. Anaesth.* 93, 105–113 (2004). 5. Baselet, B., Sonveaux, P., Baatout, S. & Aerts, A. Pathological effects of ionizing radiation: endothelial activation and dysfunction. *Cell. Mol. Lanalysalife Sci.* 76, 699 (2019).





Ulster Med J 2022;**91(2):**178-179

Curiositas

UNDERGRADUATE QUIZ 1

1. What device is responsible for this cranial opening?
2. What was the reasoning behind the use of this technique?
3. Is this technique employed today?

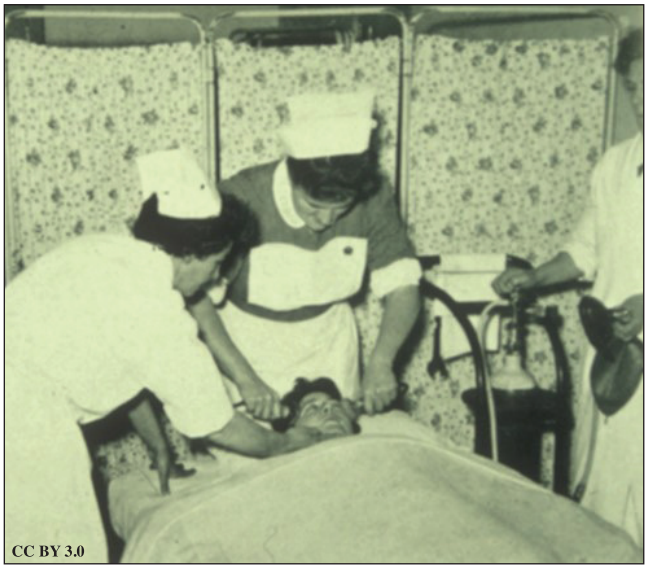
Aaron Vage (PhD Student, Centre for Medical Education, Queen's University Belfast), Mr Thomas Flannery (Consultant Neurosurgeon).

POSTGRADUATE QUIZ 1

1. What does this case contain?
2. In what era were they used?
3. Are they still used today?

Aaron Vage (PhD Student, Centre for Medical Education, Queen's University Belfast), Prof Mary Frances McMullin (Consultant Haematologist).

UNDERGRADUATE QUIZ 2



1. What is happening here?
2. Why would this procedure be employed?
3. Does it have any place it modern medicine?

Aaron Vage (PhD Student, Centre for Medical Education, Queen's University Belfast), Dr Aidan Turkington (Consultant Psychiatrist).

POSTGRADUATE QUIZ 2

1. What is this contraption?
2. What is its purpose?
3. Is this type of procedure popular today?

Aaron Vage (PhD Student, Centre for Medical Education, Queen's University Belfast), Mr Brendan Hanna (Consultant ENT Surgeon).

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Curiositas: Answers

UNDERGRADUATE QUIZ 1

1. The technique of trephination is one enshrouded in lore, reminiscent of a more primitive time in our human existence. From South American tribal ritual to the emergent medicina of the Roman Empire, the trephine has been a source of terror for millennia. Archaeological sites in Europe, Asia, Australasia, and The Americas have yielded a series of archaic crania exhibiting the circular openings often associated with trephination; the oldest dating back to 8, 000 BCE[1].

2. Within Peruvian tribal culture the skulls of those suffering from severe headaches, delirium and behavioural abnormalities were penetrated with blades of obsidian known as 'Tumi', creating a gateway through which afflicting spirits could leave. In ancient Greek medicine it was believed that the use of a trephine to create a cranial opening allowed stagnant blood to drain from the head before turning to pus[2]. Proponents of trephining in Western medicine often used the technique in the treatment of cranial fractures[3]. However, the use of trephination as a therapeutic technique continued; shockingly, English miners in the 19th century insisted on having their skulls punctured after a blow to the head, despite no obvious signs of fracture[4].

3. In the modern era of neurosurgery, mini-craniectomies or burr hole openings in the skull are commonly employed to drain chronic subdural haematomata or facilitate ventriculostomies to combat hydrocephalus[5] and could thus be considered forms of trephination. Indeed, a more generous form of trephination, in the guise of decompressive craniectomy (with temporary storage of the bone flap in an abdominal subcutaneous pouch), may be required in patients with raised intracranial pressure secondary to traumatic brain injury[6]. Thankfully, the days of using trephination, per se, as a therapeutic intervention are past. However, it always makes one think, what practices are currently in vogue that may be deemed barbaric in the future?

[1]Parapia, LA 2007. British Journal of Haematology, 139, 14-19.

[2]Bender, GA 1966. Great moments in history: trephining in ancient Peru. Detroit. Northwood Institute Press.

[3]Newman, WC *et al* 2016. World neurosurgery, 92, 148-150.

[4]Gross, CG 1999. Neuroscientist, 5, 263-269.

[5]Bartlet, HH *et al* 2021. World Neurosurgery, 155, 115-121.

[6]Flannery, T & McConnell, RS 2001. British Journal of Neurosurgery, 15, 518-520.

