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- AI in Endoscopy - VEXAS Syndrome - Assisted Dying

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Editorial

The New Absence

David J Armstrong

Iam seges est ubi Troia fuit[1] Corn now grows where once Troy flourished. All good things come to an end, and regrettably this will be my last Editorial for the Ulster Medical Journal. My tenure has been slightly shorter than others in recent years, owing to pressures of clinical work and other responsibilities making demands on my time, but I am delighted to place the journal in the capable hands of Dr James Lucas, who will be taking over the role for the next issue. For a small medical society to run its own peer reviewed international medical journal is a remarkable feat in the twenty first century, and filling the role of Honorary Editor is a busy, responsible but also extremely rewarding and satisfying task. I am certain James will be afforded the same generous support from the Board and Society which I and our predecessors have received.

I based my first Editorial[2] around the word 'anger' – the first word of Homer's Iliad, and a common theme in any discussion about the Northern Ireland health service at the time. Not only did we have many problems, but with neither Health Minister nor local assembly in place, we did not have the means to deliver a solution. Over two years later, we have the Assembly up and running in Stormont, and we are on our second Health Minister. Most would agree we are no further forward. We still have too many hospitals and many in the wrong place, connected by a poor road and rail infrastructure keeping everyone as physically siloed as possible, junior doctors leaving in droves for better pay, better training and better quality of life in the Antipodes, and both primary and secondary care in permanent crisis, overwhelmed by demand and starved of funding. Everyone, it seems, remains as angry as ever.

One area where the pressures are felt keenly, and where anger and division are increasing, is at the primary/secondary care interface. This has always been a particular concern of mine, and it is a great shame that some contact between GPs and hospital staff has become so fraught and at times almost adversarial. We trained together at medical school and as junior doctors, took the same Hippocratic Oath and look after the same patients, yet the pressures we work under at present are causing ever deepening stress between the sectors. It was not always so.

I qualified as a doctor thirty years ago this year. As a junior doctor in a large district general hospital, from 8am to 5pm you were the general dogsbody – phlebotomy, giving intravenous antibiotics, ordering and 'chasing up' X-rays, making referrals after the ward round and so forth. But from 5pm to 8am, you became a real doctor. Admitting the 'unselected medical or surgical take' direct from GPs was where you learned your trade. Making a diagnosis and giving the initial treatment was at first terrifying, then exciting and eventually satisfying – after about 6 months you felt like a real doctor. But my point is that the contact with local GPs was constant. No-one was sent to 'Casualty' unless gravely ill. Most admissions came from the local GP phoning from a patient's home giving you the presenting complaint, and within 30 minutes the patient could be in a bed on the ward, admission done, oxygen on, chest x-rayed, intravenous cephalosporin given (it was before we knew about clostridium difficile). You became quite friendly with whichever local GP was on call in the community that night, you recognised their voice and they yours. GPs still attended lunchtime education meetings in the hospital where they sat with juniors, seniors and medical students, and one local GP often called into the ward to borrow blood culture bottles or stock up on other minor equipment for his evening home visits. We had tea together and he asked about the patients he had admitted earlier in the week. He was, in fairness, something of an outlier, but the point remains that primary and secondary care were in very real terms integrated.

Of course Ovid was correct that that we cannot return to former days – seges est ubi Troia fuit – but the divisions developing between us now are good for neither the patient nor the profession. Most hospital juniors would not recognise most of the local GPs if they passed them in the street, nor would some consultants, and I am sure the situation is the same the other way around. I have the privilege of having a GP registrar attend one of my clinics several times a month, and have done so over many years as they pass through a rotation. Most if not all have become friends. They can email me with questions and I can ring them with advice many years later on good terms. Those tricky conversations, where my GP colleague has to tell me why they cannot take on another task in caring for our mutual patient, or where I have to explain why I simply cannot see the patient any sooner, are I believe better because we know each other and respect each other's roles. Exchanges I hear between some primary and secondary colleagues might be politely described as 'curt', and on both sides. We did not start off intending to be like this, and we must not let the pressures of the ongoing healthcare crisis in Northern Ireland drive us apart.

If I had more money to spend on our health service, I would spend most of it in Primary Care and Social Care. Better Primary Care keeps patients out of hospital, and better Social

Care gets patients in hospital back out more quickly. I am sure some of my consultant colleagues might baulk at my opinion, but I believe it is supported by facts.
I was speaking on the phone last year to the senior nurse manager of an excellent local nursing home whose bed numbers have dropped, and who are therefore unable to take as many medically well patients ready for discharge from hospital as they used to. Her analysis was surprising – the local branch of a big supermarket chain, and a local American owned call-centre, paid school leavers a higher hourly rate to stack shelves or listen to customer complaints than she could ever pay them as care assistants to feed, toilet and enrich the lives of residents – and of course have their lives enriched in turn. So the number of beds in the care home dropped as care assistant posts went unfilled.

The lady ready for discharge from our ward could no longer be offered a place in her home, so the man with a stroke in the Emergency Department could not move to her bed, so the patient with a community acquired pneumonia could not leave the ambulance parked up all day outside, so the highly skilled paramedics could not take that ambulance to a confused woman found collapsed at home. Not quite the loss of a kingdom for the want of a horseshoe nail, but everything is connected, and neither the patient's GP nor hospital consultant can do anything about the hourly wage paid by call centres. I have no easy answer, but primary and secondary care must work together, as must social care and the nursing home sector. We should look for more opportunities to establish links between the hospital and the community. The Ulster Medical Society is one of the last places where a retired surgeon can sit beside a medical student and listen to a presentation by a psychiatry registrar followed by one from a GP. It is a shame that the membership of the society represents such a small percentage of medical professionals in Northern Ireland. It has the potential to be a source of cohesion for local doctors when so many other stresses and pulling us apart.

One new issue for our profession even in the last 12 months, is the Terminally Ill Adults (End of Life) Bill 2024-25 which received its second reading in the UK parliament in November 2024[3]. Many doctors remain deeply concerned about its consequences for the profession, and for our most vulnerable patients. The views of local Palliative Care specialists were covered in our last issue[4], and Michael Trimble explores the 'slippery slope argument' in the Medical Ethics section of this one. Words are important, and the use of the term 'assisted dying' rather than 'assisted suicide' is indicative of just how careful we need to be with the use of language. Generous use of morphine in the last few hours of a cancer patient's life might well be easing the dying process; there is little doubt that patients in their twenties with mental health problems being assisted to end their own lives by doctors, as happens legally in the Netherlands[5], is assisted suicide. And once relative rather than ultimate value is placed on a human life, then I would argue the two outcomes outlined above are definitely on opposite ends of the slippery slope.

What do we mean by the word 'doctor'? For 3000 years it has meant someone who might do many things, but could be trusted by even the most vulnerable and mentally disturbed never to deliberately end their life. This has changed elsewhere in the world, and might well change very soon here. There is sometimes a perception that the main opposition to the change comes from those, like me, who profess Christian faith, but on discussing the issue I find otherwise – some of the most vocal opponents I have encountered in Northern Ireland do adhere to other world religions - but many adhere to none, and yet still believe that coercion of the vulnerable and value judgement on the quality and dignity of the lives of people living with handicaps are terrifying spectres. The nature of 'being a doctor' will change forever, unless we are very careful indeed.

It has become a custom for editors of this journal, in their last Editorial, to allow themselves some licence to develop personal themes or interests by way of valediction. It will come as no surprise to any regular readers that I have a keen interest in ancient history, languages and literature, and indeed an interest in literature generally extending right up to the present day. I have left myself too little space to share many of my favourites, but here are two.

A series of plays about how greed, lust and bravado lead men to war. How war destroys towns, families, places of worship and futures. How women and children suffer more than most. The taking of hostages and retaliation for taking of hostages. Trafficking of civilians on a massive scale. Not, as I expect you will have anticipated, works written in the last five years, but a trilogy by the ancient Greek playwright Aeschylus, first performed in 458BC.[6]

Aeschylus was one of the greatest playwrights of his age or any age. That an entire three play trilogy has survived from his 70 plus known works, most of which have perished, is remarkable in itself. That it is the Oresteia is truly providential, for it is hard to find a work produced for the stage in the last 2500 years which has better encompassed the whole range of human experience. War, the aftermath of war, the taking of hostages, power, pride, adultery, murder, mental breakdown, revenge and attempted redemption are contained within its three plays, and one might wait until Shakespeare to see them handled as well. Anyone who suggests that such ancient works have nothing to teach us might consider Cassandra – her mental illness misunderstood, captured in war and trafficked as a sex slave, given a clear vision of her own death which like the rest of her prophecies no one will believe and then led away to that death – these are not easy themes. And yet the same scene could be set in several different parts of the world now.
Many English translations exist, and I recommend them strongly.

At the other end of the scheme of time lies the English poet Philip Larkin, a librarian in Hull (and indeed briefly in Belfast) who died in the 1980s. The publication, perhaps

unfairly, of his private correspondence after his death cast shadows on his memory for some, but he remains to me one of the greatest poets in the English language.
'Aubade'[7], his frank exploration of an atheist's 'furnace fear' of his own forthcoming death, and the ultimate meaningless of his own life - 'not to be here, not to be anywhere, and soon' – is both a beautiful and difficult read. It might be useful for anyone considering assisted suicide legislation, or indeed their own eternity, though neither Larkin's rationalism nor Aeschylus' philosophy, offer any hope of the soul's redemption, the answer to which is to be found elsewhere.

My final words however will be a few lines from one of Larkin's later and lesser known poems The Mower[8]. Larkin, often viewed as a grumbling misanthrope, has made friends with a small hedgehog which lived in his garden, even feeding it once. He had then, quite unintentionally, run over it with his lawnmower. He was genuinely distraught, and it is one of his very last verses.

The next morning I got up and it did not.
The first day after a death, the new absence
Is always the same; we should be careful
Of each other, we should be kind
While there is still time

David Armstrong

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Clinical Paper

Chest computed tomography and plain radiographs demonstrate vascular distribution and characteristics in COVID-19 lung disease – a pulmonary vasculopathy

Graham Lloyd-Jones [1], James Shambrook [2], Alastair Watson [3,4], Anna Freeman [2,4,5], Tom M.A. Wilkinson [2,4,5]

ABSTRACT

Introduction

Early in the COVID-19 pandemic, CT was demonstrated as a sensitive tool for diagnosing COVID-19. We undertook a detailed study of CT scans in COVID-19 patients to characterise disease distribution within lung parenchyma, respiratory airways, and pulmonary vasculature, aiming to delineate underlying disease processes.

Methods

We characterised acute phase chest CT of 40 participants with COVID-19 from the REACT study, 31 with CT pulmonary angiography (CTPA), 4 with intravenous contrast enhanced CT and 5 with non-intravenous contrast enhanced CT. Participants had neither been vaccinated nor received systemic steroids. We further correlated the distribution of lung parenchymal damage on CT with contemporaneous chest radiographs.

Results

Parenchymal lung damage was found in all subjects. However, airways inflammation was present in only 23% (9) and limited to small areas. Notably, vascular abnormalities were dominant and characterised by dilated peripheral pulmonary vessels supplying areas of lung damage in a gravity-dependent distribution bilaterally in 95% (38), basally in 90% (36), peripherally in 92.5% (37), and posteriorly in 90% (36). Macrothrombosis was demonstrated in 23% (7) of CTPAs. Wedge-shaped peripheral lung damage, resembling areas of pulmonary vascular congestion, were distinct in 53% (21) with or without visible macrothrombosis. Pleural effusions were seen in 28% (11). Notably, lung opacification distribution in 98% of the plain radiographs matched distribution on CT (39).

Conclusion

Our study frames COVID-19 as a pulmonary vasculopathy rather than a more conventional pneumonia which may be important not only for guiding mechanistic study design but also for the development of novel targeted therapeutics.

Key Words: COVID-19; CT imaging; Chest Radiographs; Vasculopathy; Respiratory Infections

INTRODUCTION

The importance of CT was highlighted early in the pandemic when it was established to be sensitive for diagnosing COVID-19 in the absence of polymerase chain reaction (PCR) testing, even in asymptomatic patients[1,2]. Lung damage with ground glass opacities (GGOs) was quickly identified as a typical diagnostic feature of COVID-19[3-6]. However, at that time the main focus was on making a diagnosis and little consideration was given to the underlying disease processes responsible for the lung damage.

Lung damage with GGOs or consolidation has been widely attributed to alveolar cellular pathology[5] and thromboembolic phenomena were initially considered to be complications of a respiratory tract infection in patients, rather than an intrinsic part of COVID-19 disease itself[4]. The term *COVID-19 pneumonia* is still widely used by many investigators. However, GGOs are a non-specific feature of lung damage and other causes are possible, including vascular phenomena and interstitial oedema[1]. Pulmonary vascular congestion with thrombi of small peripheral vessels can give rise to GGOs on CT, such as is found in peripheral wedge-shaped pulmonary infarcts in the context of conventional pulmonary thromboembolic disease. However, despite emerging histological evidence of vasculopathy being a typical finding at autopsy in the context of COVID-19[7,8], the contribution of vasculopathy to CT and radiographic findings is not fully delineated and COVID-19 is still viewed by some as more similar to a conventional respiratory pneumonia than primarily a pulmonary vasculopathic disease.

Therefore, we undertook a study to deeply characterise CT scans of inpatients with acute COVID-19 to confirm the extent to which disease affects the respiratory airways, the pulmonary vessels, and the lung parenchyma. In doing so,

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we aimed to gain insights into the pathological processes responsible for radiologically visible abnormalities and the nature of mechanistic processes in disease pathogenesis. We further correlated the distribution of lung damage on CT with plain chest radiographs, a more readily available resource in the emergency setting.

METHODS

Study design

Data were collected for COVID-19 positive patients as part of the Research Evaluation Alongside Clinical Treatment in COVID-19 (REACT COVID-19) observational and biobanking study[9-11]. Participants in this present study were admitted to a University Hospital in the UK between 3rd March and 10th November 2020. This was prior to the widespread availability of vaccination. Dexamethasone was introduced into clinical guidance in June 2020, but at the time of imaging participants included within our cohort had not been treated with dexamethasone.

Participants

Participants were included in the study if they tested positive for SARS-CoV-2 on real time reverse transcription PCR from a nasopharyngeal swab and had a chest CT (n=54). All requests for CT stated clinical indications relating to investigating chest symptoms of COVID-19 and no history of other infection to explain symptoms. None of the participants (smokers or non-smokers) were stated to have a history of pre-existing pulmonary vascular disease. Participants with major pre-existing lung or heart disease and those imaged for reasons other than to investigate COVID-19, such as trauma, were excluded (n=13), or those with scans of inadequate diagnostic quality (n=1). A total of 40 participants met the inclusion/exclusion criteria and were included in this study. 31 participants were imaged with CT pulmonary angiography (CTPA), 4 with intravenous contrast enhanced CT (arterial phase), and 5 with non-intravenous contrast enhanced CT.

Variables

Core demographic information (including, age, sex, body mass index, smoking history and COVID-19 symptom onset date) was collected as part of this study, alongside other data collected as part of routine clinical care (**Table 1**). This information, alongside CT scans and radiographs, were compiled into a database. Participant records, including radiological records, were continuously updated during hospital stay and their follow-up period.

CT Analysis

Detailed analysis of CT included the following categories: distribution of lung parenchymal damage; characteristics of parenchymal lung damage; respiratory phenomena (central and distal airways were considered separately); vascular phenomena; non-specific features in the lungs; and other features in the chest associated with pneumonias. All CT and plain radiographic images were analysed independently by two radiologists (one specialist cardiothoracic radiologist and one general radiologist with specialist interest in chest imaging, both with 13 years' experience). Definitions for all radiographic phenomena were agreed prior to the study, except for the 'vascular tree-in-bud' sign (highlighted in the results). CTPAs were assessed to determine the presence of macroscopic pulmonary arterial filling defects. Where there was disagreement, consensus was gained following discussion.

Ethics statement

Ethical approval was obtained from the HRA Specific Review Board for waiver of informed consent for the database-only cohort; the procedures conform with the Declaration of Helsinki. The study design, protocol, and patient-facing documentation for the biobanking arm of the study have been approved by the regional Ethics Committee as an amendment to the University Hospital National Institute for Health Research Clinical Research Facility-managed Research Biorepository.

Outcome Measures

CT lung parenchymal damage characterisation

Areas of lung parenchymal damage were defined by the presence of ground glass opacities (GGOs) or consolidation. If both GGOs and consolidation were present we determined whether they were equal in their contribution to overall lung damage, or which was dominant. Other lung parenchymal changes were also recorded including lobar consolidation, and the reverse-halo sign (atoll sign)[12] which, for the purposes of characterisation, we considered as a non-specific feature of parenchymal damage[13].

Distribution of lung parenchymal damage was recorded as unilateral or bilateral. Bilateral disease was defined as any amount of acute parenchymal damage in both lungs. The predominance of disease distribution was also recorded as upper versus basal, anterior versus posterior, and central versus peripheral. Perihilar lung damage was considered central, and disease distributed in the subpleural areas was considered peripheral. The posterior and peripheral segments of the upper lobes were also considered to contribute to this overall pattern of disease distribution if they were involved predominantly compared to their adjacent more anterior segments.

CT phenomena affecting the respiratory airways

Observations in the central and peripheral airways – bronchial wall thickening centrally (tracheal or bronchial) and peripherally (segmental or subsegmental) – were recorded separately. Mucous secretion plugging was documented to be present if either central or peripheral. Subsegmental and distal bronchioles were also assessed for presence of

the 'respiratory tree-in-bud' sign – a sign of small airways inflammation (bronchiolitis)[14,15].

CT phenomena affecting the pulmonary vessels

We documented the presence of dilated pulmonary vessels, reported to be a key feature of COVID-19[16]. Both arteries and veins were considered dilated if larger than expected for the location in the vascular tree, and their association with areas of lung parenchymal damage was documented. We also documented the presence or absence of the 'vascular tree-in-bud' sign, reported as a specific feature of COVID-19 lung disease[17].

CTPAs were assessed for evidence of macrothrombosis (pulmonary embolus or in situ thrombus), as defined by visible pulmonary arterial filling defects. We also looked for the presence of wedge-shaped areas of sub-pleural parenchymal lung damage resembling areas of pulmonary vascular congestion, analogous to the morphology of pulmonary infarcts found in the context of conventional pulmonary thromboembolic disease, and not thought to be due to a cause other than acute COVID-19, such as fungal infection, bacterial septic emboli or neoplasm.

Other CT features

The presence or absence of pleural effusions (unilateral or bilateral), thoracic lymph node enlargement and any other lung parenchymal or pleural abnormalities were also recorded.

Correlation of CT and chest radiographic findings

CT lung parenchymal disease distribution was subsequently correlated with lung shadowing on plain radiographs, both those most contemporaneous to the CT and, if different from the most contemporaneous, those obtained on presentation to the Emergency Department. Severity and any change in severity was observed in accordance with the standard scoring system in operation clinically (**Box 1**).

Box 1

Chest radiograph severity scoring system

Normal = no abnormality

Mild disease = lung opacification affecting <25% of lung area

Moderate = lung opacification affecting 25-50% of lung area

Severe = lung opacification affecting >50% of lung area

Distribution was assessed as above, with the caveat that frontal plain chest radiographs cannot be used to determine anterior versus posterior distribution of disease.

RESULTS

Cohort characteristics

40 subjects were included within this study (**Table 1**). 23 were male (57%) and the median age was 61 (interquartile range (IQR) 54, 70). The majority were never-smokers (23, 58%). 3 subjects (8%) had been prescribed inhaled corticosteroids prior to scanning, but none had received systemic steroids or a COVID-19 vaccination. 31 participants had a CT pulmonary angiography (CTPA), 4 had a contrast enhanced CT (arterial phase), and 5 had a non-contrast CT. 23/31 of those with a CTPA had already received prophylaxis doses of parenteral anticoagulants (commencing 1-17 days prior to scanning). The majority of subjects had both raised D-dimers (86%) and raised fibrinogen (86%). CRP was raised in 37 participants (92.5%). 33 participants (75%) required oxygen support to maintain oxygen saturations >94%.

CT distribution of lung parenchymal damage

Distribution of lung damage (GGO and/or consolidation) was dominantly bilateral (95%), basal (90%), peripheral (92.5%), and posterior (90%). In the 2 patients who had unilateral disease both had limited lung damage which was confined only to a small area. Where a basal or peripheral dominance was not observed, widespread disease was present throughout both lungs, so no dominance of distribution was distinguishable. 10% of scans (4) in which posterior disease was not dominant showed uniform lung damage, which was both anterior and posterior, so no dominance was distinguishable. No scans demonstrated lung damage dominantly in an upper, central, or anterior distribution.

CT characteristics of lung parenchymal damage

Lung parenchymal damage was present on all CT scans. 15% of scans demonstrated GGOs without consolidation and 5% showed consolidation without GGOs. 80% of CT scans (n=32) showed both GGOs and consolidation **(Fig. 1).** Of those 32 scans, GGOs were dominant over consolidation

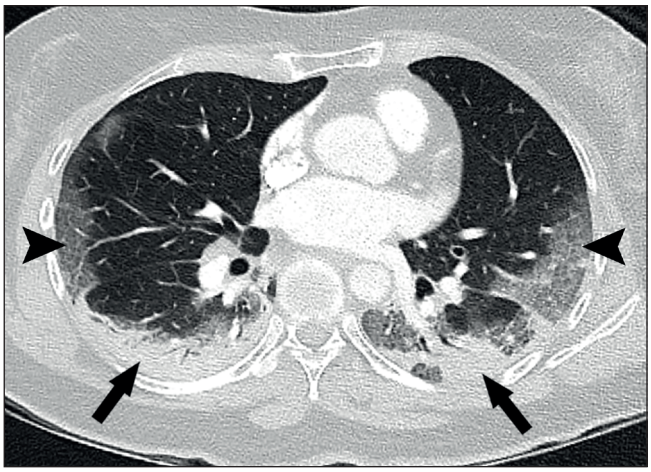

Figure 1
CT chest of a patient with COVID-19 lung disease showing areas of consolidation (arrows) and GGOs (arrowheads) in a peripheral, posterior and basal distribution bilaterally.

Table 1: Patient demographics according to cohort

	Total n = 40
Age, median (IQR)	61 (54, 70)
Male/Female, (% Male)	23/17 (57)
Smoking History, Current/ex/never, n (%)	2/15/23 (5/37.5/57.5)
Hypoxic on air (oxygen saturation of <94%) or requiring oxygen support, n (%)	33 (75)
Number who received prophylactic parental anticoagulation prior to scan, n (%)	24 (60): enoxaparin, 23 (58); apixaban 1 (3)
Use of Inhaled Corticosteroids, n (%)	3 (8)
Median interquartile range (IQR) timeframe (in days) from admission to CT scan	7.4 (1, 14)
CRP mg/L, median (IQR)	129.0 (40, 181)
Creatinine µmol/L, Median (IQR)	75 (64, 101)
D-dimer ng/mL, Median (IQR)	552 (335, 1508)
Fibrinogen g/L, Median (IQR)	7.8 (6, 8)

in 63% (20/32, 50% of total 20/40), dominant consolidation in 19% (6/32, 15% of total 6/40), and equal contributions to parenchymal lung damage due to GGOs and consolidation in 19% (6/32, 15% of total 6/40). Therefore, GGOs were the dominant or only form of lung damage in 65% (26). Consolidation was the dominant or single form of lung damage in 20% (8).

CT phenomena affecting the respiratory airways

Anatomical elements of the macroscopic airways (trachea, major bronchi, lobar bronchi, segmental, subsegmental bronchi, or distal airways) showed abnormality on 23% of scans (9) limited only to small areas. Of these 9 scans the central bronchial walls were thickened in isolation in 3 subjects, the peripheral bronchial walls were thickened in isolation in 1 subject, and both were thickened in 3 subjects. Segmental bronchiectasis was observed in 2 subjects. Neither of these 2 subjects demonstrated signs of acute inflammation within the bronchiectatic airways (no bronchial wall thickening or mucous plugging). Bronchiolectasis with airways traction was also observed in two subjects but without bronchial wall thickening.

Inflammatory phenomena affecting the respiratory airways were not widespread or the dominant pattern of disease in any subject and if present were limited to only a small area of lung (maximum of two lung segments). Significantly, respiratory tree-in-bud phenomenon, a sign usually ascribed to acute small airways inflammation (bronchiolitis) and commonly seen in influenza, was completely absent from any areas of the lungs in all subjects.

CT phenomena affecting the pulmonary vessels

Abnormal blood vessels supplying all areas of lung parenchymal damage were present on 95% (38) of scans, and in all subjects these dilated vessels were observed to be both pulmonary arteries and veins **(Fig. 2)**. In the two subjects in whom dilated vessels were not observed distinctly, one had severe consolidation and the other was considered to have resolving COVID-19 with development of organising pneumonia and early fibrosis, characteristic of intermediate to late phases of disease[18].

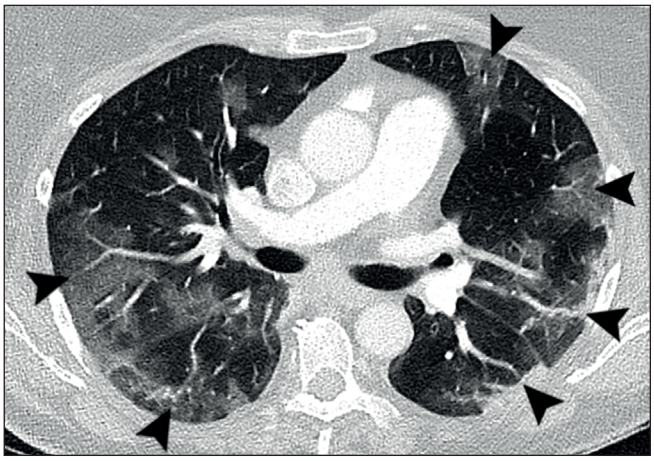

Figure 2
CT chest of a patient with COVID-19 showing areas of lung damage (GGO or consolidation) accompanied by dilated blood vessels (arrowheads). Analysis showed dilatation of both the pulmonary arteries and veins in these areas of lung damage.

We observed vascular tree-in-bud as a distinct phenomenon in

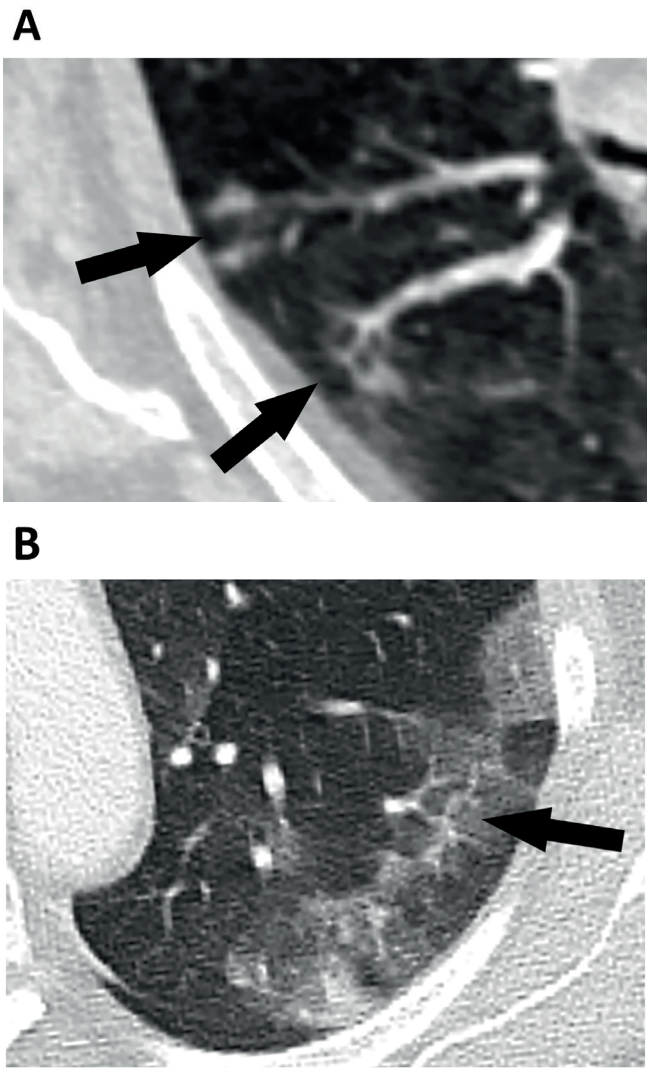

Figure 3
(A) CT chest in a patient with COVID-19 lung disease showing vascular tree-in-bud opacification in isolation of lung damage. **(B)** CT chest in a patient with COVID-19 lung disease showing vascular tree-in-bud opacification in an area of lung damage. This phenomenon was not considered a feature distinct from dilated vessels within GGOs.

areas not affected by lung damage in 5% (2/40) **(Fig. 3a)**. One observer documented its presence also within GGOs in 73% (29/40) **(Fig. 3b)**, but this was not considered to be a feature distinct from dilated vessels within GGOs. As no definition of this phenomenon was agreed prior to engagement in the study, we did not attempt to gain consensus on this feature and present variance in description for discussion below.

Thrombotic and other CT phenomena considered potentially vascular

7 of the 31 CTPA scans (23%) demonstrated macroscopic pulmonary arterial filling defects, indicating macrothrombotic disease. This was observed in 5 subjects who had already received prophylaxis doses of parenteral anticoagulants (commencing 1-17 days prior to scanning). Wedge-shaped areas of subpleural lung damage (GGOs or consolidation) were observed in 53% (21) **(Fig. 4)**. This phenomenon, which is reported elsewhere as representing the presence of microthrombosis in situ, or so-called *infarct pneumonia*[19], was present both with macrothrombosis (77% 16/21) or without visible macrothrombosis (19% 4/21). Macrothrombosis without a pattern of wedge-shaped subpleural lung damage was observed on one CT scan (5% 1/21). We also observed lung parenchymal damage (GGOs or consolidation) in a distinct pattern which spared the immediate subpleural lung in 35% (14), discussed below.

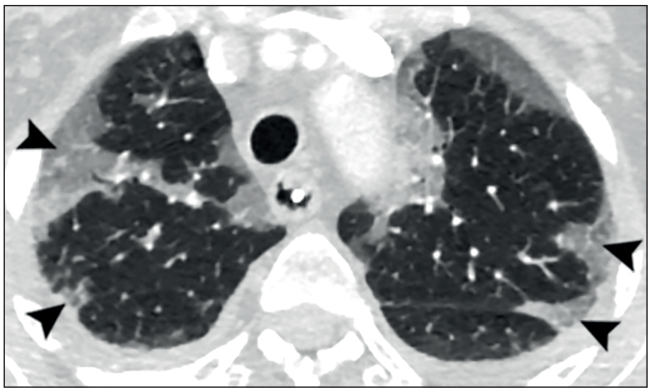

Figure 4
CT chest in a patient with COVID-19 lung disease showing multiple areas of wedge-shaped lung damage in the lung peripheries (analogous to pulmonary infarcts or areas of vascular congestion in the context of conventional pulmonary thromboembolic disease).

Other non-specific CT lung and pleural observations

Lobar consolidation was observed in 5% (2). Pleural effusions were observed in 28% (11) – 10% bilateral (4) and 18% unilateral (7). Enlarged thoracic lymph nodes (hilar and/or mediastinal) were observed in 33% (13) and the reverse halo sign in 5% (2). Other findings included subpleural atelectasis in 13% (5), a lung nodule with benign characteristics 3% (1), minor emphysema 5% (2) and calcified pleural plaque 3% (1). Pericardial effusion was not observed.

Comparison of CT with contemporaneous chest radiographs

To gain insights about COVID-19 processes underpinning lung opacification on chest radiographs, the distribution of disease recorded on the reference CT was compared with distribution of lung opacification observed on the most contemporaneous chest radiograph. Median time between reference CT and contemporaneous chest radiograph was 26.5 hours (IQR 7,69). 95% (38) of contemporaneous chest radiographs were abnormal. Indirect comparison of imaging modalities (CT versus contemporaneous chest radiograph) showed matching bilateral, basal and peripheral distribution of opacification in 98% (39) **(Fig. 5)**. The subject in whom lung damage distribution varied was an outlier with an interval from reference CT to contemporaneous chest radiograph of 360 hours and demonstrated improvement in lung damage.

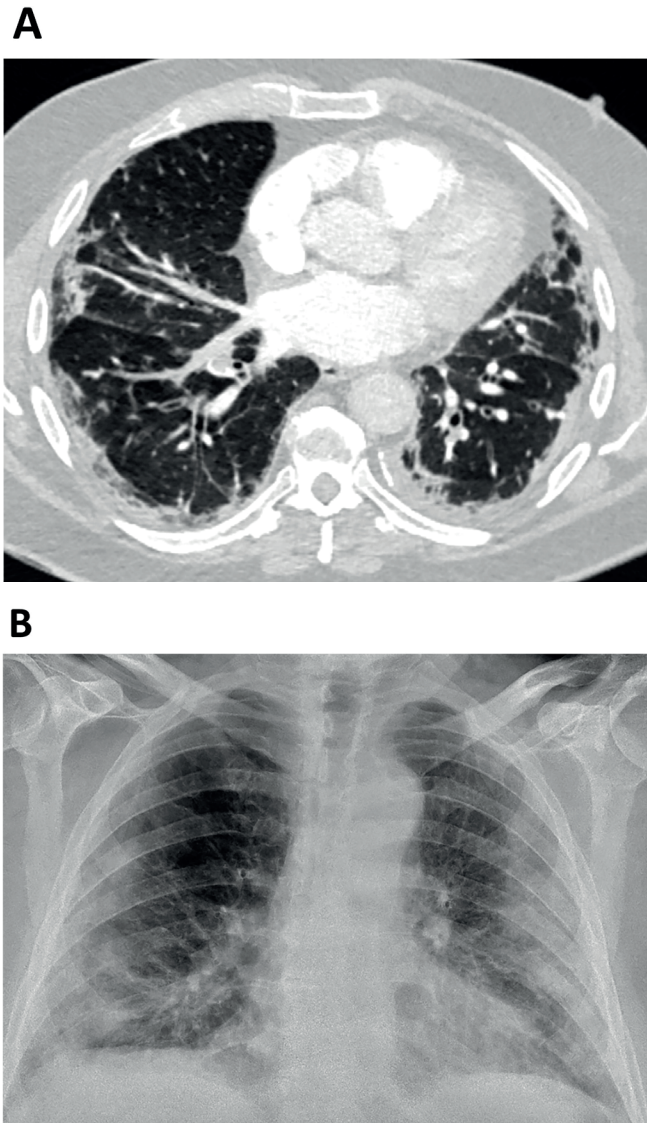

Figure 5
(A) CT and **(B)** contemporaneous chest radiograph in a patient with COVID-19 lung disease. The typical distribution of opacification due to lung damage shown on CT (bilateral, basal, peripheral, and posterior) is matched by bilateral, basal and peripheral distribution of opacification on the contemporaneous radiograph.

If different from the contemporaneous radiograph, the chest radiograph acquired closest to the time of admission to the Emergency Department was also assessed for disease severity. The contemporaneous radiograph was different from the admission radiograph in 23 subjects. Change in severity scoring was documented for these subjects. All but one subject demonstrated no change or worsening of severity scoring during admission until the point of CT scanning. This is predictable as the population studied all had the reference CT – a criterion for inclusion in the study – for the purpose of investigating the cause of worsening or persistence of symptoms. Significantly, although severity changed over time, the pattern of lung shadowing did not change in terms of dominant areas of distribution affected between admission versus contemporaneous radiographs. Below we discuss the significance of this observation in relation to clinical management of COVID-19 in the Emergency Department.

DISCUSSION

We undertook a detailed study to characterise chest CT scans of hospitalized patients with COVID-19 to determine distribution and characteristics of lung disease and involvement of the airways versus pulmonary vessels. We demonstrate that pulmonary vascular processes were dominant, and that lung damage (GGOs or consolidation) was characterised by dilated pulmonary vessels supplying all areas of lung damage in a distinctly vascular distribution. We further demonstrate that distribution of opacification on chest radiographs is analogous to distribution of lung damage visible on CT. Further understanding this correlation could provide insights for chest radiographs use in early clinical decision-making in the Emergency Department.

Within our cohort, we determine the presence of dilated blood vessels within areas of lung parenchymal damage (GGOs or consolidation) to be the hallmark feature of COVID-19 lung disease, rather than GGOs in isolation. These areas of lung damage were dominantly in the most vascularised gravity-dependent regions of the low-pressure pulmonary circulation; basal, peripheral, bilateral and posterior. These findings provide rationale for framing COVID-19 as a vasculopathic disease. It is interesting to note that this vascular distribution of lung damage also represents areas of the lung least accessible to an inhaled pathogen, making it possible to speculate that a vascular delivery of pathological viral components and their endovascular interaction could be contributing to this lung damage[20]. Future mechanistic studies are required to test this hypothesis.

There are various potential mechanistic explanations for our findings. For instance, dilated pulmonary vessels seen in COVID-19 are identical to arteriovenous shunts seen in pulmonary arterial hypertension[21] and could explain the clinical phenomenon of 'silent hypoxia' in COVID-19[22]. Microangiopathic phenomena and subsequent pulmonary vascular congestion could be a key mechanism driving the dilated peripheral vessels and associated lung damage seen in our study. Histopathological studies have demonstrated pulmonary vascular congestion with thrombi of small peripheral vessels to be typical in COVID-19 lungs. Autopsy findings in COVID-19 include microscopic clotting in small peripheral pulmonary vessels[7] (both in arterioles and venules[23]), immunothrombosis[24], endotheliitis[25], and platelet aggregation[26]. These phenomena visible histologically could be responsible for the vasculopathic lung damage demonstrated on imaging. Whichever mechanism is responsible, we consider the dilated pulmonary vessels to be intrinsically linked to underlying pathophysiology in the lung disease of COVID-19 and indicative of vasculocentric processes.

Over half of the cohort within our study had wedge-shaped lung damage in the lung periphery analogous to

pulmonary infarcts, regardless of the presence or absence of macroscopic arterial filling defects. This could be explained by pulmonary vascular congestion following thrombosis, which has a higher propensity to occur within small peripheral vessels rather than central vessels[27]. Ridge et al. identified wedge-shaped perfusion defects analogous of pulmonary infarcts in acute COVID-19 using Dual Energy CT[28]. Other studies compared pre-mortem CT studies with post-mortem histology and highlighted capillary dilatation, congestion and microthrombosis as drivers of lethal disease, and even revealed microvascular damage and thrombosis in areas of the lungs on autopsy which were normal on pre-mortem CT[29,30]. A further recent study using optical coherence tomography demonstrated *in vivo* microscopic distal pulmonary arterial thrombosis, even when CTPA was negative, in patients with acute COVID-19[31]. Therefore, our observations are in accordance with the findings of others that thrombotic phenomena are key in COVID-19 lung disease and differ in distribution compared with conventional thromboembolism[19,32,33] .

Diffuse alveolar damage (DAD), as found in autopsy studies of fatal COVID-19, has previously been taken to indicate that primary alveolar processes are driving disease. However, our study highlights that thrombotic and endothelial cell damage could explain the phenomena visible on imaging. Indeed, alveolar capillary endothelial cell damage is intrinsic to the definition of DAD[34]. Also, DAD is reported to be atypical in COVID-19 with airways containing fibrin[35]. In line with this concept of underlying microscopic thrombotic processes, a post-mortem study using hierarchical phase-contrast tomography (HiP-CT) demonstrated well-preserved alveolar structure with alveolar obstruction reported to be due to the presence of thrombi[36]. This aligns with our study which suggests that alveolar damage is not primarily due to airways inflammation, but rather by vascular-driven pathology in the lung peripheries.

Immunothrombosis (inflammatory-mediated clotting) has been proposed as an underlying mechanism of microthrombosis *in situ* in the context of COVID-19[24,32]. This pathological process could explain the vasculocentric distribution of lung damage and vasculopathic characteristics of disease observed in our study. The phenomenon of vascular tree-in-bud opacification is considered specific to acute COVID-19 and is thought to represent immunothrombosis[37]. Reference Figure 3A, our study identified this finding as a distinct entity separate from areas of lung parenchymal damage in 5% of subjects. Reference Figure 3B, furthermore, one observer considered it also to be present within areas of GGOs in 73%, broadly in line with others who report the finding in 64%[17]. However, when documented in the presence of GGOs, we did not consider vascular tree-in-bud opacification as a distinct phenomenon from dilatation of blood vessels within GGOs. Both phenomena are considered to represent vasculocentric pathology.

The distinct pattern of GGOs which spare the immediate subpleural lung observed in our study could also represent vasculopathic processes. This phenomenon is similar to the pattern seen in pulmonary haemorrhage[38], another feature described on autopsy in fatal COVID-19[23,39]. Nevertheless, we consider this a non-specific CT feature as it is observed in the context of acute respiratory distress syndrome (ARDS) of any cause[40]. We demonstrated a similar incidence of macroscopic pulmonary arterial filling defects relating to thromboembolic disease (23%) compared to some studies (22-37%)[41] but lower than in other studies (44%)[42].

In addition to the vasculocentric distribution and vasculopathic characteristics of lung parenchymal damage, our study demonstrates a striking lack of airways inflammation on CT, as would be expected in influenza or influenza-like pneumonias[43]. This paucity of airways disease confirms the findings of others which have suggested airways inflammation on CT to be inconsistent with the diagnosis of COVID-19[44]. Taken together, our findings challenge the prior notion of COVID-19 being a conventional respiratory pneumonia and highlights that the term *pulmonary vasculopathy* is a more accurate term to describe COVID-19 lung disease in the acute phase[45,46].

Correlation of contemporaneous radiographs with CT provides evidence that radiographic lung opacification is analogous to the lung damage associated with vasculocentric phenomena visible on CT in COVID-19 lung disease. This further highlights that plain chest radiograph opacification in the context of acute COVID-19 should not be considered to be due to a conventional respiratory pneumonia, which may later be complicated by vascular processes, but rather to represent the pulmonary vasculopathy itself. In view of the greater availability of chest radiographs and the lower exposure of radiation, future work elucidating these correlations could potentially inform early clinical decision-making pathways on patient presentation to the Emergency Department.

Our study was a single centre, relatively small study which aimed to deeply characterise CT scans of subjects with acute COVID-19 lung disease to generate insights into disease distribution and characteristics. In accordance with the CT scans studied, the number of matching chest radiographs was also relatively small. Furthermore, due to the broad inclusion criteria of all suitable patients with an appropriate CT scan, CTs were obtained at different disease stages, thus limiting assessment of some CT features. A variety of CT techniques were included in the study, necessitating the caveat that CTPA can occasionally exaggerate GGOs. Our study used participants admitted in 2020, before the widespread use of vaccination and dexamethasone treatment, thus providing insights about the native disease phenomena prior to influence by these interventions. This, and the emergence of later variants, potentially limits the clinical applicability of our findings as Omicron is considered to cause a different phenotype of radiological disease from Delta and pre-Delta variants[47]. However, with the continual emergence

of new COVID-19 strains, and the burden of long COVID, understanding the acute and lasting impact of the pulmonary vasculopathy could be pivotal.