UNDERGRADUATE QUIZ 2

1. As Nazi Germany annexed neighbouring Austria during the 1938 Anschluss, over 900 kilometres away in Rome, colleagues Ugo Cerletti and Lucio Bini had developed a device to treat the symptoms of psychosis – a technique that would become known as electroconvulsive therapy (ECT). In the early 20th century asylums were overflowing with untreatable psychiatric patients. Therefore, on reporting a 'staggering' improvement in the psychotic symptoms of a number of patients post-ECT, it wasn't long before Cerletti and Bini's brand of shock therapy was being rolled-out in psychiatric institutions across the globe[1].

2 & 3. The way in which ECT acts as a therapeutic intervention is multifaceted – neurotrophic factors, modulation of emotional circuitry and neurogenesis all touted as key elements [2]. ECT's public image is controversial. On one hand, there are parts of the world where the practice is banned – largely due to its horrific application within the Nazi era[3]; not to mention its unfavourable portrayal in Ken Kelsey's novel, 'One Flew Over the Cuckoo's Nest.' On the other hand, ECT now has an established evidence base and is recognised as one of the most effective treatments for severe depression[4, 5]. In recent years, the technique of transcranial magnetic stimulation (TMS) has emerged as a more 'acceptable' procedure in terms of treating major depression. However, ECT has consistently outperformed TMS in a number of randomised control-trials[6]. It is therefore no shock that ECT has gained a foothold in modern medicine that it won't give up so easily.

[1]Faedda, GL *et al* 2010. Journal of Affective Disorders, 120, 12-15.

[2]Gazdag, G & Ungvari, GS 2019. World Journal of Psychiatry, 9, 1-6.

[3]Gazdag, G *et al* 2017. History of Psychiatry, 28, 482-488.

[4]Nordanskog, P *et al* 2015. Journal of ECT, 31, 263-267.

[5] UK ECT Review Group. 2003. Lancet, 361, 799-808.

[6]Milev, RV *et al* 2016. Canadian Journal of Psychiatry, 61, 561-575.

POSTGRADUATE QUIZ 1

1 & 2. Blood, phlegm, black and yellow bile are the four constituent humours of the human: according to the godfather of medicine, Hippocrates. The notion of letting blood was largely influenced by the theories of Hippocrates, and his Greek counterpart, Galen; both believing that an unbalanced proportion of these aforementioned humours was to blame for all illness[1]. In the early days, a selection of crude instruments were employed to allow blood to escape from the afflicted[2]. However, as with most outrageous medical practices, the 19th century is where bloodletting reached its dizziest heights. The humble leech eventually became the creature of choice concerning the letting of blood. Although, a French surgeon by the name of Charles Louis Heurteloup thought that an artificial version of the organic bloodsucker would be a more precise tool; thus, creating the spring-loaded, vacuum pump device known as the artificial leech, in 1840[3].

3. As the medical world eventually realised the error in many ancient Greek theories, techniques such as bloodletting fell by the wayside; one of its last endorsements appearing in the 1923 edition of Principles and Practice of Medicine[4]. Today therapeutic phlebotomy is used to manage conditions such as haemochromatosis and polycythaemia vera, in order to reduce the iron load or lessen the risk of cardiovascular events[5].

[1]Greenstone, G 2010. BC Medical Journal, 52, 12-14.

[2]Bell, TM 2016. Journal of Lancaster General Hospital, 11, 4.

[3]Feldman, H 1994. Laryngorhinootology, 73, 551-555.

[4]Osler, W & McCrae, T 1923. The principles and practice of medicine. New York. D. Appleton & Co.

[5]Assi, TB & Baz, E 2014. Blood Transfusion, 12, s75-83.

POSTGRADUATE QUIZ 2

1 & 2. As the 19th century drew to a close, the tonsillectomy was reaching its zenith as the surgeons' procedure of choice in the battle against a variety of infectious respiratory diseases. Fast forward to the modern era, and the advent of antibiotics has seen a steady decline in the need for this procedure. The removal of human tonsils has been performed since antiquity; the Roman encyclopaedist Cornelius Celsus documented a tonsillectomy with use of the fingers during the 1st century[1]. As time passed, a variety of string- and snare-based contraptions were employed in the business of tonsil removal[2]. However, the distinct lack of anaesthesia in the 18th century saw the rise of blade-like instruments, unaffectionately termed tonsil guillotines. The so called 'tonsil guillotine' was adapted from a device known as the uvulotome; developed by the Norwegian, Canute of Thorbern, as a means to remove oedematous uvulae[3].

3. In 2002, Matthews et al.[3] conducted a postal survey of 329 UK consultants, aiming to examine the role of guillotine tonsillectomy in modern otolaryngology. Interestingly, they found that more recently appointed consultants (< 10 years in post) preferred the use of guillotine tonsillectomy over other methods. However, due to the advent of intracapsular techniques, like 'Coblation', the use of guillotine tonsillectomy has since fallen from the cutting edge.

[1]Younis, RT & Lazar, RH 2002. Laryngoscope, 112, 3-5.

[2]Hultcrantz, E & Ericsson, E 2013. ORL, 75, 184-191.

[3]Matthews, J *et al* 2002. Journal of Laryngology, 116, 988-991.

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