Conclusion

Our study of chest CT findings highlights COVID-19 as a pulmonary vasculopathy, with the distribution and characteristics of COVID-19 lung disease being dominantly vasculopathic. We further show a lack of visible airways inflammation in this cohort, indicating that COVID-19 lung disease is not a conventional respiratory pneumonia.

STATEMENTS

Funding Statement

No funding was received for this work.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

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Clinical Paper

Spontaneous rupture of uterine artery in a non-pregnant woman with adenomyosis: a case report and review of current literature

Nick Lung, Gillian McKeown

Abstract

Spontaneous rupture of a uterine artery is a rare occurrence and more often associated with postpartum haemorrhage. It is even more unusual outside pregnancy. In this report, we will describe a case of spontaneous uterine artery rupture in a 40-year-old non-pregnant female with adenomyosis who presented with severe vaginal bleeding. We will also review the aetiology of rupture of uterine artery based on the current literature.

Case report

A 40-year-old woman, para 1, presented overnight to the emergency department of her local hospital with vaginal bleeding. It was her second attendance within 24 hours. She reported onset of menstruation six days previously, and the bleeding was increasingly heavy with clots, associated with intermittent lower abdominal cramps and fainting episodes. Her last pregnancy was more than 15 years ago. She had stopped a combined oral contraceptive pill two months before for a planned discectomy. On examination, she was pale with mildly tender suprapubic region, but her vital signs were stable. Initial blood results were as follows: haemoglobin 110 g/L, white cell count 11.5x10^9/L, platelet count 261x10^9/L. She was initially managed conservatively with tranexamic acid and medroxyprogesterone.

In the next few hours, she had multiple episodes of hypotensive shock and continued to bleed despite medical management. On vaginal examination, cervix felt normal and a significant amount of blood clot was evacuated with active bright red bleeding. Bedside transvaginal ultrasound was performed, and it showed an endometrial thickness of 2 mm, clots in uterus and vagina, and no fibroids or free fluid in the pelvis. Her haemoglobin dropped to 62 g/L. The massive haemorrhage protocol was activated, and she received 8 units of packed red cells, 2 units of fresh frozen plasma and 2 units of cryoprecipitate in total.

She therefore underwent a computed tomography (CT) of abdomen and pelvis with abdominal angiography. CT showed active extravasation of contrast from a branch of the right uterine artery into the endometrial cavity, tracking through the cervix into the vagina vault, but no evidence of a discrete vascular abnormality (Figure 1).

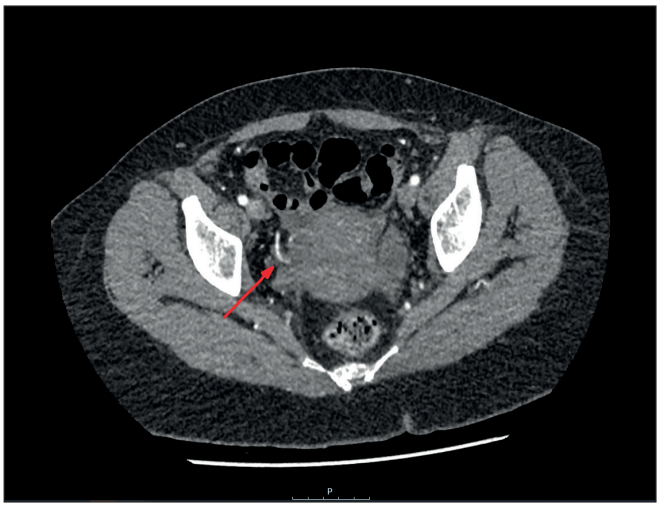

Figure 1.
Arterial phase of CT angiogram showing extravasation of contrast from a branch of the right uterine artery (red arrow) into the endometrial cavity.

Trans-arterial embolisation was considered, but due to the patient's ongoing bleeding and worsening pain, compounded by the delay to transfer to a tertiary centre with interventional radiology, a decision was made to undergo transabdominal hysterectomy. Intra-operative findings included haemoperitoneum, mild features of endometriosis on the uterus and normal adnexae. The procedure was uncomplicated, and her post-operative recovery was largely unremarkable, except for ileus and atelectasis. Histopathological examination of the specimen confirmed adenomyosis and no evidence of malignancy.

Discussion

Aetiology

Spontaneous rupture of uterine artery is a rare occurrence. As such, to date, no systemic review or large studies have been conducted on this. The electronic database PubMed was searched looking for the following terms 'spontaneous uterine artery rupture', 'spontaneous uterine vessel rupture'

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and 'spontaneous uterine artery erosion'. A number of cases have been reported and patients with this condition presented during pregnancy, labour, puerperium[1-8], or up to two years following a gynaecological intervention[9].

In relation to pregnancy, the exact aetiology is not well understood[3], but factors including pressure dynamics, anatomic disruptions and hormonal changes were proposed[10]. Other causes that have been identified[3] include aneurysm and pseudoaneurysm, congenital abnormality, vascular defect caused by inflammation or oestrogen[7], erosion from endometriosis[11-14], iatrogenic damage[15-18], and termination of pregnancy[9,19]. As described in Williams Obstetrics, uterine artery pseudoaneurysm is a known rare cause of postpartum haemorrhage[20]. A case series in China concluded that pseudoaneurysm can develop after traumatic pelvic operations and non-traumatic delivery/abortion[21]. Another observational study in Japan estimated the incidence of uterine artery pseudoaneurysm to be 0.3-0.6% of deliveries and suggested that some may be undetected due to the absence of massive bleeding and/or spontaneous resolution[22]. A case series in Pakistan[23] suggested that bleeding as a result of acquired and iatrogenic uterine vascular abnormalities can be attributed to previous caesarean section, gestational trophoblastic disease, pelvic tumours[24-28] and malignancies[29,30], pelvic infection, and dilatation and curettage.

Of all reported cases, uterine artery rupture that are truly spontaneous (i.e. unprovoked by pregnancy or trauma) are exceptionally rare. There was one case where no cause was identified[31], and few cases where the haemoperitoneum occurred as a complication of rupture of a massive fibroid[24,32,33]. In some case reports, local erosion of the uterine artery by an endometriotic lesion was described in non-gravid women[11,12,34]. Given the similar histopathology, we speculate that the adenomyosis in our case behaves similarly to this endometriosis case, causing local ulceration to the adjacent uterine artery, leading to eventual rupture and subsequent haemorrhagic event. In one case in Japan with similar presentation, a patient had a cardiac arrest secondary to severe haemorrhage from severe adenomyosis with fibroid[33].

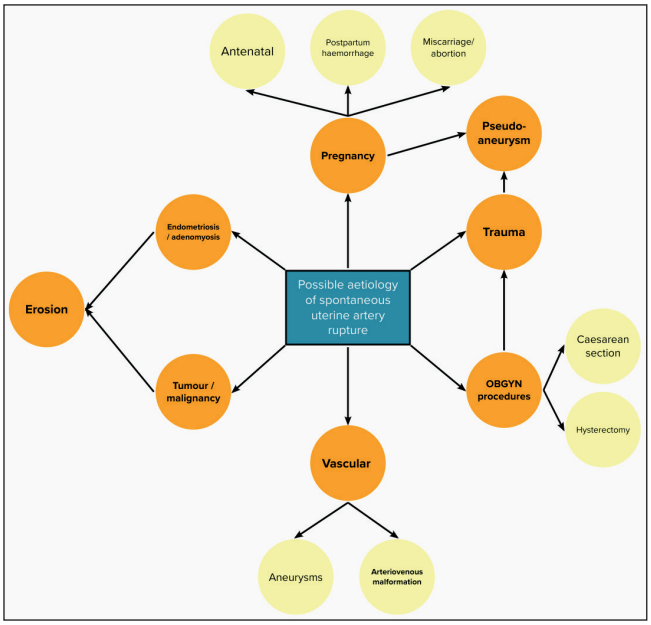

Figure 2.
Possible aetiology of spontaneous rupture of uterine artery. Eventual rupture of the artery can be multifactorial and causes can be interlinked (as demonstrated by the arrows). We deduce, in our case, the patient had a rupture of uterine artery secondary to erosion by adenomyosis.

Based on the literature and cases discussed, we have summarised the possible aetiology of spontaneous uterine artery rupture in Figure 2.

Treatment

In patients with severe haemorrhage such as ours, resuscitation and maintaining haemodynamic stability is the initial management. In terms of definitive treatment, trans-arterial embolisation is the treatment of choice for uterine artery rupture secondary to pseudoaneurysm[35-38], and this would also have been an appropriate treatment for the patient described in this case report. However, due to the lack of interventional radiology facilities in our local hospital, deterioration of the patient and completion of child-bearing, the more invasive management of hysterectomy was performed.

Conclusion

Spontaneous rupture of uterine artery is a rare event but an emergency with high mortality rate. Clinical suspicion in patients with unexplained ongoing severe vaginal bleeding should prompt further investigations and urgent input from obstetrics and gynaecology and interventional radiology. We suggest that, in patients with history of adenomyosis and endometriosis, the threshold for further investigations should be lower to allow rapid recognition and treatment.

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Clinical Paper

Artificial Intelligence in Endoscopy: A Narrative Review

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Introduction

In the last few years, Artificial Intelligence (AI) has shot to prominence in the public eye with the recent development of platforms such as ChatGPT. AI is now diffusely incorporated into our everyday human lives without most of us even realising. The expanding use of AI in healthcare shows exciting potential which could transform the future of medicine.

This narrative review is an update on the role of AI in gastrointestinal endoscopy.

What is Artificial Intelligence?

Artificial Intelligence is a broad term that refers to the development of computer systems that can perform tasks that usually would require human intelligence. This is created by programming computers with algorithms that allow them to learn from data, recognise patterns and make decisions without explicit human instruction.[1]

When it comes to understanding AI systems they can be subdivided into two main categories; Narrow/Weak AI and General/Strong AI. Weak AI are specialised in a particular domain and are only able to perform tasks within their pre-programmed domain.[2] For example, the popular household device Alexa is considered a weak AI as it is only able to create responses based on pre-inputted data, meaning it lacks broad understanding and capability to adapt to new non-programmed information. Whereas General/Strong AI is the theorised development of software capable of understanding and utilising knowledge across a broad range of domains.[3] Strong AI is envisioned to be able to learn and make decisions independent of trained inputted data, making it scarily comparable to the intrinsic capabilities of the human mind.[2,3] The concept of Strong AI is demonstrated in films like Terminator, where Skynet, the military AI gains self-awareness and begins to wage war against humanity. In the current year of 2025, no Strong AI exists.

Generative AI refers to AI that can create new original content such as audio, videos, or text, based on its programmed database, for example Open AI's ChatGPT.[4] Vast amounts of data, over 45 terabytes of text, was inputted into chat GPT's algorithm enabling it to use this information to learn and create content.[5] It is still considered to be a weak form of AI.

AI Terminology

It is important to have a basic understanding of types of AI to help understand and interpret AI models and research studies.

Machine Learning (ML) is a type of AI where the computer uses inputted algorithms to analyse and learn patterns of information from a given set of raw data.[1] For example, fitness watches use ML to track and analyse user data, providing insights into physical activity, sleep patterns, and overall health. Similarly our email accounts have the ability to detect incoming junk mail and adequately filter this into a separate inbox (albeit not 100% accurate at all times).

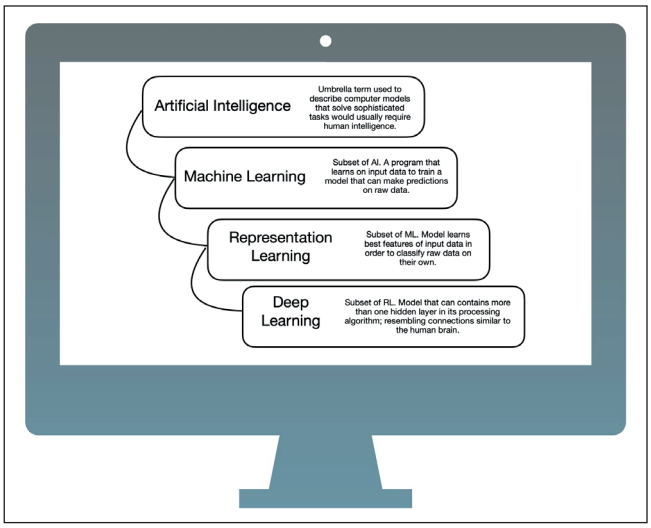

Figure 1:
Diagrammatic representation of the definitions of subsets of Artificial Intelligence.[1,8]

Representation Learning (RL) is a form of ML where the computer uses the best features of inputted data to enable them to classify data on their own. They do this via Artificial Neural Networks (ANNs).[6] ANN's are an AI creation of mathematical models designed to function similarly to the human brains complex connection of signaling neural networks.[1]

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Deep Learning (DL) is a type of RL that uses Deep Neural Networks (DNNs) to form multiple layers of links between vast amounts of data thus enabling it to recognise patterns and automatically make decisions on output.[1] For example, facial recognition is a form of RL which enables smart phones to analyse and recognize faces in images or videos. And Spotify, the music streaming service, is an example of DL where the app forms layers and connections to create areas like personalized recommendations, content classification, and music analysis.

In recent years, a main area of interest has leaned heavily on the Large Language Models (LLMs) of AI. These LLMs are types of AI that use Natural Language Processing (NLPs). NLP enables machines to be able to convey information in a human-like response.[1,7] Examples of LLMs are Siri, the virtual voice assistant in apple products or ChatGPT that can reply like a human in text form in milliseconds.

AI in the NHS

The UK is considered one of the leading countries in AI research and development. In 2020, the UK ranked third in the world for private investment into AI companies, behind the USA and China. At that time, the government had invested £2.3 billion into AI research across a range of initiatives since 2014.[9]

In 2019, over £250 million was invested to create the NHS AI Labs for healthcare to help accelerate the safe, ethical and effective development of AI technologies in healthcare.[10] The NHS AI Lab aims to collaborate academic research and technology companies to help tackle some of the toughest challenges in NHS healthcare.[10] As of March 2023, a total of £123 million had been invested in to 86 different AI technologies used within the NHS.[11] The AI in use helps support patients across a range of specialties, and from screening to diagnosis and management of chronic conditions.[11] In June 2023, the NHS announced a further £21 million funding for further research into the AI Diagnostic Fund.[12] NHS Trusts will be able to bid for funding to accelerate the deployment of the most promising AI tools across hospitals.[12]

AI in Endoscopy

Within the role of endoscopy; two major AI programs have been studied - Computer assisted detection (CADe) and Computer assisted diagnosis (CADx).[13] The role of AI in endoscopy could be hugely beneficial especially considering over 1.5 million endoscopic procedures were performed in 2020 within the NHS alone.[14]

1. AI in the Oesphagus

Oesophageal cancer is the 7th most common cancer worldwide and the 6th leading cause of cancer-related death.[15] Within oesophageal cancer there are two distinct types; oesophageal squamous cell carcinoma (OSCC) being the most common, and oesophageal adenocarcinoma (OAC) following behind.[15] Globally the incidence of OAC is rapidly rising in developed, high-income countries, linked to the increasing rate of key risk factors such as obesity, gastro-oesphageal reflux disease (GORD) and Barretts Oesphagus (BO) within this demographic.[15] Patients with oesophageal malignancies tend to remain relatively asymptomatic until the tumour has progressed, meaning diagnosis is typically at an advanced stage when survival rate is poor.[16] Therefore, the early detection of oesophageal cancer and precancerous lesions is crucial, especially as these early lesions can be treated via endoscopic resection techniques.[17]

At present, screening for dysplastic BO is composed of targeted biopsies followed by the Seattle protocol in selected individuals.[18] This protocol requires physicians to take biopsies every 1-2cm in 4 quadrants and is known to be an inefficient and a time-consuming task.[13,18] Endoscopic surveillance then depends on the length of the BO segment and the grade of dysplasia found.[19] The critical goal of surveillance programs is for early detection of dysplasia and hence earlier interventions.[19,20]

AI has used ML models to differentiate between dysplastic and non-neoplastic lesions in numerous studies, with many models showing promising results. Horie et al used over 8,000 endoscopic images to train its AI-CNN network model to be able to detect OSCC and OAC. The model was able to diagnose oesophageal cancer with a sensitivity of 95%, with an impressive 100% detection rate of cancers smaller than 10mm. This model had a remarkably high diagnostic accuracy of 98% in differentiating between superficial and advanced oesophageal cancer.[21] Cai et al developed a DNN for CADe using 2,478 endoscopic images with the aim to help improve detection of OSCC. Interestingly, when compared to sixteen endoscopists (senior, mid, and junior level) the system was proven to be superior to both experienced and inexperienced endoscopists in detecting OSCC in endoscopic images, with higher sensitivity and specificity values. The study concluded that their DNN-CAD system could assist in helping endoscopists detect lesions.[22]

In 2020, Groof et al published one of the first real-time applications of using a CADe system for the detection of neoplasms in patients with Barretts Oesphagus during live gastroscopy in a small pilot study of 20 patients. Of these patients, 10 had nondysplastic BO and 10 patients had confirmed dysplastic BO. The CAD system accurately identified Barrett's neoplasia at a given level in the Oesophagus with overall 90% accuracy.[23]

More recently, in 2023 Yuan et al performed a large multi-centre, tandem, double-blind, randomised controlled trial on AI-assisted assessment of early stage OSCC and precancerous lesions. In this study over 5,900 patients were assigned to either AI-first gastroscopy or routine-first gastroscopy. The results showed that AI reduced the miss-rates per lesion from 6.7% to 1.7%.[24]

At present, AI in the oesophagus shows promise for aiding detection of early cancer or pre-cancerous lesions although it is not available for widespread commercial use yet.

2. AI in the stomach

Worldwide each year approximately one million people are diagnosed with gastric cancer, ranking it 4th for cancer-related mortality globally.[25] The prognosis of gastric cancer is largely linked to the stage at which it is diagnosed. Patients with advanced gastric cancer have an extremely poor prognosis, whereas early gastric cancer (EGC) has a 5-year survival rate of more than 90%.[26] These differences in figures highlight the importance of early detection and prompt treatment. At present, detection of EGC relies on the direct visualisation of lesions during gastroscopy with the help of some image-enhancing tools.[13] EGCs can have variable morphology and hence detection can be challenging even for expert endoscopist. High-quality gastroscopy with full mucosal visualisation is a vital component in improving early detection.

Wu et al created a DNN-AI model using over 9,000 endoscopy images of either gastric cancer or benign lesions to train its model to detect EGC. It then used over 24,000 images for the AI-model to train the model to detect blind spots. The study demonstrated that the trained AI model had a 92.5% accuracy in the detection of EGC in comparison to non-malignancy (with 94.0% sensitivity and 91.0% specificity).[27]

A large multi-centre study led by Luo et al. Created the GRAIDS model (Gastrointestinal Artificial Intelligence Diagnostic System), for the diagnosis of upper GI cancers using endoscopic images. It used over 1 million images to develop and test the GRAIDS program. The performance of GRAIDS showed a high diagnostic accuracy of 95% with a sensitivity comparable to expert endoscopists. The AI model proved to be superior compared to the endoscopists categorised as competent or trainee.[28]

In 2020 in Wuhan, China, a randomised control trial with live endoscopy in over 1,800 patients who were undergoing gastroscopy for screening, surveillance, or investigation of symptoms was undertaken. Patients either had an AI-assisted gastroscopy or routine conventional gastroscopy. A conventional gastroscopy showed a neoplasm miss rate of 27.3%, with the AI-assisted endoscopy group being significantly lower with a miss rate of 6.1%. This shows that AI-assisted endoscopy improved the yield of diagnosing gastric neoplasms by endoscopists.[29]

ENDOANGEL is another example of an AI system showing promising potential for use in gastroscopy. ENDOANGEL, formerly known as WISENSE, was created in 2019 and was aimed at monitoring and reducing rates of blind spots during gastroscopy.[30] They then created a DL-AI models, ENDOANGEL-LD (lesion detection), to detect gastric abnormalities and diagnose gastric neoplasms. Over 10,000 patients were enrolled in the study, with results showing in internal and external participants sensitivities of 96.9%/95.6% for detecting gastric lesions and 92.9%/91.7% for diagnosing neoplasms.[31]

Another key factor when detecting EGC's is to determine the extent of invasion into the gastric mucosa, which can be challenging in itself. This information is crucial as according to current guidelines, endoscopic resection should only be performed for lesions extending into the mucosal or superficial submucosal layer, regardless of lymph node involvement. For those with deeper invasion the recommended treatment is surgery.[32] In 2019, Zhu et al developed a CNN-CAD model using 790 endoscopic images to train the AI system to determine the invasion and depth of gastric cancer. The model was then tested on another 203 images showing an overall accuracy of 89.16%, with higher accuracy and sensitivity when compared with endoscopists, at 71.49% accuracy.[33]

In summary, AI shows promise in increasing the detection rate of EGCs and to determine the extent of invasion into the gastric mucosa. Cancer Research UK recently awarded a new grant to further develop AI programs for EGC detection showing ongoing dedicated research into endoscopy within the NHS.[34] At the current time of writing, no AI models are validated for real-time clinical use. However, at present there is an ongoing multi-centre, randomised, controlled, patient-blinded, trial to test ENDOANGELs new ENDOANGEL-GC (gastric cancer) which will run in real-time endoscopy and combines the functions of blind spot monitoring and lesion detection. The study plans to enroll 30,000 participants from > 20 large-scale primary digestive centres in China.[35]

3. AI for the detection of H.Pylori

Helicobacter pylori, H.Pylori, is a gram-negative bacterium that specifically colonises the gastric epithelium and is the most common bacterial infection globally, with nearly 50% of the world's population being infected.[36] H.Pylori is well known for its association with gastroduodenal ulcers, gastric carcinoma, or MALT lymphoma.[37]

At present, testing for H.Pylori during endoscopy requires gastric biopsies with rapid urease test, histology, or culture.[38] AI-technology models have been trained to assess and detect the presence of H.Pylori infection during standard endoscopy without the need for a biopsy sample.

In 2018, Itoh et al. created an AI model which used 596 training images for detection of H.Pylori. When the model was tested it showed a sensitivity and specificity of 86.7% and 86.7% respectively.[39] In 2023, Lin et al designed several CNN networks to test the detection of H.Pylori in images. They concluded their scSE-CatBoost classification CNN-model can achieve a high accuracy for the diagnosis of H. Pylori infection with white light endoscopic image, with an accuracy of 90%, sensitivity 100% and specificity of 81%.[40] Whilst AI for assisted detection of H.Pylori is not currently

available; studies show that it is entirely possible to detect H.Pylori with visual detection alone in endoscopy. This could in turn reduce the need for unnecessary biopsies and further diagnostic testing, thus widely reducing the cost and carbon footprint.

4. AI in the colon

Every year over 500,000 colonoscopies are performed within the NHS.[20] Some for screening purposes, some for diagnostic and others for therapeutic reasons. One of the most common indications for colonoscopy is the investigation of /screening for bowel cancer. Bowel cancer is the 4th most common cancer and the 3nd most common cause of cancer related death worldwide.[41] Over 15,000 people die from bowel cancer in UK on an annual basis.[42] This figure has been falling since the 1970s, partly due to screening programs and improved treatment techniques.

A key standard in colonoscopy is Post Colonoscopy Colorectal Cancer (PCCRC) rate, that is to say colorectal cancer that develops prior to or seen at the next surveillance colonoscopy.[43] It has been shown that an endoscopist's adenoma detection rate (ADR), the percentage of patients with at least one histologically proven adenoma or carcinoma during colonoscopy, is inversely correlated to PCCRC.[43] This highlights that a lower ADR is suggestive of an increased likelihood of missed precancerous adenomas/ malignant lesions. Corley et al meta-analysis of over 300,000 colonoscopies reported that for every 1% increase in ADR the rate of PCCRC drops by 3%.[44] Other than ADR, the RCP Joint Advisory Group (JAG) on endoscopy has outlined performance indexes that indicate high quality endoscopy. With regards to colonoscopy these are outlined as >100 procedures by the endoscopist annually, 100% DRE examination, 90% Caecal intubation rate, Adenoma Dectection rate (ADR) 15%, Polyp Retrieval rate 90%, withdrawal time at least 6 minutes, rectal retroversion 90%, adequate bowel preparation in 90%, and targets relating to adverse outcome and patient satisfaction/sedation.[43] Of note, European guidelines set a minimal target ADR of 25%.[45]

To date there have been numerous studies on whether AI leads to an improvement in ADR or not. Rapici et al in Italy showed during a RCT that even in an expert centre ADR was increased from 40.8% in the control to 54.8% with the aid of AI enhanced colonoscopy using Medtronic's GI Genius.[46] Multiple other studies have replicated this data; the caveat however is that they often fail to comment on the level of expertise of the endoscopist. The largest RCT performed to date, by Mangas-Sanjuan et al in Spain, displayed no difference in ADR when their AI program was in the hands of expert endoscopists.[47] In this study there was an exceptionally high ADR of 62% within the control group. The wide variance in the performance of endoscopists depending on level of expertise, and various capabilities of the tested AI systems, may be responsible for such discrepancies in reports. And ADRs vary widely, 7 to 53% respectively depending on the endoscopists competence.[44] The precursor to ADR is PDR (polyp detection rate) but the two might not be correlated as strongly as one might think. AI increases PDR in nearly all studies one can come across. A substantial proportion of this increase in polyp detection are diminutive polyps (5mm or less).[48] They respectively have the lowest pre-test risk of malignant transformation.[48] With the practice of excising all detected polyps this leads to an increased, and possibly unnecessary, polyp resection which puts the patient at increased risk of resection related adverse events and increases demand on histopathology services.

Whether this all correlates to an important end-goal outcome, the reduction in PCCRC, that evidence is not available currently. What has been shown is that AI assisted colonoscopy can reduce Adenoma Miss Rate (AMR) on tandem colonoscopies from 37% to 14%.[49] The assumption could be made that given a reduction in AMR, there will inevitably be a reduction in PCCRC.

In 2022, M.Ariea et al published their article on a Markov model microsimulation in the Lancet. They hypothesised the effect of AI assisted colonoscopy in a screening program compared to non-augmented colonoscopy within the US population. Their model theorised that on a national level AI assisted colonoscopy would lead to 7,194 less cases of CRC and 2,089 less deaths secondary to CRC and a yearly cost saving of $290 million dollars.[50] However many of the authors in this paper had conflicts of interests as they were consultants to companies developing AI programs for endoscopy.

Then there is the second possible capability of AI - CADx. AI point of care diagnosis. The ability to competently differentiate between precancerous adenomas and other types of polyp such as hyperplastic or sessile at the time of visualisation. Current standards stated by PIVI (The American Society for Gastrointestinal Endoscopy Preservation and Incorporation of Valuable Endoscopic Innovation) recommend that if a greater than 90% negative predicative value at visual diagnosis for adenoma, then a diagnose and leave strategy could be implemented in the sigmoid colon, and a resect and discard strategy could be employed in the remaining colon for diminutive polyps (<5mm).[51] The ability to implement a dissect and discard approach based of effective CADx is of perceived great economic benefit as a number of diminutive polyps may not require pathological analysis. Multiple studies have shown that AI-augmented colonoscopy surpasses PIVI standards and supports a dissect and discard/diagnose and leave strategy.[52,53] There is suggestion there is reluctance to employ these strategies by endoscopists as they inherently come with perceived increased medical-legal risk.[54] It has however been shown to improve confidence of endoscopists attempting to visually diagnose polyps at resection.[52] Expert endoscopists trained in optical diagnosis can exceed these PIVI standards.[55] By implementing CADe technology this could help expert endoscopists feel confident enough in their

own ability, enabling them to adopt a resect and discard/ diagnose and leave approach when AI is in concordance with their decision, i.e. a second pair of expert eyes in agreeance. Currently these strategies are scarcely used worldwide. AI may be the tool that overcomes the barriers to entry with this approach, increasing endoscopist performance and confidence.

In June 2023, the UK government awarded a fund of 2.5million for use of Medtronic's GI genius AI endoscopy system. This is called the NAIAD trial (Nationwide study of Artificial Intelligence in Adenoma Detection for colonoscopy). It is led by Kings College London, and taking place over a 2-year period, it will involve 4,000 colonoscopy patients in 20 different hospitals across England. So far, this is the largest study on use of AI in gastroenterology within the NHS.[56]

At present, there are commercially available AI systems that can be used as an adjunct during colonoscopy to increase adenoma detection. GI Genius of Medtronic (Ireland), EndoBrain of Cybernet (Japan) and Endo-Aid of Olympus (Japan) as a few examples.

Other than detecting and diagnosing polyps with the assistance of AI there are other areas undergoing evaluation. AI programs have been developed that can assist endoscopists in determining quality of colonoscopy by providing immediate feedback on certain aspects. These include percentage of bowel mucosa visualised, grading of bowel preparation, quality of image resolution, the appropriateness of bowel distension and the adequacy of the withdrawal speed.[57] With regards to analysing the degree of mucosal invasion AI has been shown to distinguish non-invasive and superficially invasive neoplasms from invasive neoplasms with an accuracy of 91%.[58]

Investigation into IBD has also been promising with AI programs being shown to be able to detect persistent histological inflammation based on endoscopic images with an accuracy of 91%.[59]

5. AI in Small Capsule Endoscopy (SCE)

Capsule Endoscopy is a less invasive procedure compared to gastroscopy and colonoscopy. The patient swallows a vitamin sized capsule that contains a camera, light array and transmitter which is connected to an external storage device worn by the patient. The capsule then travels the length of the digestive tract capturing images along the way, most importantly of the small intestine. The small bowel can be visualised in entirety during successful double balloon enteroscopy but SCE has much fewer inherent risks, is more tolerable by patients and achieves complete imaging of the small bowel in a greater percentage of studies.[60] Its major drawback being the inability at present to implement treatment at time of visualisation. The indications for SCE are wide. In the small bowel SCEs are the first line investigation for suspected small bowel bleeds, have use in the detection of small bowel tumors and aiding the diagnosis and evaluation of Crohn's and Coeliac disease.[61] They also have their benefits in the oesophagus and large bowel, particularly when sedation for slightly more invasive procedures would be deemed risky or delays procedure due to logistical reasons.[61]

The duration from ingestion to complete passage through the small bowel varies greatly during SCE. The average time taken to reach and pass through the ileocecal valve can be expected to be around 4-6 hours.[62] This results in the acquisition of approximately 50,000 images, all of which require detailed review. Quality standards recommend expert readers set more than 45 minutes aside to review one single investigation, with regular breaks to avoid fatigue and associated lapses in concentration.[63]

Reducing the time required for clinician analysis and improvement in diagnostic accuracy are the two perceivable outcomes from well working AI in SCE. By reducing the number of redundant/duplicate images the clinician is required to review and presenting images determined to contain pathology a clinician's time can be effectively prioritised.

Most studies analyse the ability of an AI program to detect a particular type of lesion. Aoiki et al showed an accuracy of 90.8% for the detection of erosions and ulcers, while Fan et al. found an accuracy of 95.2%.[64,65] Yuan et al displayed an accuracy of 98% for AI assisted detection of polyps.[66] As AI programs become even more sophisticated it is hoped that accuracy will continue to improve. Ideally the AI programs in question would be proficient in detecting multiple abnormalities. For this there are fewer studies to draw from but Ding et al showed a sensitivity of 99.9% for AI augmented reading vs 74.6% for gastroenterologists alone (field of 20) in over 5000 investigations with a mean reading time of 5.9 minutes vs 96.6 minutes.[67] This study failed to comment on the gastroenterologists expertise level and their sensitivity of 74.6% is remarkably low compared to expert standards. It does however highlight the benefits AI can achieve in readers with lower expertise.

The introduction of various capsule systems with inbuilt artificial intelligence reached the market. The Navicam SB of ANX Robotica (USA), OMOM HD of Jinshan (China) and the Mirocam of IntroMedic (S.Korea) are some commercially available systems.

Limitations for AI

The growing research in AI in endoscopy is exciting for future practice, however it also comes with new challenges and limitations that need to be recognised. The major limitation inherent to AI, is hallucinations. This is a computer term relevant to AI but it can be understood as errors on the programs part. For example, a chatbot or computer tool can produce impressive and seemingly correct answers however these are non-sensical and not based on any training data.

In healthcare this may translate as an incorrectly diagnosed malignant lesion based on no recognised input algorithm. In endoscopy, this could lead to unnecessary biopsies or intervention, or conversely result in ignoring pathology of concern. Thankfully, there are ways to reduce AI hallucinations. The major factors that impact the occurrence of hallucinations are discussed here.

Modern AI systems develop CNNs from a catalogue of input data that teaches it to the desired output. We live in the age of big data where AI systems have the potential to be exposed to an enormous amount of input training data. However, that is not always for the better. There is evidence to suggest that past a certain point, the more data imputed into the AI for training, the more likely that the algorithm will be specific to the training set and not applicable to a wider population.[68] Overtraining of the program leads to overfitting. This can result in an increased chance of incorrect responses to new data. I.e. the quality of the training data is just as important as the volume of data used for training. Training an AI program with diverse, high quality raw data is one approach to reducing the rate of hallucinations.

Another way incorrect responses arise is from inappropriate use. Clinicians will be required to ensure that they are using any AI technology in the setting that it was validated for use in. For example, a program developed with the ability to detect sites of bleeding within the large bowel during colonoscopy. It would be inappropriate for a clinician to use this software to aid detection of bleeding during gastroscopy unless validated to do so. While the software may still recognise and detect bleeding sites during gastroscopy, if it has not been validated to do so, then the risk of missed or inappropriately labelled pathology is unknown. It may be that AI programs will be intelligent enough to know when they are being used inappropriately and therefore direct clinicians to this nature.

Generally, DLL models output a response without explaining the decision process and diagnosis basis. With any given response interpreters are unable to ascertain how AI has arrived at that particular response – this issue is referred to as the 'Blackbox' of AI. With this, physicians are directed to place their trust in AI programs, while these programs are unable to explain how or why they arrived at a particular outcome. Clinicians are unable to fact check the logic behind the program's response. If an adverse outcome were to manifest from an incorrect response that a clinician acts on – it raises the issue as to who is responsible, clinician or computer? In our opinion, the clinician has the ultimate responsibility for clinical care and decisions made. They should be aware of the potential shortcomings of their investigative tools. Its for this reason, AI programs will always require a degree of clinician oversight. AI programs should assist clinicians but be overruled when the clinician's clinical acumen would lead them to take a differing response. A way to help overcome the 'Blackbox' issue is through developing AI systems in which the program can logistically explain how it arrived at a specific response. Within endoscopy, ENDOANGEL- ED (Explainable Diagnosis) has been developed for EGC.[30] It presents its responses identifying six key analysis areas that aided its decision making. AI programs with inbuilt functions of this nature will help to improve trust and confidence in produced responses.

One perceived benefit of AI in endoscopy is the view that when computerised CADx and CADe systems are in place this will improve standardisation across the field, as it makes endoscopy a less operator dependent procedure. This can also help compensate for human errors that occur due to many factors such as fatigue, stress, or inattention. Whilst this is an agreeable point, there is the antagonistic view of - are we then making endoscopists reliant and dependent on AI? Will this limit their skill set and reduce their role in autonomous decisions in patient care or will it simply increase the speed of their learning curve?

Summary

AI-assisted endoscopy has the potential to improve both patient outcomes and simultaneously reduce clinician workload. While the clinician will never be replaced, these systems will endeavor to act as an assistant with capabilities that a human cannot possess, such as heightened visual acuity, advanced pattern recognition and increased processing speed. Clinicians will be required to educate themselves on new innovative technologies and use them effectively for their intended purpose, whilst also acknowledging the limitations and challenges created when working with AI.

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Clinical Paper

An Atypical Presentation of VEXAS Syndrome: A Diagnostic Conundrum

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Abstract

VEXAS syndrome is a rare and recently identified autoinflammatory disorder recently, characterized by the involvement of multiple organ systems, with manifestations in dermatology, hematology, and rheumatology. The syndrome results from a somatic mutation in the UBA1 gene, leading to defective ubiquitin-mediated protein degradation, which triggers a cascade of inflammatory responses. We report the case of a 76-year-old male who presented with a recurrent rash initially suggestive of Sweet's syndrome. Following a comprehensive diagnostic workup, including genetic testing, the patient was diagnosed with VEXAS syndrome due to the identification of a pathogenic variant in the UBA1 gene. This case highlights the diagnostic challenges clinicians face when confronting rare syndromes with nonspecific clinical features. The absence of formal diagnostic criteria and its overlap with more common inflammatory and haematologic diseases complicates prompt diagnosis and management. Timely recognition, genetic confirmation, and early intervention are critical for preventing disease progression and improving outcomes in VEXAS patient.

Introduction

VEXAS syndrome (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) is a rare autoinflammatory disorder first described in 2020 . VEXAS syndrome is due to an acquired somatic mutation affecting the methionine-41 codon (p.Met41) in UBA1[1]. This gene encodes the major E1 enzyme involved in the activation of ubiquitin, a small regulatory protein which attaches to substrate proteins by a process know as Ubiquitination which is a cellular mechanism that tags proteins for degradation. Ubiquitination involves variations of ubiquitin chains and branches and is known to play a role in the degradation of unwanted proteins to control signal transduction during cell survival, immunity, and inflammation[2,3]. A somatic mutations post conception involves non germline cells DNA, and is not inherited from either parent.

VEXAS Syndrome is X-linked as the **UBA1 gene** is located on the **X chromosome.** The disease is more commonly expressed in males because in males **(XY)**, there is only one copy of the X chromosome, so a mutation in the UBA1 gene on that chromosome is more likely to result in the development of VEXAS Syndrome. The somatic mutation in their haematopoietic cells can manifest features of the disease.

The syndrome is associated with a wide array of symptoms, including dermatological manifestations, haematologic abnormalities, and systemic inflammation. Despite its recent delineation diagnosing VEXAS is difficult due to its varied presentation and rarity. Patients often undergo extensive workups for more common conditions before the diagnosis is considered, and there are no established diagnostic criteria to guide clinicians. The following case illustrates the diagnostic complexity of VEXAS syndrome. A 76-year-old man presented with a 5 year history of an intermittent rash characterised by erythematous, granulomatous , discoid plaques on his trunk, arms, and back [figure 1,2,3]

Case Presentation

A 76-year-old man presented with a 5 year history of an intermittent rash characterised by erythematous, granulomatous , discoid plaques on his trunk, arms, and back [figure *1*,2,3]

The rash flared intermittently with new areas persistently developing throughout the 5 year period. He had no joint swelling, no night sweats, and no weight loss. As part of his dermatological investigation a number of skin biopsies were performed. The first biopsy [figure 4] demonstrated a superficial dermal inflammatory infiltrate of histiocyte-like cells and scattered neutrophils. The original reporting pathologist suggested several possible differential diagnoses including sweet's syndrome and interstitial granulomatous dermatitis. Sweet's syndrome is a rare inflammatory disorder characterized by painful red or purple skin lesions (plaques or nodules) and fever, often triggered by infections, medications, or underlying conditions like cancer. It is caused by an abnormal immune response leading to neutrophil accumulation in the skin. He was commenced on a 3 monthly trial of Colchicine 500 micrograms BD with no improvement in his rash.

He had a background history of normocytic anaemia, left

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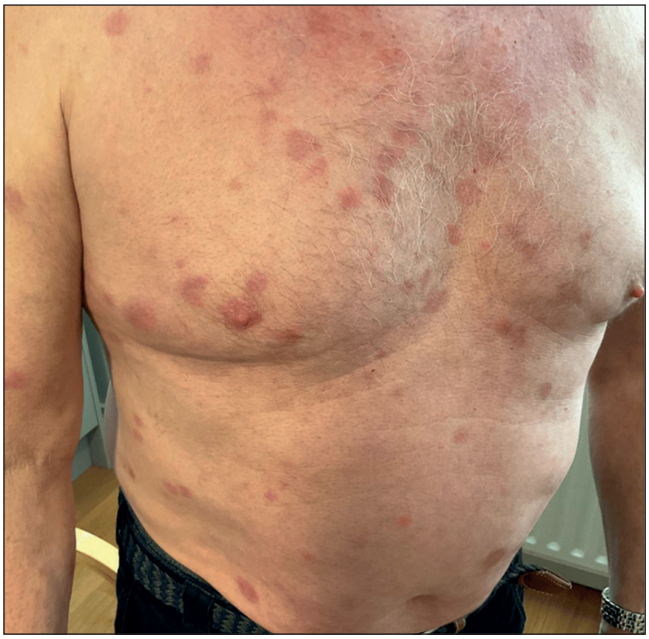

FIGURE 1: Erythematous , granulomatous like , discoid plaque on trunk.

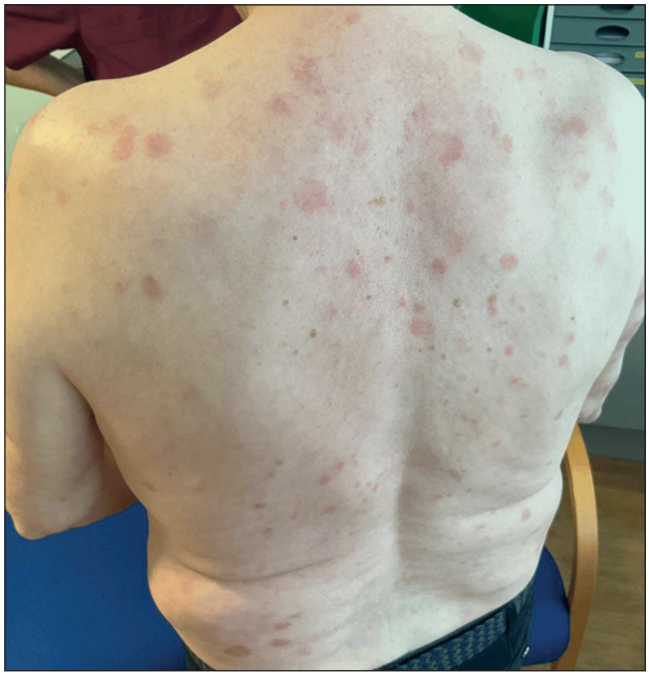

FIGURE 2: Erythematous , granulomatous like , discoid plaques on back.

lower para-aortic lymph node , inguinal hernia, prostatism, hyperlipidaemia and hip osteoarthritis . Laboratory tests showed normocytic anaemia, thrombocytopenia, and elevated inflammatory markers [Table *1*]

As his condition evolved, the rash reappeared with a new-onset inflammatory arthritis affecting his shoulder, wrist and 1st metacarpal phalangeal joint. This was associated with fatigue, joint pain and stiffness in hands particularly affected

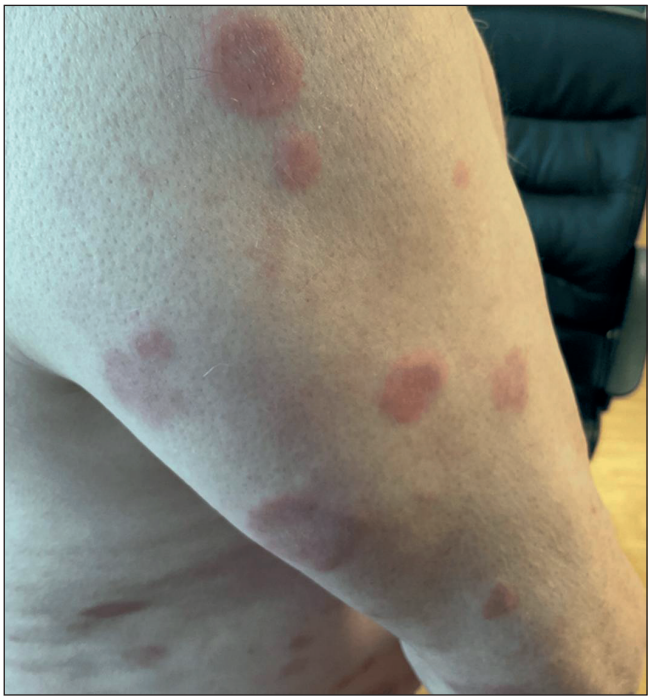

FIGURE 3: Erythematous , granulomatous like , discoid plaques on arms.

him as he was a musician playing the saxophone and flute. He was administered I.M. Depomedrone which gave him relief for few days but his joint pain recurred again.

A further skin biopsy [figure *5*] of the rash was performed which demonstrated similar features to the original. This contained more prominent papillary dermal edema. In addition to the superficial dermal interstitial, histiocyte-like cells and scattered neutrophils a small number of lymphocytes were present. The case was referred for specialist regional hematopathology opinion who confirmed the diagnosis of histiocytoid sweet's syndrome.

The reporting haematopathologist upon review of the patient's electronic clinical record (noting thrombocytopenia, arthritis, blood investigations) considered the possibility of VEXAS syndrome. Subsequently dermatopathology reviewed and agreed with haematopathological interpretation, altering the clinicians to possibility of VEXAS syndrome and thus Genetic testing was recommended. Whilst awaiting molecular confirmation of VEXAS disease, therapeutic trials of colchicine and hydroxychloroquine proved of little benefit.

Subsequent genetic testing identified a pathogenic variant in the UBA1 gene with a variant allele frequency

(VFA) of 27.7%[1], confirming the diagnosis of VEXAS.. He was placed on long-term steroid therapy of Prednisolone . He responded very well to his recent course of steroids. His rash completely cleared. There have been no further flares. His shoulder pain also settled. He was scheduled for regular follow ups.

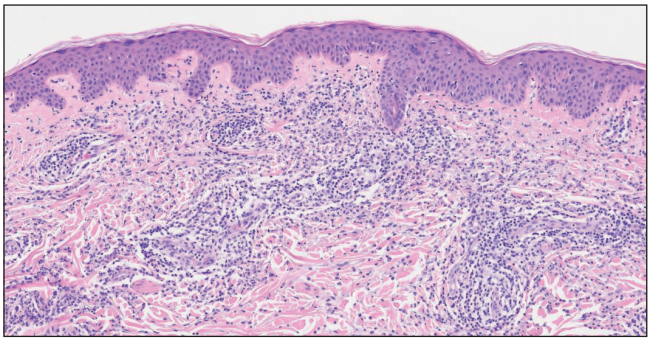

FIGURE 4: The first biopsy : demonstrates a superficial dermal inflammatory infiltrate of histiocyte-like cells and scattered neutrophils. The histiocyte-like cells contain eccentric, kidney/ crescent-shaped nuclei. There is no interface activity. The inflammation is predominantly interstitial with perivascular and periadnexal condensation. Focal leukocytoclasis and phagocytosis of nuclear debris is noted, but there is no evidence of vascular injury (endothelial swelling/ fibrinoid necrosis/ erythrocyte extravasation). Very mild excess of interstitial mucin is highlighted within the papillary dermis upon staining with Hales colloidal iron. The original reporting pathologist suggested several possible differential diagnoses including sweet's syndrome and interstitial granulomatous dermatitis.

Blood tests	Lab Values	Reference
Hb	105 g/L	130–170 g/L (men)
MCV	97.4 fL	80–100 fL
MCHC	316 g/L	320–360 g/L
WBC	3.18 x 109/L	4.0–10.0 x 109/L
Platelets	102 x 109/L	150–400 x 109/L
CRP	37 mg/L	3 mg/L
ESR	58 mm/hr	Male (50+ years): 2–10 mm/hr

TABLE 1: Lab values showing the blood investigations .

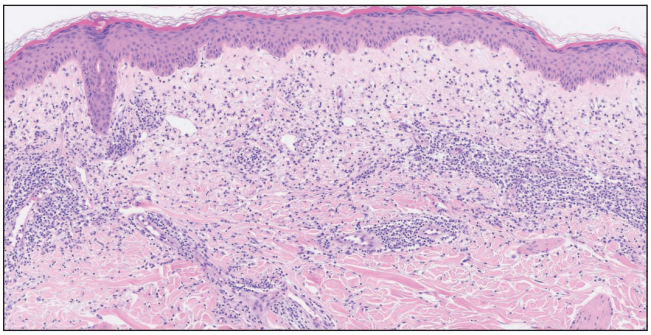

FIGURE 5: The second biopsy demonstrates similar features to the original. This contains more prominent papillary dermal oedema. In addition to the superficial dermal interstitial, histiocyte-like cells and scattered neutrophils a small number of lymphocytes are present. Both neutrophils and histiocyte-like cells stain with myeloid cell nuclear differentiation antigen and myeloperoxidase. This indicates that the histiocyte-like cells are in fact immature myeloid precursors and confirms the diagnosis of histiocytoid sweet's syndrome

Discussion

VEXAS syndrome presents a significant diagnostic challenge due to its rarity and its clinical overlap with other inflammatory conditions such as Sweet's syndrome, lupus and shared care between dermatology and rheumatology. Key features include male gender, late onset, sweet's like skin lesions, hematologic abnormalities (e.g., anemia, thrombocytopenia), and constitutional symptoms. However, the clinical presentation is heterogeneous, and there are no formal diagnostic criteria. Epidemiological studies suggest that VEXAS is rare; a retrospective observational study identified a prevalence of 1 in 4269 men over the age of 50[4].

In this case, the patient's presentation with Sweet's-like cutaneous lesions, arthritis, anaemia, and thrombocytopenia were key clues. The absence of some hallmark features of VEXAS, such as chondritis and macrocytic anaemia, multiorgan involvement, varied presentation contributed to the diagnostic delay.

Genetic testing for UBA1 mutations is currently the definitive diagnostic tool for VEXAS and should be considered in male patients with unexplained inflammatory syndromes, especially when accompanied by treatment refractory inflammatory conditions in multiple organ systems with progressive haematological abnormalities.

Currently, there is no specific therapy for VEXAS syndrome, and treatment mainly focuses on managing the symptoms. This may involve the use of anti-inflammatory medications, immunosuppressive drugs, and supportive therapies tailored to the individual patient's needs[5].

Complications of VEXAS include -anaemia, thrombocytopenia[1], histiocytoid and neutrophilic dermatosis, neutrophilic urticarial dermatosis, cutaneous vasculitis, septal panniculitis and lupus like eruption[6], pulmonary infiltrates[7], vasculitis affecting multiorgan systems[8], haematological malignancies[9]. The optimal treatment for VEXAS remains under investigation, though corticosteroids and other immunosuppressive therapies have shown some efficacy. The long-term prognosis appears poor:

the mortality rate in a Netherlands study was 50% and in a series from the USA, 9/16 died from diseaserelated causes[10]. The high mortality rate associated with VEXAS highlights the importance of early diagnosis and treatment to prevent multi-organ involvement and progression of the disease.

Conclusions

This case underscores the importance of recognizing VEXAS syndrome in male patients presenting with atypical cutaneous and haematological findings. Patients often undergo extensive workups for more common conditions before the diagnosis is considered, due to lack of clinical awareness to trigger genetic testing. This case illustrates the diagnostic complexity of VEXAS syndrome. Haematologic

abnormalities can lag behind other inflammatory conditions which may require steroid sparing agents and if bone marrow failure occurs- hypomethylating agents and transplant are options. Management is also based on organ involvement. Early identification and intervention is critical to manage the disease and prevent life-threatening complications

Additional Information

Disclosures

Human subjects: Consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Categories: Rheumatology, Dermatology, Haematology

Keywords: haematological manifestations, treatment choices, complications', uba1, rare genetic diseases, sweet's sydrome, derm-rheum, rare skin disease, vexas syndrome

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Short Communication

Clinical Trials involving *Mycobacterium abscessus*: An update

J E. Moore and B C. Millar

Mycobacterium abscessus (*M. abscessus*) has now emerged as a significant bacterial pathogen in human infection, particularly in pulmonary disease, including in those with cystic fibrosis (CF)[1,2]. Several recent (2022-2023) reviews successfully describe (i) treatment options, including drug discovery[3-7] and (ii) pathogenesis of *M. abscessus*-related disease[1,8-11]. Due to its pathogenesis in disease, accompanied by its resistance to antibiotics and biocides used to disinfect healthcare facilities[12], as described in the above reviews, this makes *M. abscessus* a formidable challenge in terms of infection prevention and control, as well as with its antibiotic treatment and clinical management. Whilst there are numerous anti-*M. abscessus* approaches, strategies and innovations that have been proposed academically, as previously described[13], few of these will ever progress to being adopted as a clinically effective licenced treatment modality against this organism. Healthcare professionals therefore wish to learn about potential treatment options that are currently in the clinical trials pipeline, which could serve as new clinical interventions, as well as to inform their patients, about possibilities of becoming involved, if eligible. This review aims to highlight and briefly describe what trials involving *M. abscessus* are currently under examination in registered clinical trials globally.

The US National Library of Medicine Clinical Trials register[14] and the EU Clinical Trials register[15] were examined, using the key term "*Mycobacterium abscessus*". The US database returned 22 trials and the EU database returned 1 trial. These are listed in Table 1. Given that the sole EU listed trial had the same title as that in the US database, this was treated as a duplicate trial in two databases. Of these, 9 were observational and 13 were interventional.

Several of the observational studies examine patient registry data, optimisation of existing antibiotic interventions, genomic data and pharmacological PK/PD data. The interventional studies wish to explore novel interventions including nitric oxide, as well as anti-infectives including omadacycline, gallium, azithromycin, tigecycline, delpazolid, clofazamine, amikacin. What is currently missing from this list are interventional studies involving bacteriophage therapy, as is the case with *Pseudomonas aeruginosa* and cystic fibrosis.

More recently in May 2024, a case-control observational trial was initiated which hopes to identify new biological markers by characterizing the response/inflammation associated with the development and progression of *M. abscessus* lung disease in patients suffering from cystic fibrosis with the aim of increasing current knowledge available on the development and progression of lung disease [NCT06413459].

Readers can access current up-to-date information on each of the clinical trials listed, by accessing this via its assigned clinical trial number at clinicaltrials.gov.

Keywords: *Mycobacterium abscessus*, clinical trial, nitric oxide, antimicrobial resistance, cystic fibrosis, pulmonary disease.

Ethics Statement

Ethical approval was not required as no research was performed on any human or animal subject.

Author Contributions

CRediT authorship contribution statement:
John E Moore: Conceptualization; Formal analysis; Methodology; Roles/Writing - original draft; Writing - review & editing
Beverley C. Millar: Conceptualization; Formal analysis; Methodology; Roles/Writing - original draft; Writing - review & editing

Disclosure of Conflict of Interest

John E. Moore: None to declare
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Table 1: Current clinical trials targeting Mycobacterium abscessus (n=22)
(Source: ClinicalTrials.gov)

NCT01354912	The Incidence of Nontuberculous Mycobacterial Pulmonary Infection in Bilateral Bronchiectasis and Bronchiolitis	Bronchiectasis; Bronchiolitis	OBSERVATIONAL:
NCT03597347	Trial of Inhaled Molgramostim in Cystic Fibrosis Subjects With Nontuberculous Mycobacterial Infection	Mycobacterium Infections, Nontuberculous Cystic Fibrosis (CF)	INTERVENTIONAL: DRUG: Molgramostim nebulizer solution: DEVICE: PARI eFlow nebulizer system.
NCT03339063	The Italian Registry of Pulmonary Nontuberculous mycobacteria	Nontuberculous Mycobacteria	OBSERVATIONAL:
NCT04310930	Finding the Optimal Regimen for Mycobacterium abscessus Treatment	Pulmonary Disease Due to Mycobacteria (Diagnosis)	INTERVENTIONAL: DRUG: Amikacin, Tigecycline, Imipenem, Cefoxitin, Azithromycin, Clarithromycin, Clofazimine, Ethambutol, Amikacin, Linezolid, co-trimoxazole, Doxycycline, Moxifloxacin, Bedaquiline, Rifabutin.
NCT04685720	A Pilot Study to Assess the Effect of Intermittent iNO on the Treatment of NTM Lung Infection in CF and Non-CF Patients	Non-Tuberculous Mycobacterial Pneumonia; Cystic Fibrosis; Mycobacterial Pneumonia; Mycobacterium abscessus Infection; Mycobacterium avium Complex	INTERVENTIONAL: DEVICE: LungFit
NCT05101915	Study of a Nebulised Nitric Oxide Generating Solution in Patients With Mycobacterium abscessus	Cystic Fibrosis	INTERVENTIONAL: DRUG: RESP301.
NCT04922554	Oral Omadacycline vs. Placebo in Adults With NTM Pulmonary Disease Caused by Mycobacterium abscessus Complex (MABc)	Mycobacterium Infections, Nontuberculous;Mycobacterium abscessus Infection; Nontuberculous Mycobacterial Lung Disease; Nontuberculous Mycobacterial Pulmonary Infection	INTERVENTIONAL: DRUG: Omadacycline Oral Tablet; DRUG: Placebo.
NCT04294043	IV Gallium Study for Patients With Cystic Fibrosis Who Have NTM (ABATE Study)	Nontuberculous Mycobacterium Infection	INTERVENTIONAL: DRUG: Gallium nitrate.
NCT00599079	Azithromycin in the Treatment of M. avium Complex Lung Disease	Mycobacterium avium Complex Lung Disease	INTERVENTIONAL: DRUG: Azithromycin.
NCT00600600	Tigecycline for Treatment of Rapidly Growing Mycobacteria	Mycobacterium abscessus Lung Disease;Rapidly Growing Mycobacterial Lung Disease	INTERVENTIONAL: DRUG: Tigecycline.
NCT02832843	Genome-Wide Association Study in Patients With Nontuberculous Mycobacterial Lung Disease	Mycobacterium Infections, Nontuberculous	OBSERVATIONAL:
NCT06004037	Study to Evaluate the Efficacy of Delpazolid as Add-on Therapy in Refractory Mycobacterium abscessus Complex	Nontuberculous Mycobacterium Infection; Mycobacterium abscessus Infection	INTERVENTIONAL: DRUG: Delpazolid.
NCT05354583	Treatment Outcome Between Mycobacterium abscessus Infection in Chronic Lung Disease and Acquired Interferon-gamma Autoantibody Syndrome	Mycobacterium abscessus Infection; Adult-Onset Immunodeficiency With Acquired Anti-Interferon-Gamma Autoantibodies; Nontuberculous Mycobacterial Pulmonary Infection	OBSERVATIONAL: DRUG: Appropriate treatment.
NCT05676138	PK and PD of Antibiotics for Treatment of Mycobacterium Abscessus Pulmonary Disease	Nontuberculous Mycobacterial Pulmonary Infection	OBSERVATIONAL: I
NCT05294146	Pharmacokinetic Study With a Loading Dose of Clofazimine in Adult Patients With Nontuberculous Mycobacterial Disease	Nontuberculous Mycobacterial Diseases	INTERVENTIONAL: DRUG: Clofazimine.

NCT01528930	Inhaled Amikacin Treatment for Nontuberculous Mycobacterial Lung Disease	Pulmonary Non-tuberculous Mycobacterial Lung Disease	INTERVENTIONAL: DRUG: Amikacin.
NCT03208764	Inhaled Nitric Oxide for Patients With MABSC	Mycobacterium abscessus Infection	INTERVENTIONAL: DRUG: Nitric Oxide.
NCT02005094	The Role of Inflammasome in Inflammatory Macrophage in Mycobacterium avium Complex-lung Disease and Mycobacterium abscessus-lung Disease		OBSERVATIONAL:
NCT04024423	Healthcare-associated Links in Transmission of Nontuberculous Mycobacteria in Cystic Fibrosis	Cystic Fibrosis;Nontuberculous Mycobacterium Infection	OBSERVATIONAL:
NCT03038178	Liposomal Amikacin for Inhalation (LAI) in the Treatment of Mycobacterium abscessus Lung Disease	Mycobacterium Infections, Nontuberculous;Mycobacteria, Atypical	INTERVENTIONAL: DRUG: LAI plus multi-drug regimen.
NCT04163601	Liposomal Amikacin Inhalation in M. abscessus Patients	M.abscessus Pulmonary Disease	OBSERVATIONAL:
NCT00018044	Study of Mycobacterial Infections	Mycobacterium Infections	OBSERVATIONAL:

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James Logan Prize Essay 2024

Understanding Cancer Pain Syndromes

Alexandros-Gazi Bsarat [1]

The James Logan Trust is a registered charity set up to encourage medical students to learn about and think about the treatment of cancer pain. It has sponsored an essay prize on the topic of treatment of cancer pain for undergraduate students at the Queen's University of Belfast since 2010.

This is the winning entry from 2024.

Introduction:

Pain is a commonly reported symptom in cancer patients during different stages of active disease, active treatment and even post-curative treatment. A systematic review and metanalysis looking at 122 articles concluded that pain prevalence in cancer patient groups of all stages was as high as 50.7%. Furthermore, 55% of patients experienced pain during active cancer treatment. The underlying cause of the pain could be as a result of the cancer or due to the treatment itself (iatrogenic)(1). A more recent study, looking at 444 articles indicated a slight decrease in overall cancer pain prevalence at 44.7%, yet remaining close to the 50% mark. Despite the high prevalence of pain in these patients, approximately 40% on analgesic treatment will find it inadequate in relation to the intensity of the pain experienced(2). In addition, the European Association for Palliative Care emphasises a gap in evidence-based practice for cancer pain treatment therefore resulting in guidelines being largely based on expert opinion. The efficacy of different cancer pain treatments relies on the understanding of the vast physiological pathways of the pain and the underlying causes which may fall under the generalised umbrella term of cancer pain syndromes. This essay aims to define cancer pain syndromes, explore the pathophysiological pathways of pain, classify the commonest cancer pain syndrome types, provide an overview of current pain assessment and management guidelines and finally identify any further research.

Definition:

Cancer pain syndromes can broadly be defined as a collection of syndromes that result from one or more of the following causes: pain directly related to tumour cells, iatrogenic pain due to active cancer treatment and lastly pain resulting from physiological pathways unrelated to the cancer or its treatment in cancer group patients. Furthermore, these syndromes can be classified as acute or chronic and visceral, somatic or neuropathic in nature depending on the tissue responsible (3).

Understanding the different mechanisms by which cancer pain syndromes arise:

In order to fully appreciate these mechanisms, we need to look at the basic pathophysiological pathways which can trigger the pain stimulus in cancer patients. These pathways can be divided into two main groups.

The first is nociceptive pain defined as a pain due to activation of nociceptors in response to chemical, thermal and mechanical stimuli resulting from direct or threatened damage of non-neuronal tissue. Nociceptive pain can be further subdivided into visceral and somatic. Visceral pain originates from the internal organs such as the heart, lungs, stomach, gut and genitourinary system often presenting with poorly localised, deep, dull pain(4). Somatic pain originates from the skin and musculoskeletal system. It is easier to localise than visceral pain, however cutaneous injury is often more localised than deeper somatic pain (e.g. a bone fracture). It can present as a burning, sharp or throbbing pain (5). Somatic pain is very prominent in cancer patients and bone metastasis is the commonest cause (4).

The second main group, is neuropathic pain, defined as pain resulting from inflammatory mechanisms or damage to the central or peripheral nervous systems. In the cancer group this is caused by external compression from the tumour or by malignant cells directly infiltrating the nerve. Furthermore, it may, too, be caused by iatrogenic means. It frequently presents as burning in character and with a stabbing sensation intermittently. It may also present as pain resulting from otherwise non-pain provoking stimuli, known as allodynia or nerves can become sensitised therefore causing a more severe pain response to pain-provoking stimuli, known as hyperalgesia (3).

Classification of common Cancer Pain Syndromes:

It is important to take into consideration the nature of the pain experienced by each individual patient and attempt to understand the relationship between the primary or secondary metastatic cancer and the pain experienced. Cancer pain can be challenging to identify and manage, however more targeted therapy aimed towards the underlying aetiology of the cancer pain has the potential to improve outcomes for the patient and reduce the risks associated with strong

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analgesics such as opioids. Table 1 aims to classify some of the commonest cancer pain syndromes resulting directly from solid tumours (6,7).

Additionally, it is important for a clinician to recognise that pain can be related to the cancer treatment rather than the pain being caused by the tumour. Often pain may be caused by both the tumour and treatment therefore making it more difficult to provide targeted analgesic management. Awareness of iatrogenic causes of cancer pain may further assist in planning targeted management for the patient and the pain experienced. Table 2 categorises some of the most prevalent cancer pain syndromes caused by specific cancer treatments (8,9).

Cancer Pain Assessment and Tools:

Cancer pain assessment poses a challenge in the oncological field due to the complex nature of the disease, the subjectiveness of each individual experiencing the pain and the difficulty pin-pointing a single underlying cause of the pain. A thorough assessment is of vital importance in achieving more efficacious pain control and limiting adverse effects.

Table 1. Classification of Cancer Pain Syndromes resulting directly from solid tumours

Neoplastic damage to bone and joints	1. Base of the skull syndrome. Headache due to calyarial, maxillary, or mandibular lesion
	2. Vertebral syndromes, including sacrum
	3. Pelvic, long bones, direct infiltration of a joint
	4. Generalized bone pain: a. due to multiple bone metastasis b. due to bone marrow infiltration/expansion
	5. Chest wall pain from rib lesion
	6. Pathologic fracture of: a. long bone b. vertebrae c. pelvis d. rib e. other
Neoplastic damage to viscera	7. Oesophageal mediastinal pain.
	8. Shoulder pain from diaphragmatic infiltration a. pain from distention of hepatic capsule b. obstruction of biliary tract c. left upper quadrant pain from splenomegaly
	9. Epigastric pain from pancreas or other upper abdominal neoplasm "Midline rostral retroperitoneal syndrome"
	10. Diffuse abdominal pain from abdominal or peritoneal disease: a. with obstruction b. without obstruction
	11. Suprapubic pain from infiltration of bladder. Perineal pain from infiltration of rectum or perirectal tissue (including vagina)
	12. Obstruction of ureter
	13. Damage to oral mucous membranes. Infiltration of skin and subcutaneous tissue
Neoplastic damage to soft tissue and miscellaneous	14. Infiltration of muscle and fascia of in the chest or abdominal wall. Infiltration of muscle and fascia in the limbs
	15. Infiltration of muscle and fascia in the head and neck
	16. Retroperitoneal tissue infiltration excluding rostral retroperitoneal syndrome
	17. Pleural infiltration
Lesions of Nervous Tissue	18. Peripheral nerve syndromes a. due to paraspinal mass b. due to chest wall mass c. due to retroperitoneal mass other than paraspinal d. due to other soft tissue or bony tumour e. peripheral polyneuropathy
	19. Radiculopathy or cauda equina syndrome a. due to vertebral lesion b. due to leptomeningeal metastases c. due to other intraspinal neoplasm
	20. Plexopathy a. cervical plexopathy b. brachial plexopathy c. lumbosacral plexopathy d. sacral plexopathy
	21. Cranial neuropathy a. due to base of the skull tumour b. due to leptomeningeal metastases c. due to other soft tissue or bony cranial tumour
	22. Pain due to central nervous system lesion a. due to myelopathy b. intracerebral lesion
	23. Headache due to intracranial hypertension
	24. Neck, back pain or headache due to leptomeningeal disease

Table 2. CANCER PAIN SYNDROMES ASSOCIATED WITH CANCER THERAPY

Chemotherapy-Related Pain Syndromes	Bony complications of long-term corticosteroid use
	Avascular necrosis
	Vertebral compression fractures
	Carpal tunnel syndrome
	Chemotherapy-induced peripheral neuropathy
	Raynaud's syndrome
Hormonal Therapy–Related Pain Syndromes	Arthralgias
	Dyspareunia
	Gynaecomastia
	Myalgias
	Osteoporotic Compression fractures
Radiation-Related Pain Syndromes	Chest wall syndrome
	Cystitis
	Enteritis and Proctitis
	Fistula formation
	Lymphoedema
	Myelopathy
	Osteoporosis
	Osteoradionecrosis and fractures
	Painful secondary malignancies
	Peripheral mononeuropathies
	Plexopathies (brachial, sacral)
Stem Cell Transplantation-Mediated Graft Versus Host Disease	Arthralgias/Myalgias
	Dyspareunia/vaginal pain
	Dysuria
	Eye pain
	Oral pain and reduced jaw motion
	Paraesthesia
	Scleroderma-like skin changes
Surgical Pain Syndromes	Lymphoedema
	Post-amputation phantom pain
	Post-mastectomy pain
	Post-radical neck dissection pain
	Post-surgery pelvic floor pain
	Post-thoracotomy pain/frozen shoulder
	Post-surgery extremity pain (e.g. sarcoma)

J.M. Brant summarises the key areas that can formulate a thorough cancer pain assessment. First the clinician conducting the assessment should look at the cancer type and stage as these can assist in determining the cancer pain syndrome and estimating the pain severity. The later the stage the more common for a more severity pain to be present. Then it is important to look at the treatments that are ongoing, finished or planned to start (e.g. surgery, chemotherapy, radiation). Comorbidities should also be assessed as conditions like fibromyalgia, diabetes and arthritis can significantly affect cancer pain. A thorough history of the pain should be taken. Site, intensity (0-10), character, temporality which refers to the patterns and variations in the pain experienced including breakthrough and background pain and lastly effects of pain on patient behaviour such as splint use or gait impairment. Diagnostic modalities such as CT or MRI can identify structural causes of pain. Previous attempts to relieve cancer pain and their outcomes may be useful. For example, exercise, physiotherapist or occupational therapist input, pharmacological and complementary treatments (e.g. acupuncture). Last but not least a thorough functional assessment of pain interference with day-to-day life as well as psychological, social and spiritual assessment is important to be undertaken. The above are all important factors than can significantly impact cancer pain (10).

The use of assessment tools may be used in conjunction with the initial assessment to assist in classifying the pain

into specific cancer pain syndromes. One of these tools is the Brief Pain Inventory (BPI) which allows a patient to rate their pain severity as well as the impact it has on their quality of life. It allows for quantification of several parameters into a 0-10 scale and essentially categorises pain severity into mild, moderate and severe (11). Another tool is the 35 item Patient-Reported Outcomes Measurement Information System (PROMIS). It can be used to quantify interference with many aspects of daily life as a result of the cancer pain within the period of a week. Furthermore, the face pain rating system can be used in patient groups who have difficulty understanding other rating systems such as children and patients with language barriers. There is a wide range of tools than can be used for cancer pain assessment and should be used in relation to individual needs and circumstances and by an appropriately qualified clinician with knowledge on the use of these tools (8).

Cancer pain syndrome management and guidelines:

There have been many advancements in cancer therapies over the recent years with promising efficacy and massively improved overall survival rates. However, the basis of cancer related-pain has remained fairly constant since the development of the WHO 3-step analgesic ladder. This has been revised to include a fourth step for "Invasive and minimally invasive treatments" as shown in figure 1 (12).

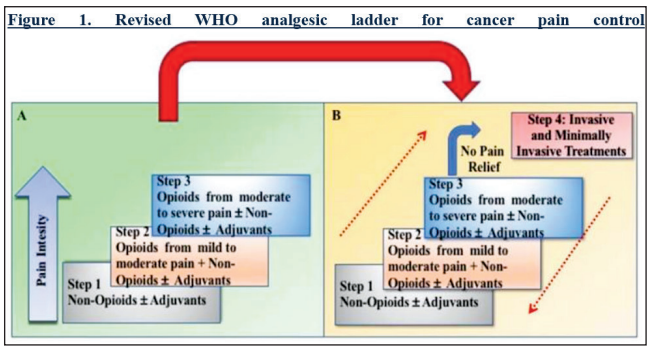

Figure 1. Revised WHO analgesic ladder for cancer pain control

Furthermore, The National Comprehensive Cancer Network (NCCN) has emphasised the importance of the "5As" in cancer pain management in its newly revised guidelines. The 5As include the following five domains: Optimisation of **Analgesic** therapy, optimisation of **Activities** of daily living, minimising **Adverse** effects, avoidance of **Aberrant** drug taking to minimise addictive outcomes and finally **Affect** which refers to the effect of pain on the patient's mood. Both the NCCN and the European Society for Medical Oncology (ESMO) have produced extensive and detailed guidelines for the management of cancer pain which should be referred to for further clarification (13,14). They both incorporate the WHO analgesic ladder at their centre. Even though the initial step looks at the use of acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), they are not frequently, if at all, used in isolation in practice for the management of cancer pain. This is the case, especially in patients undergoing chemotherapy who may have overlapping adverse effects such as hepatorenal toxicity. Additionally, it is of vital importance to be able to recognise opportunistic infections in patients undergoing chemotherapy and NSAIDS may cause difficulty with their antipyretic effects. Due to the large percentage of cancer patients still experiencing refractory pain even on maximally titrated opioid use, the need for alternative adjuvant therapies was necessary, therefore resulting in the addition of non-pharmacological means to manage cancer pain. These include but are not limited to use of local anaesthetic and analgesic drugs through the intrathecal route (into the spinal canal or subarachnoid space), epidural analgesia, nerve blocks and palliative radiotherapy.

It is important to mention that there is no supporting evidence for the use of opioids in neuropathic pain and as such it is not recommended. According to NCCN guidelines corticosteroids may be used for pain caused by nerve compression or inflammation but with extra caution as they may interfere with novel cancer therapies. Antidepressants, anticonvulsants and topical agents may be trialled in combination or alone in the management of neuropathic pain (13).

Integrative medical therapies are increasing in popularity and there is promising evidence for their use in cancer pain management. They are non/minimally invasive with a low risk profile when performed by an appropriately trained specialist. However, they have the disadvantage of being expensive as they may not be offered routinely by health care systems such as the NHS. Music therapy, hypnosis and acupuncture have shown to be effective in combination with other conventional management options in the overall outcome of adequate pain management. Acupuncture may prove useful in lowering opioid doses, thereby reducing adverse effects such fatigue, nausea, constipation and sedation. Severe pain in the cancer patient group can be multifaceted and cause distress, anxiety and even depression. In such cases therapies like mind-body exercises (e.g. yoga, tai chi) and massage therapy may be helpful and should be considered (15). It is vital for individual preference, cultural background and belief system to be considered.

Conclusion:

In conclusion, even with the successful advancements in novel therapies for the treatment of malignancy, challenges in the management of cancer pain remain, with a significant proportion of patients experiencing refractory pain despite titrated opioid therapy. Cancer pain can be multifaceted with nociceptive and neuropathic components to it and the adverse effects of strong opioid use for chronic pain can further complicate management. Therefore, the importance of an in-depth assessment as described above is emphasised. This will ensure a more targeted approach in pain management depending on the cancer pain syndrome present. There remain gaps in evidence-based approaches to cancer pain management and more tools are necessitated for clinicians to have available. The NCCN and ESMO guidelines are

extensive and should be referred to for assistance. Finally, popularity in integrated and complementary therapies is increasing. We know pain has a major psychological component to it, and may become the cause of distress, anxiety and depression in cancer patients therefore complementary methods such as mind-body therapy and acupuncture should be discussed in conjunction with the patient's wants and belief systems. Patient-centred care should be the basis of cancer pain management to be able to provide the best quality care possible.

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Student Overseas Elective Reflections

Towards the end of their medical training, students at Queen's University Belfast Medical School are encouraged to undertake overseas medical electives, especially in areas of the world where experience of medical care may be very different from that in the United Kingdom. On return, they are invited to submit reflective essays on their experiences, and these two essays have been chosen as the best submissions for the 2024 round of electives.

Women at the Heart of Tribal Healthcare: A Reflection from a Rural Medical Elective in Southern India

Alicia Downey[1], Sandra Van Schaeybroeck[2]

This summer, I had the privilege of completing my elective placement in Gudalur, a rural town in the Nilgiris region of Tamil Nadu, Southern India. I was based at ASHWINI (Association for Health Welfare in the Nilgiris), a charitable society founded in 1990 to serve the local tribal communities, including the Paniya, Bettakurumba, Mullakurumba and Kattunaykar tribes. ASHWINI's mission centres around empowering these marginalised communities through healthcare, addressing poverty, malnutrition, and disease. It was inspiring to witness how much of ASHWINI's management is now led by members of these tribal communities themselves.[1]

My focus during the elective was on rural medicine, with an emphasis on community healthcare, family medicine, and obstetrics. As a woman in healthcare, I was particularly interested in exploring women's healthcare in tribal settings, eager to understand the care provided to mothers and babies in these populations. During my time at ASHWINI, I encountered diseases rarely seen in the United Kingdom (UK), such as sickle cell disease, leptospirosis, dengue fever, tuberculosis, and malnutrition. My involvement included field visits to tribal villages for antenatal check-ups, mental health assessments, and sickle cell reviews, as well as hands-on clinical practice in the hospital. Working with the obstetrics department, I assisted with ultrasound scans, abdominal exams, and blood sugar monitoring, all of which sharpened my technical skills and deepened my medical knowledge.

During the field visits, I faced a personal challenge in encountering numerous young mothers from the tribal communities, many of whom were younger than myself. Research shows that around 40% of Indian tribal women marry before the age of 18, and many experience their first pregnancy before this.[2] Interacting with these women, I found myself reflecting on how vastly different their lives were from mine, shaped by cultural practices, economic constraints, and limited access to education and healthcare. ASHWINI's ethos of empowering women through healthcare education particularly resonated with me, especially the Health Animator training program, which equips tribal women with basic healthcare skills and knowledge. I felt both fascinated and moved to witness these women, stepping beyond their traditional cultural roles to educate themselves and contribute to their tribe in meaningful ways. This experience compelled me to inspire and support the young women in any way I could.

I contributed to various aspects of female health including breast cancer screening through clinical examinations. I observed a significant lack of awareness and understanding among women regarding the importance of the exams. This highlighted the need for education to remove cultural stigma and raise awareness about preventive healthcare. I also participated in discussions surrounding sickle cell pregnancies, a pressing issue given India's large population of sickle cell patients. Many women had little understanding of the risks associated with sickle cell disease during pregnancy, nor the potential benefits of contraception in mitigating these risks in the future.[3] The need for specialised care, including access to obstetricians and blood banks in these cases, further complicated their situation due to lack of access.

Cultural sensitivity was essential throughout my work. For example, tribal beliefs surrounding the use of tape measures in examinations of the pregnant abdomen and their association with evil spirits, meant alternative palpation methods had to be used. Also, many women were unfamiliar with the date of their last menstrual period, complicating gestation tracking further. In each of these situations, I found myself deeply reflecting on the significant gap in awareness and education that many tribal women have about their own bodies. This lack of understanding not only heightens their risk of various conditions but also delays their seeking medical attention. I was struck by the stark contrast between the level of patient education among the tribal women and the routine awareness of gynaecological screenings that many women in the UK, through the NHS, possess. The

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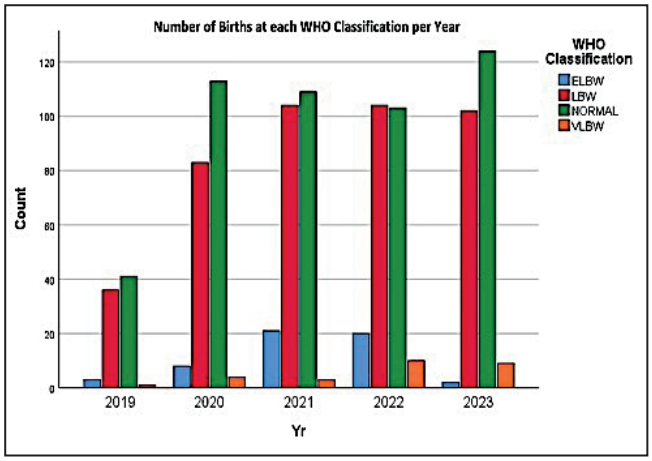
contrast underscored the importance of ASHWINI's role in educating and empowering women about their health.

Reflecting on my role, as a fellow female in healthcare, I took great satisfaction in contributing to the education of other female healthcare professionals at the hospital (Figure 1). Given the significant underrepresentation of tribal women in India's healthcare sector compared to the NHS, I was driven to empower these women.[4] I provided sessions on basic life support and head to toe assessment, adopting the Airway, Breathing, Circulation, Disability, Exposure (ABCDE) technique for student and senior nurses. Supporting the education of these women felt immensely rewarding, knowing that it not only helps them economically but also strengthens their ability to provide critical care in their communities.

Figure 1: Empowering future female healthcare professionals: A teaching moment with young female nursing students in rural India, focusing on practical skills and community care.

Malnutrition, particularly among mothers and new-borns, was another significant issue I observed and was deeply impacted by. This prompted me to delve deeper into this issue, and my research revealed that between 2019 and 2023, nearly 43% of tribal births were classified as low birth weight according to WHO standards (Figure 2).[5] The average birth weight among these tribal populations was 2.44 kg, compared to the global average of 3.3 kg. This stark contrast, especially when compared to the UK average of 3.4 kg, led me to reflect on the complex factors behind this disparity—limited healthcare access, poor maternal nutrition, and cultural practices. ASHWINI is actively addressing these issues through



Percentage of each WHO Classification 2019-2023

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	ELBW	54	5.4	5.4	5.4
	LBW	429	42.9	42.9	48.3
	NORMAL	490	49.0	49.0	97.3
	VLBW	27	2.7	2.7	100.0
	Total	1000	100.0	100.0	

Figure 2: Data provided by ASHWINI research department and analysed personally to create a table and graph showing the annual birth distribution by WHO classification. A breakdown of births categorised under the WHO classification for extremely low birth weight (ELBW), low birth weight (LBW), normal and very low birth weight (VLBW), highlighting trends in maternal and neonatal health between 2019 and 2023, within the tribal community.

https://www.who.int/health-topics/health-workforce#tab=tab_1

maternal nutrition programs and health education, but cultural challenges remain. For example, nutrition provided to mothers is often shared amongst the entire family, diluting its impact. On reflection, the experience of witnessing these challenges first-hand has reinforced my commitment to continuing research and advocacy in maternal and child health. ASHWINI's dedication to addressing these critical issues is truly inspiring, and I am motivated to contribute to this important work in the future.

My elective placement also gave me a deeper understanding of how healthcare in Gudalur differs from the NHS. The hospitals are smaller and more resource-limited, with

restricted access to medical equipment. ASHWINI's approach of bringing healthcare directly to the community contrasts with the more centralised system of the NHS. The ingenuity and adaptability of the healthcare workers in Gudalur were impressive, as they consistently found solutions despite the constraints. This experience has given me a newfound appreciation for the resilience required to deliver quality healthcare under such challenging conditions.

Through field visits and tutorials, I gained insight into how cultural beliefs, socioeconomic factors, and community practices shape health behaviours and access to care. This immersion in a diverse cultural setting enhanced my cultural competence, a skill that has become increasingly important as the NHS becomes more multicultural. Recent data shows that 32% of the NHS workforce now comes from Black, Asian, and Minority Ethnic (BAME) backgrounds, yet challenges persist in achieving equality. [6] My time in India has prompted me to confront any unconscious biases I may have had, reinforcing the importance of culturally sensitive care in all settings.

Reflecting on my elective, I realise it was a transformative experience, both professionally and personally. It expanded my cultural perspectives and significantly enhanced my clinical skills. The dedication of ASHWINI's team to empowering women and improving maternal and child health has deeply inspired me. The resilience of the women I encountered, whether in healthcare roles or tribal communities, has left a lasting impression, strengthening my resolve to advocate for women's health in my future career. The lessons and experiences from this elective will undoubtedly enrich my future medical practice, both in the UK and globally.

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My Himalayan Health Experience

Sean Diamond[1], Sandra Van Schaeybroeck[2]

We had arrived in Chhatru in Himachal Pradesh, North India. Due to the nature of camping, we woke up with the first light. Myself and four other students sleepily meandered from the luxury of our sleeping bags to the roaring banks of the Chenab River. I think I will always be able to picture that scene. Sitting at an altitude of 4000m, all four of us wrapped up in our 'warm gear' that we finally put to good use after a fortnight of humidity and heat. Sandwiched in a valley between snow-capped peaks standing proudly some 6000m tall, the Chenab River ferociously stampeding towards the bridge like a pack of bison. This may have been a medical elective, but it taught me so much about the geography of our natural world as I learnt the river intensified as the day went on with rising temperatures causing the glaziers to melt. The roaring, whirling rapids, the gentle pop of a stone falling off the rock tower that Chris was carefully constructing, and the occasional long, sharp whistle of a White-capped Redstart were the triad of sounds that provided our soundtrack of serenity. As the world was starting to wake up and the sun was peeking out from behind a colossal peak in the Spiti range of the Greater Himalayas, Jonathan came from the camp with the only thing that could make the morning even more perfect, fresh coffee.

Figure 1: Three young Buddhist monks and student Sean Diamond on their clinic day at Key Monastery. (Photographer: Chris Launchbury)

The day was approaching 8am, this was when we would all gather round the communal tent and listen to a talk on, wilderness and adventure medicine, paediatrics, cardiology and many more topics. I had just enough time to squeeze in a morning run and a true ice-cold dip. Being now back in Belfast on my way to General Practice placement, I often remember those precious morning times feeling fully invigorated and alive. The best morning routines I will probably ever have. During breakfast, we listened and debated Seth's morning talk on 'Loneliness', something I couldn't have felt further from as I looked around at all the friends from various walks of life, friends I was lucky enough to get so close to over the past few weeks. Today was our 'Day Off', although I wouldn't exactly call treating Buddhist monks, nuns and people of the Himalayas in their villages a standard day at work (Figure 1). We hiked for a few blissful hours across views and terrains that would take your breath away, both figuratively and literally, traversing the valley through rolling hills, gaping crevices, and passing herds of mountain goats with their shepherd.

In the afternoon, I plunged into my second crystal-clear cold-water exposure of the day, in 'Shepherds waterfall', fittingly named. After a taxing ascent, the icy water was warmly welcomed. That night we ate the comfort food I would look forward to all day in Dahl and Roti, and watched the campfire roar and crackle, its embers becoming indistinguishable from the stars of the night sky, as they flickered away. The conversation slowed as each person ambled to their tent after a tiring day until I couldn't keep my eyes open any longer. The peaceful setting of our campsite at Chattru is depicted in Figure 2, where we were preparing for a night under the stars.

Several hours later, my awakening wasn't so blissful. Lorcan shook me awake and gestured to the tent walls which were being lit up sporadically with spots of light. As I slowly returned from my sleeping stupor, the shouting became apparent too. I didn't know what was happening, or how to feel. Should I be scared or was I just woken abruptly and that was why my heart was thumping. I poked my head out of the tent, I could see Kai running with a torch, the rain dancing off the saturated ground around us. I asked him what was

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Figure 2: The campsite at Chhatru as everyone was getting ready to sleep under the stars.
(Photographer: Chris Launchbury)

going on and he couldn't tell me. I came back into the safe confines of our tent and Lorcan said, 'I think the safest thing we can do now is go back to sleep.' So, we did.

It mustn't have been five minutes later, when Kunal rattled our tent and shouted for us to get up and quickly explained that there had been a landslide. At this point, it was true fight or flight mode. I could hear my heart in my ears as we grabbed our passports and phones and left everything else, including our stethoscopes! We ran, flustered and barely awake, to the communal tent that just yesterday had been the host of our idyllic morning and beautiful stargazing. We were met with the calming presence of Ravi who told us there had been a flash flood, some tents had been destroyed, some bags and equipment were lost but everyone was okay. On hearing this, the situation and my racing heart immediately calmed. I felt a flurry of conflicting emotions: relief, thankfulness and excitement as strange as that may seem. Being caught in a 'cloudburst' in the largest mountain range on earth, isn't something you do every day. I was with my friends; some were more shaken by the morning's events than others and it was interesting to see how differently everyone responds to these situations, yet beautiful to experience how the group rallied together to support each other. The team of staff literally jumped into action. Some were knee deep rescuing luggage from the river, which looked even more aggressive in the darkness, some were helping salvage tents. Tsering was preparing a big pot of chai tea: despite the mayhem and destruction of the flood, he still had our comfort at the forefront of his mind. Their immense kindness and work-ethic will always remain with me.

"*One must be flexible and resilient whilst travelling in the Himalayas*". This was a quote from Ravi, the founder of the expedition, before we embarked on this journey. This phrase resonated with me throughout our travels and was consolidated after my experience of the flash flood. On this trip, I learnt a lot about primary preventive care and many aspects of medicine to take with me throughout my career, but I learnt a lot more about life. The cultural differences between this region and home in Ireland were immense. These people have extremely tough lives, working long and gruelling labour-intensive jobs, for money so little they couldn't dream of coming to visit Ireland. Nevertheless, the most staggering thing I noticed was their extreme happiness, appreciation and kindness towards people. This 'get-up-and-go' attitude with no complaining is the product of the extreme resilience these people have had to build up over years. I was in absolute awe and since returning home, the attitude of this inspirational group of people has put a lot of our 'Western problems' into perspective. I hope I have become a more resilient person and if I could have half the attitude to life that the people of North India have, I will be happy and content for a lifetime.

Another lesson this genuinely life-changing experience taught me is to appreciate the simple but infinitely more important factors of life such as that of the human connection that we often rush past in our busy careers and lives. As the Dalai Lama wrote: "*This is a time of more degrees but less sense, of more medicines, but less healthiness, a time we have become long on quantity but short on quality".*[1]

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Letters

Oestrogel HRT regimens prescribed in General Practice

Editor,

The use of hormone replacement therapy (HRT) with oestrogel requires adherence to specific guidelines to ensure patient safety, particularly regarding endometrial protection in women with a uterus. This study aimed to assess the appropriateness of oestrogel HRT regimens prescribed at a GP Surgery in Belfast over a period of 8 months, between July 2023 and March 2024, focusing on compliance with British Menopause Society (BMS) guidelines (1). A retrospective study was conducted using electronic medical records from the EMIS system at Ballyowen Health Centre. All patients prescribed oestrogel between July 2023 and March 2024 were reviewed, with a total of 72 identified. After excluding 8 patients (including those who had stopped HRT or switched therapies), 64 eligible female patients were included. Prescription regimens were compared against BMS criteria: women with a uterus must receive endometrial protection via a progestogen or Mirena coil, and women post-hysterectomy may receive oestrogen-only therapy.

Out of the 64 eligible patients, 54 (87.5%) were found to be prescribed the appropriate HRT regimen according to BMS guidelines. Of the remaining 10 patients, 9 required adjustments due to variations in prescription duration or the need to revert to their original regimen following a shortage of Utrogestan. Notably, one patient lacked endometrial protection, having not received a progestogen prescription since July 2023 which was flagged for urgent follow-up.

The study revealed a compliance rate of 87.5% with BMS guidelines. Most non-compliance cases were linked to medication shortages, with patients not being reverted to their original regimen post-resolution of supply issues. One critical case of unprotected endometrium was flagged for urgent follow-up. Future steps include direct patient communication for regimen adjustments and ensuring regular HRT reviews to maintain appropriate therapy.
We recommend careful monitoring when prescribing HRT regimens. For patients newly started on HRT, reviews should be conducted within three months, while those on established HRT should be reviewed at least once a year.

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Thoughts on the Passing of Dr John Geddes.

Editor,

Narrative, in both history and literature, has often relied on the idea of the "Great Man" – individuals who due to superior intellect or skill have a decisive impact. Sometimes this ignores the contribution of partners or other team members. It is, after all, Holmes and Watson and even Frodo has his Sam!

The Ulster Medical Journal rightly celebrated the achievements of the late Professor Frank Pantridge with publication of a supplement dedicated to his life's work.[1] We feel it would be wrong however for the passing of Frank's collaborator, the late Dr. John Geddes to go without comment in the pages of the Journal.

Having qualified in 1963 at the age of 24, John worked alongside Frank as registrar in the Cardiac Unit of the Royal Victoria Hospital, Belfast.

They noted that many patients died suddenly from arrhythmia during myocardial infarction before reaching the safety of a hospital. The chief culprit, Ventricular Fibrillation, required rapid defibrillation to restore normal rhythm.

To prevent this, two innovations were required. Firstly, the bulky mains powered defibrillators of that era had to be made portable and secondly, a team to administer this intervention had to arrive in time.

A team of Belfast doctors and engineers solved the portability problem, then on the 1st January 1966, the World's first Mobile Coronary Care Unit was launched with a trained doctor and nurse travelling with the equipment directly to the patient in response to a GP phone call.

The results were reported in *The Lancet* in August 1967 and rapidly lead to adoption of the method around the world resulting in many lives being saved. [2]

It is worth pausing for a moment to note that this landmark paper had just two authors and that John was 4 years qualified when it came out!

John was appointed as Consultant Cardiologist to the RVH in 1971 and in 1987 became Medical Director of the Pacemaker Defibrillator Program at Health Sciences Centre, Winnipeg, Manitoba.

Pacemakers, electrophysiology and defibrillation remained major interests. He was involved with a major public access defibrillation study when Qantas, Australia's national airline trialled automatic external defibrillators on international aircraft and all major terminals. Results of the first 64 months were positive and published in *Circulation* in 1997.[3]

John and wife, Florence retired to Florida in1999, but he continued to work part-time, commuting back and forth to Winnipeg for a few years. In retirement, he enjoyed golf, entertaining and photographing Florida's rich wildlife.

His last publication "*The Evolution of Pre-Hospital Emergency Care: Belfast and Beyond*" (with co-authors Tom Baskett and Ronald Stewart) celebrated 50 years of mobile coronary care in Belfast and 20 years of emergency medical services in Nova Scotia.[4] John was proud that the book received a standing ovation when presented to Nova Scotia's legislature.

After a lifetime devoted to his family, patients and promoting rapid defibrillation, John passed away in Florida after a short illness on 9th October 2024. He is survived by wife Florence and sons, Stephen and Johnny.

SW Webb, JA Purvis

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Medical Ethics

First steps down the slippery slope?

An analysis of the slippery-slope argument and its application to the question of assisted suicide

Abstract

On 29 November 2024, the House of Commons voted in favour of legalising assisted suicide. The aim of the Bill is to "allow adults who are terminally ill, subject to safeguards and protections, to request and be provided with assistance to end their own life." At the time of writing, the Bill is under consideration at the Committee stage. This paper considers the implications of the bill and the appropriateness of using the "slippery slope" argument in its critique. It may be seen that when considering the practice of assisted suicide in jurisdictions where it has been legalised, the empirical form of the argument is shown to be valid. However, the logical form of the argument is less relevant as, once the principle is conceded, there are no further significant barriers and the slope is, in fact, a cliff edge. History shows that the proposed safeguards are unlikely to be robust or sufficient to withstand challenge.

Background

Among the list of fallacies described in Madsen Pirrie's guide to debating, one can find the *slippery slope* argument.[1] Pirrie describes this as a fallacy "of supposing that a single step in a particular direction must inevitably and irresistibly lead to the whole distance being covered."

On 29 November 2024, the House of Commons voted in favour of a Private Members' Bill proposed by Kim Leadbetter entitled the *Terminally Ill Adults (End of Life) Bill*. The aim of the Bill is to "allow adults who are terminally ill, subject to safeguards and protections, to request and be provided with assistance to end their own life."[2]

The supporters of the Bill state that robust safeguards will be put in place to prevent the expansion of criteria as has happened in other jurisdictions.[a] Critics of the Bill who raise concerns that the proposed safeguards are likely to be ineffective, and that, if the proposed legislation is passed, the scope of practice will inevitably expand, threatening the vulnerable are often accused of using *slippery- slope* arguments which may, as such, be easily dismissed. Is this the case? This article will first analyse the form of the 'slippery slope' argument before examining how it may apply to the assisted suicide debate.

As an aside, I should explain why I am using the term *assisted suicide* rather than the less alarming *assisted dying*. In part, this reflects the effect the debate has already had on the social imaginary and the use of language. As philosopher Kathleen Stock notes,

> Campaigners for assisted dying seek to eliminate messiness of various physical and emotional kinds, and their language is adjusted accordingly. At times, it can sound as if one is being offered a particularly relaxing spa treatment. With a pleasing ring of supportiveness, you are now being "assisted" in achieving something, rather than killed by a doctor or killing yourself.[3]

Taking one's own life is suicide. Helping in this process is assisting suicide. The wording of the Leadbeater bill avoids confronting this reality.

The nature of slippery slopes

Sociologist John H Evans describes the slippery slope argument as follows:

> A slippery slope is a metaphorical slope with the most meritorious position at the top, and at the bottom is the position that is maximally objectionable from the view of the top. Stepping onto the top of the slope at option A, it is more likely in the future that we will select the currently objectionable somewhat downslope option of B. If we get to B, we are more likely to select an even more objectionable option of C further down the slope. The morally worthy decision at the top changes the social and argumentative context of the next decision, making the more objectionable choice below more likely. Eventually, we are at the bottom of the slope, which we had no intention of reaching when we started onto the slope. For example, such an argument about euthanasia would be that once euthanizing the terminally ill becomes normalized (step A), it is more likely that people will accept euthanizing those who just do not want to live any more (step B), which makes it more likely that people will accept euthanizing those who do not contribute to society (step C).[4]

He continues

> To understand how a slope may be slippery, we have to understand its terrain. The terrain is defined by what is morally relevant about the position on the slope. [3]

[a] As I write, it seems that even at the committee stage, some of the more robust sounding safeguards in the first draft of the Bill have been weakened with proposals for a review of cases in the High Court being replaced by "an expert panel".

Wibren van der Burg, professor of Legal Philosophy and Jurisprudence at Erasmus University Rotterdam, provides some more detailed analysis. He recognises that there are subtypes of the argument which he classifies as logical and empirical.[5] We shall first deal with the logical form of the argument.

The logical form

This may be further divided into two types. In the first subtype, "there is either no relevant conceptual difference between A and B, or, that the justification for A also applies to B, and therefore acceptance of A will logically imply acceptance of B." In the second subtype of the logical argument step A at the top of the slope is acceptable but B further down the slope is not. Whilst "there is a difference between A and B, but that there is no such difference between A and *m, m* and *n… y* and *z, z* and B, and that therefore allowing A will end in the end imply the acceptance of B."

Reflecting on the first subtype, it may be seen that it describes not so much a slippery slope as a cliff edge. If steps A and B are wrong for the same reasons, then step A should not be taken. If step A is not wrong, then there is no reason to fear step B. The second subtype introduces the difficulties where a significant grey area exists between the top and the bottom of the slope. This describes a truly slippery slope – once the barrier at the top has been passed and the first step down the slope has been taken, it is difficult to see where further barriers may be placed.

The empirical form

In the empirical version of the slippery slope as described by van der Burg, argues that "allowing A, and especially doing A, will ultimately cause the acceptance of B."[4] The causal processes suggested vary from changes in the attitude those who will perform the act to a general shift in the ethos of society. van der Burg discusses likelihood of society eventually accepting the morality of B as a consequence of having accepted A in terms of law, positive morality (defined as "the morality actually accepted and shared by a given social group or society, also… called popular or social morality"), and critical morality (defined as "the general moral principles used in the criticism of actual social institutions, including positive morality"). Whilst it may be convenient to talk of "legal norms, moral norms and societal practice", in reality, there is an interplay between these categories and, as an individual's acceptance of A might influence the views of others, this in turn may influence the strength of institutional structures and eventually may result in a change in the law. In reverse robust laws and the views of institutions can influence the thinking of individuals and society in general – what Charles Taylor describes as the "social imaginary". [6]

Placing barriers on the slope

Those who deny the validity of the slippery slope argument often propose what they deem to be acceptable barriers to prevent slippage. If the barriers hold, there will be no danger of slipping down the slope. Barriers on such a slope may be justified on a social or psychological basis rather than by a strong argument. Robust barriers may be difficult to establish, as Evans notes "steps down slippery slopes are the result of an absence of a sharp line between cases" and "a barrier is structurally strong if there is a strong dissimilarity between the acts on the immediate upslope acceptable side and the immediate downslope unacceptable side." [3] Strong barriers are important as, ultimately, "whether the consensus in the moral limit slips down the slope depends on whether the barriers hold." [3]

The slippery slope and assisted suicide

I will begin by considering the use of the empirical form of the argument. Is there empirical evidence that in jurisdictions where assisted suicide has been legalised the scope of practice has changed? Proponents of assisted suicide often refer to both Switzerland and the state of Oregon (USA). The reference to Switzerland is misleading as there has been no specific legislation passed regarding the matter. Historically punishment for assisting suicide was only a criminal offence if done for selfish reasons. The position of the Swiss Academy of Medical Sciences is that assisting suicide is not part of a physician's practice as it goes against the aims of medicine.[7] The Oregon Death with Dignity Act has been in place for over 25 years is frequently cited as an example of successful legislation supporting physician assisted suicide (PAS).[8] However, even in Oregon the numbers are rising and the reasons given for requesting PAS have changed.[9]

For more relevant examples of the practice of PAS and euthanasia it is useful to look to the experience of Canada and the Benelux countries (Belgium, Luxembourg and the Netherlands). In each of these jurisdictions there has been expansion of PAS programmes with extension of the eligibility criteria.

Belgium

Euthanasia was decriminalized in Belgium in 2002. The safeguards that were put in place to prevent misuse of the provisions of the law were (1) the legally defined due care criteria for eligibility for euthanasia; (2) the consultation of a second (and sometimes third) physician; and (3) the reporting of euthanasia cases to the Federal Control and Evaluation Commission for Euthanasia. However, each of these has been shown to be insufficient. [10] The criteria for assisted death have expanded and in 2014 the law was amended to allow competent minors to seek euthanasia. [11]

The Netherlands

In April 2002 the Netherlands became the first country in the world to pass legislation permitting both euthanasia and physician assisted suicide. Although assisted suicide and euthanasia remain part of the Criminal Code, the law provides

special grounds for exemption from criminal liability if the doctors who terminate life on request or assist in a patient's suicide satisfy the statutory due care criteria and notify death by nonnatural causes to the appropriate regional euthanasia review committee. [12] The six criteria are

Doctors dealing with a patient's request for euthanasia must:

1. be convinced that the patient's request is voluntary and well-considered;
2. be convinced that the patient's suffering is unbearable and that there is no prospect of improvement;
3. inform the patient of his or her situation and further prognosis;
4. discuss the situation with the patient and come to the joint conclusion that there is no other reasonable solution;
5. consult at least one other physician with no connection to the case, who must then see the patient and state in writing that the attending physician has satisfied the due care criteria listed in the four points above;
6. exercise due medical care and attention in terminating the patient's life or assisting in his or her suicide

Statistics regarding the practice of euthanasia are published annually and are available online. The Regional Euthanasia Review Committees ((Regionale Toetsingscommissies Euthanasie, (RTE)) Annual Report for 2023 records that there were 9,068 notifications, meaning that euthanasia accounted for 5.4% of all deaths in that year.[13] The RTE reports have been criticised for focusing merely on the procedural, i.e., the manner how euthanasia was carried out, rather than the ethical question of whether or not was appropriate. It is observed that clinicians demonstrate a willingness to push the legal boundaries and since 2016 documented indications for euthanasia have included the patient feeling that their" life was complete." [14] In 2024, a 29-year-old woman came to media attention having been granted approval for euthanasia on grounds of mental suffering.[15] Euthanasia remains illegal for minors. However, the pressure to expand criteria persists and a survey of opinion among paediatricians found that many felt that it would be appropriate providing adequate criteria for assessing capacity were met.[16]

Canada

The situation regarding the practice of assisted suicide and euthanasia in Canada may be summed up in the title of a recent report *From Exceptional to Routine*.[17] Between 1991 and 2010 the Canadian House of Commons and its committees had debated six private member's bill seeking to decriminalise assisted suicide. None of these attempts were successful. However, in 2009 a woman suffering from amyotrophic lateral sclerosis went to court insisting it was her right to be able to get help in dying. In 2012, judge in the Supreme Court of British Columbia ruled in her favour and this judgement was upheld by the Canadian Supreme Court in 2015. In 2016, at the behest of the court, the Canadian parliament passed federal legislation that allowed adults facing "enduring and intolerable suffering" whose natural death is "reasonably foreseeable" to request medical assistance in dying.[18] Thus Medical Assistance in Dying (MAiD) became legal. In 2019 the Superior Court of Quebec ruled that the "reasonable foreseeability of natural death" eligibility criterion was unconstitutional, and, in 2020, a bill was introduced to drop this qualification. In 2021, the Canadian Parliament passed a bill which loosened the criteria in two ways. For those with "foreseeable deaths", "the patient's written request for Maid would only have to be signed by one independent witness, rather than two. Second, the 10-day reflection period would be eliminated."[18] MAiD was originally intended for rare situations. However, the number of cases has risen dramatically from 1018 in 2016 to 13,241 in 2022. MAiD had become the world's fastest growing assisted-dying programme. Lyon, Lemmens and Kim note that 99.9% of cases are euthanasia rather than assisted suicide. They are concerned at the rapid expansion of the MAiD programme and feel that rather than reflecting the broad consensus, the public narrative has been captured by enthusiasts.[19] However, others feel that the criteria for accessing MAiD remain too rigid and campaign for further liberalisation to extend the programme to minors and those with mental illness.[20]

From the figures noted above, it may be seen that there is clear evidence of slippage down the empirical slippery slope in each of the jurisdictions considered.

Slippery slope or cliff edge?

But what of the logical version of the argument? Would the passing of Leadbetter's bill into law be a first step or would it be conceding the whole argument around assisted suicide and euthanasia, that is the moral question as to whether it is right for doctors to take the life of another person? In discussing the nature of slippery slopes, Pirrie, cited earlier, acknowledges that, on occasions "a principle is at stake which, once yielded allows anything".[21] Logically, if Leadbetter's bill becomes law, there are no strong philosophical or ethical barriers to prevent its extension. It seems that, viewed from this perspective, we are not standing so much at the top of a slippery slope but rather on a cliff edge. If physician assisted suicide is permissible, what is to prevent its extension to euthanasia? If euthanasia is available at the request of an individual with capacity, then who is to withhold it if they feel it is in the best interests of an individual who does not have capacity?[22, 23] The potential for future developments an expansion of eligibility criteria as have happened in Belgium, the Netherlands and Canada is real.

The slippery slope and society

I have already alluded to Taylor's concept of the social imaginary. Taylor describes this as "the ways people imagine their social existence, how they fit together with others, how things go on between them and their fellows, the expectations that are normally met and the images that underlie these expectations."[24] The social imaginary is less consciously defined than the individual's worldview or philosophy of

life and more pervasive. The nature of the social imaginary has major implications for societal ethics. Aiken notes that responses to ethical questions occur at one of four levels; the expressive evocative, consideration of rules, consideration of the principles underlying the rules, and fundamental core beliefs.[25] The social imaginary reflects the latter. Figures from Dignity in Dying quote public support for a change in the law for terminally ill, mentally competent adults at 75%.[26] If the Bill becomes law, it is likely that the legalisation of assisted suicide will further influence the social imaginary and public acceptance of the principle will mean there will be little resistance to expansion of the criteria. This puts fears about the situation of the elderly, frail, and otherwise vulnerable into perspective with the worry that they may been seen to be a burden to society or consider themselves to be a burden.[27] In such circumstances, permissive access to PAS may be seen as societal validation and it would be all too easy for a right to die to become an obligation.[28]

The slippery slope and the profession of medicine

If assisted suicide become a right, then it means that there is a correlative duty to fulfil that right.[29] In the Leadbetter Bill, as in other jurisdictions, this obligation is seen to fall on the medical profession, although it is far from clear how this sits within the understanding of the nature of medicine and the duties of a doctor[30]. How does this fit with the practice of medicine which has long held to the Hippocratic tradition – Neither will I administer a poison to anybody when asked to do so, nor will I suggest such a course?[31] A right to conscientious objection cannot be presumed.[32] Indeed, the culture change in Canadian medical practice has been dramatic, and guidance from the Canadian Association of MAiD Assessors and Providers (CAMAP) warns that "not bringing up MAiD can also lead to harm by prolongment of unwanted, unnecessary suffering and missed therapeutic reduction in existential anxiety" and that "the existence of MAiD as a treatment option cannot be withheld". It reminds clinicians that they "may not impede, directly or indirectly, access to services, thus unjustifiably infringing on the rights of patients to access those services" and "Holding a conscientious objection to MAiD does not negate these obligations."[33] Similarly Boer notes that in the Netherlands professional and public attitudes have changed and it may now be that those who oppose assisted suicide and euthanasia are viewed with suspicion.[12 (p234-236)]

Conclusion

The slippery slope argument has been shown not to be a fallacy but rather to be a valid form of argument. In considering how it may be applied to the question of assisted suicide, as proposed by the Leadbetter Bill, the empirical form of the argument has been shown to hold, as those countries where assisted suicide has been legalised have seen rapid expansion in the numbers of cases, extension of indications, and weakening of safeguards. However, the logical form of the argument has been shown to be less applicable in this situation as, once the premise of taking a patient's life at their request has been accepted, there is little logical reason to prevent this principle being extended to other similar circumstances. Hence, it seems to be not so much a slippery slope but rather a cliff edge. The medical profession, and indeed society as a whole, should be wary of this precipice.

It seems likely that with the Leadbetter Bill physician assisted suicide will become legal in the England and Wales. Doubtless this will have a knock-on effect in the rest of the United Kingdom and similar proposals are before the Oireachtas Éireann. Legalisation of assisted suicide will have an irrevocable effect on the nature of medicine and the doctor-patient relationship. Indeed, I have recently had a conversation with a patient who feared that referral to the palliative care team would mean that their life will be shortened. I have previously referred to this point not in terms of a slippery slope but rather a tear or rend in the fabric of medicine. With a slippery slope you at least may have an idea where you will end up, but a tear can progress along unanticipated lines – and is always damaging.[34]

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Medical History

The Gary Love Lecture 2023
Sir William Whitla and the Apocalypse

Michael Trimble

This paper is based on the 2023 Gary Love Lecture given by Michael Trimble at a joint meeting of the Ulster Medical Society and the Ulster Society for the History of Medicine

Professor Gary Love

The lecture is named in honour of the late Professor Gary Love, former Consultant Physician at the Royal Victoria Hospital (RVH) and Professor of Medicine and Dean of the Faculty of Medicine at Queen's University, Belfast (QUB).

Andrew Henry Garmany Love was born on 28th September 1934 in Bangor Co. Down. He studied medicine at QUB achieving 1st class honours in his medical degree and in an intercalated degree in physiology and biochemistry. He began working as a house officer in the RVH and was then appointed as a lecturer at QUB attaining his MD in 1963. He took up post as a Consultant Physician in the RVH 1965. He was Dean of the Faculty of Medicine from 1981 until 1986, a member of the General Medical Council from 1981 to 1987 and Chair of the Northern Ireland Council for Postgraduate Medical and Dental Education from 1995 to 1999. He was awarded a CBE in 1995. His wider roles in medicine included serving as Censor of the Royal College of Physicians of London from 1996 to 1997 and being a founding Fellow of the Academy of Medical Sciences. He retired in 1999. He was a keen horseman and died suddenly while riding on 4th January 2001. An obituary, penned by Alf McCreary in the Belfast Telegraph, was titled 'A man of great talent and style. Professor Gary Love an appreciation'. (Figure 1)

Figure 1. Professor Gary love

Abstract

Sir William Whitla, former Professor or Materia Medica at Queen's University, Belfast was a towering figure in Ulster medicine. A physician, scholar, and philanthropist, his legacy is significant. However, few are aware that, in addition to a number of extremely successful medical texts, he also published a book on biblical prophecy based on an earlier work by Sir Isaac Newton exploring of the prophecy of Daniel and the Apocalypse of St John.

Sir William Whitla

Physician

William Whitla (figure 2) was born on 13 September 1851 in Monaghan and was educated at the Model School. He served as an apprentice pharmacist, first with his brother

Figure 2. Sir William Whitla

in Monaghan and then with Messrs Wheeler & Whittaker in Belfast, before moving on to study medicine at Queen's College in Belfast, graduating as a licentiate of the Royal College of Physicians and Surgeons at Edinburgh in 1873. Following graduation, he was appointed Resident Medical Officer at Belfast General Hospital, Frederick Street, Belfast. He also worked for a period at St. Thomas' Hospital, London where he met Miss Ada Bourne, ward sister and friend of Florence Nightingale. They were married in 1876. Whitla returned to Belfast where he was appointed Physician to the Belfast Royal Hospital in Frederick Street in 1882. He

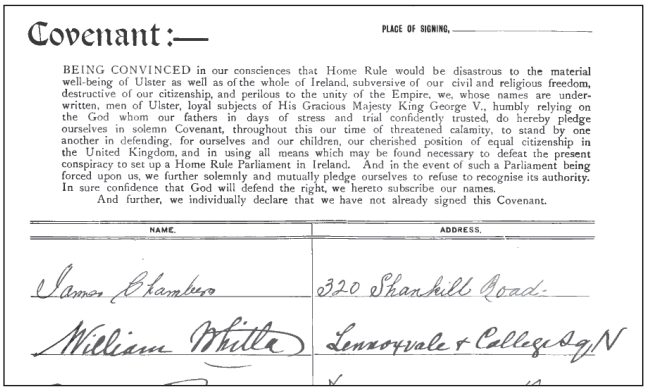
remained a visiting member of the staff here, and later at the Royal Victoria Hospital, until 1918. In 1890 he was appointed Professor of Materia Medica at Queen's College, Belfast. He was knighted for distinction in medicine in 1902. He was President of the British Medical Association in 1909, and as Pro-Chancellor of Queen's he represented the University in Parliament from 1918 to 1922. He served as honorary physician to the King in Ireland in 1919. Whitla was twice president of the Ulster Medical Society (1886-7, 1901-2).

Author

Whitla published three medical texts. The first, *Elements of Pharmacy, Materia Medica and Treatment* published in 1882 was a great success, running to 11 editions. The second, *A Dictionary of Treatment* was published in 1892 and was also a great success, helped in no small part by a decision that all ships of the Merchant and Royal Navies with a crew of less than 100 had to carry a copy. His third medical text, *A Manual of the Practice and Theory of Medicine* (1908,) was not as successful.

Politician

Whitla was elected as Member of Parliament, first representative of Queen's University in Westminster, in 1918, and re-elected unopposed in 1922. He was a Unionist and a signatory of the Ulster Covenant and Member of the Irish Convention. (Figure 3)



Covenant :—

PLACE OF SIGNING,

BEING CONVINCED in our consciences that Home Rule would be disastrous to the material well-being of Ulster as well as of the whole of Ireland, subversive of our civil and religious freedom, destructive of our citizenship, and perilous to the unity of the Empire, we, whose names are under-written, men of Ulster, loyal subjects of His Gracious Majesty King George V., humbly relying on the God whom our fathers in days of stress and trial confidently trusted, do hereby pledge ourselves in solemn Covenant, throughout this our time of threatened calamity, to stand by one another in defending, for ourselves and our children, our cherished position of equal citizenship in the United Kingdom, and in using all means which may be found necessary to defeat the present conspiracy to set up a Home Rule Parliament in Ireland. And in the event of such a Parliament being forced upon us, we further solemnly and mutually pledge ourselves to refuse to recognise its authority. In sure confidence that God will defend the right, we hereto subscribe our names.

And further, we individually declare that we have not already signed this Covenant.

NAME.	ADDRESS.
James Chambers	320 Shankill Road.
William Whitla	Lennoxvale & College Sq N

Figure 3. Sir Willaim Whitla's signature on the Ulster Covenant.

Philanthropist

The income from his books, private practice, and from private sources made him in his time probably one of the wealthiest professors on the staff of the university. He established the *Whitla Medical Institute,* (Figure 4) the founding of which has been described in a recent paper in this journal. He presented the Good Samaritan Window, to Royal Hospital in Frederick Street in 1887 and this was moved to end of the main corridor in the RVH in 1903. (Figure 5) The Whitla's had no children, and much of his wealth eventually was left to the university. He bequeathed his house, Lennoxvale, as a residence for the vice-chancellor. He left funds for construction of the Whitla Hall (Figure 6) and the establishment of the Whitla Chair of Therapeutics and Pharmacology.

Figure 4. The Whitla Medical Institute

Figure 5. The Good Samaritan Window, Royal Victoria Hospital, Belfast.

Churchman

Less well known is Whitla's commitment to his faith. He was born and raised in a Presbyterian family and converted to Methodism shortly after his marriage. Ada Bourne's family had close connections with the Salvation Army. Whitla was active in his faith serving as a lay preacher and Chairman of the YMCA. The Dictionary of Irish biography describes him thus:

> "Whitla was driven by a lifelong sense of vocation based on a strong evangelical faith."

Figure 6. The Whitla Hall © Copyright Rossographer CC BY-SA 2.0 DEED Attribution-ShareAlike 2.0 Generic

Sir Isaac Newton FRS (1843-1726)

Newton (Figure 7) is best known as a scientist and mathematician. He was Lucasian Professor of Mathematics at Cambridge producing famous text *Philosophiæ Naturalis Principia Mathematica*. His work ranged from calculus, optics, and gravitation. Although perhaps a better description of Newton is natural philosopher as this encompasses his many interests - mathematics, physics, astronomy, alchemy, and theology.

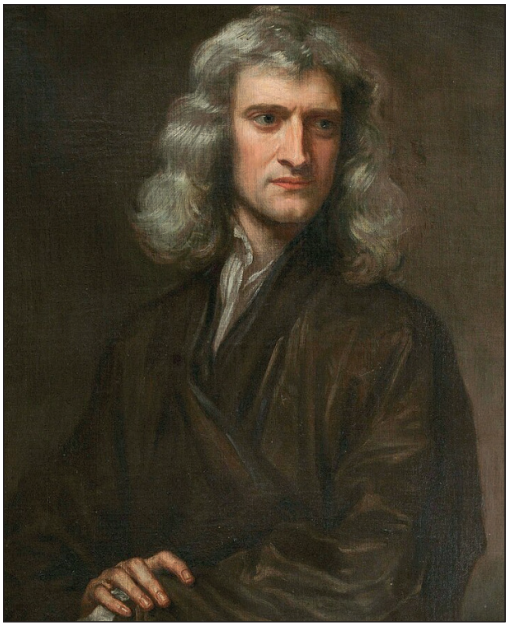


Figure 7. Sir Isaac Newton.

Theologian

Newton's theology was essentially Anglican but unorthodox. His position was that of a monotheistic but possibly a non-trinitarian Arian. He saw God as masterful creator.

> 'We are therefore to acknowledge one God, infinite, eternal, omnipresent,
> omniscient, and omnipotent, the creator of all things, most wise, most just,
> most good, most holy, and to have no other gods but him. We must love him,
> fear him, honour him, hallow his name, obey his commandments, and set
> times apart for his service....
> This always was, and always will be the religion of all God's people from the
> beginning to the end of the world.'

He had many disputes with Roman Catholic doctrinal positions, especially regarding the Papacy, but he also declined to submit to the Thirty-nine articles of the Anglican church and expressed unorthodox views about the divinity of Jesus Christ. Newton took the Christian scriptures seriously and favoured a literal interpretation of the Bible.

> 'The first principles of the Christian religion are founded, not on disputable conclusions, or human sanctions, opinions, or conjectures, but on the express words of Christ and his Apostles.'

He had a strong belief in Biblical prophecy but followed a mystical and allegorical approach in its interpretation. Newton studied the books of Daniel and Revelation in an attempt to discern the time of the second coming of Christ and the end of the present age. His *Observations upon the Prophecies of Daniel, and the Apocalypse of St. John* was published posthumously in 1733. (Figure 8)

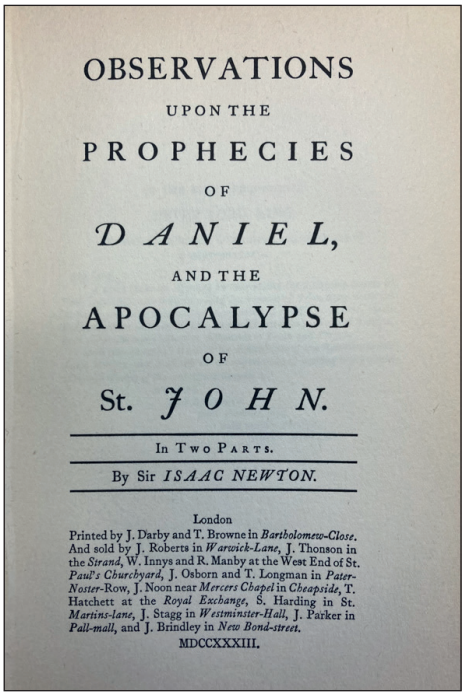

OBSERVATIONS
UPON THE
PROPHECIES
OF
DANIEL,
AND THE
APOCALYPSE
OF
St. JOHN.
In Two Parts.
By Sir ISAAC NEWTON.
London
Printed by J. Darby and T. Browne in Bartholomew-Close. And sold by J. Roberts in Warwick-Lane, J. Thonson in the Strand, W. Innys and R. Manby at the West End of St. Paul's Churchyard, J. Osborn and T. Longman in Pater-Noster-Row, J. Noon near Mercers Chapel in Cheapside, T. Hatchett at the Royal Exchange, S. Harding in St. Martins-lane, J. Stagg in Westminster-Hall, J. Parker in Pall-mall, and J. Brindley in New Bond-street.
MDCCXXXIII.

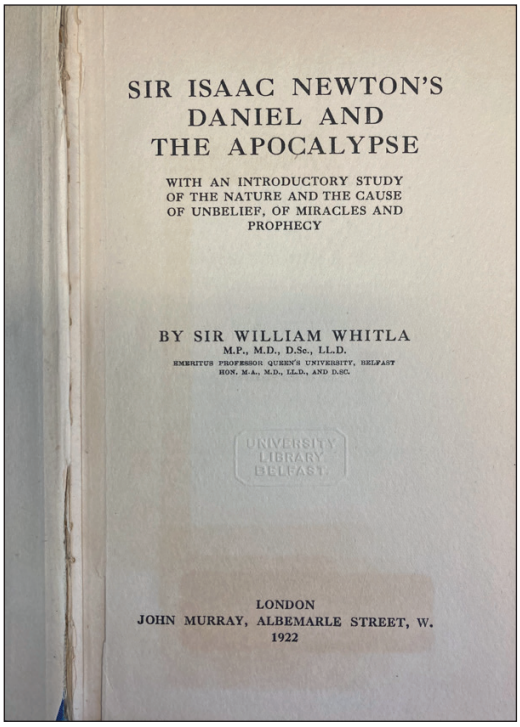
Figure 8. Sir Isaac Newton's *Observations upon the Prophecies of Daniel, and the Apocalypse of St. John.*

Whitla and the Apocalypse

In 1922, nearly two hundred years after its first publication, Newton's text was again made available to the reading public, thanks to the efforts of William Whitla. (Figure 9) For

Whitla, this was a labour of love. The book was published by John Murray and Whitla himself paid for the production costs.

> 'In these days of highly expensive printing, another difficulty was encountered; If the book was to reach any considerable number of readers, its price must be made as moderate as possible. This obstacle is met by the issue of the present volume at a price not above the cost of its publication.'


SIR ISAAC NEWTON'S
DANIEL AND
THE APOCALYPSE

WITH AN INTRODUCTORY STUDY
OF THE NATURE AND THE CAUSE
OF UNBELIEF, OF MIRACLES AND
PROPHECY

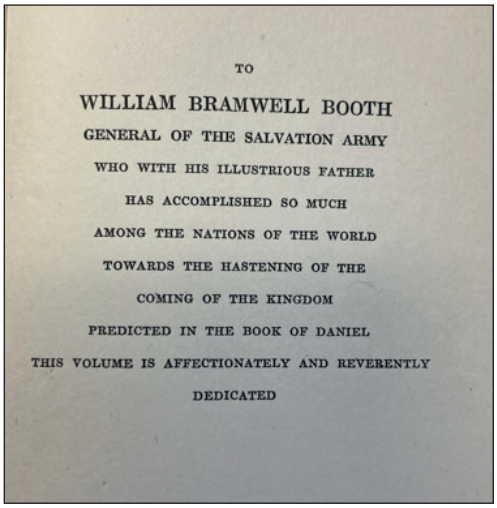
BY SIR WILLIAM WHITLA
M.P., M.D., D.Sc., LL.D.
EMERITUS PROFESSOR QUEEN'S UNIVERSITY, BELFAST
HON. M.A., M.D., LL.D., AND D.SC.

LONDON
JOHN MURRAY, ALBEMARLE STREET, W.
1922

Figure 9. William Whitla's reedition of Isaac Newton's book.

To aid readers, Latin portions of the original text were translated into English by WH Semple, Assistant to the Professor of Greek at QUB. The volume was dedicated to William Bramwell Booth, then General of the Salvation Army. (Figure 10) The new edition included an introductory section contributed by Whitla himself. In ten chapters, Whitla deals with such issues as science, prophecy, and unbelief. He counters arguments from scientific scepticism and also Higher Criticism of the Bible. He describes the fulfilment of Messianic prophecies in the life of Jesus Christ and explores the book of Daniel. Like Newton, he disputes Catholicism's view of the Papacy. On the whole Whitla's theological views much more orthodox than those of Newton.

To understand Whitla's enthusiasm for Newton's book it is perhaps helpful to understand the social, political, and theological context. It was not long after the ravages of the Great War and Spanish flu. On the political front, Ulster had experienced partition and the concerns regarding Home Rule. In the church there were threats to belief from Higher Criticism and scientific rationalism. These lead to concerns about heresy in the training college of the Presbyterian Church. Whitla sought to counter scepticism, whether from science or textual criticism.


TO

WILLIAM BRAMWELL BOOTH

GENERAL OF THE SALVATION ARMY

WHO WITH HIS ILLUSTRIOUS FATHER

HAS ACCOMPLISHED SO MUCH

AMONG THE NATIONS OF THE WORLD

TOWARDS THE HASTENING OF THE

COMING OF THE KINGDOM

PREDICTED IN THE BOOK OF DANIEL

THIS VOLUME IS AFFECTIONATELY AND REVERENTLY

DEDICATED

Figure 10. Dedication to Willaim Bramwell Booth.

So what is Newton's book about? First, we need to clarify our terminology. What is meant by the word *apocalypse?* In contemporary usage the word means 'an event involving destruction or damage on a catastrophic scale'. However, the word comes from the Ancient Greek ἀποκάλυψις (apokálupsis) and historically was used to describe prophetic literature that was a ‹revelation, disclosure' or hidden things or things that were to come. It especially came to refer to Biblical books, such as the Revelation of St John or the prophecy of Daniel.

Daniel

The book of Daniel is part biographical narrative, concerning the author's capture following the fall of Jerusalem to the Babylonians in 597BC, and part prophecy. Daniel was among a number of Jews taken from Jerusalem to serve in the court of the King of Babylon. One early prophecy concerns the dreams of King Nebuchadnezzar and Daniel's interpretation.

In the second year of his reign, Nebuchadnezzar had dreams…

> Your Majesty looked, and there before you stood a large statue—an enormous, dazzling statue, awesome in appearance. The head of the statue was made of pure gold, its chest and arms of silver, its belly and thighs of bronze, its legs of iron, its feet partly of iron and partly of baked clay. While you were watching, a rock was cut out, but not by human hands. It struck the statue on its feet of iron and clay and smashed them. Then the iron, the clay, the bronze, the silver and the gold were all broken to pieces and became like chaff on a threshing floor in the summer. The wind swept them away without leaving a trace. But the rock that struck the statue became a huge mountain and filled the whole earth.

This interpretation is often seen as the foretelling of the

successive empires of Babylon, Greece, and Rome with the subsequent rise of the church following the fall of Rome. Later in the book Daniel recounts other prophetic dreams including one with the significant character described as the Ancient of Days.

> As I looked, thrones were set in place, and the Ancient of Days took his seat. His clothing was as white as snow; the hair of his head was white like wool. His throne was flaming with fire, and its wheels were all ablaze. A river of fire was flowing, coming out from before him. Thousands upon thousands attended him; ten thousand times ten thousand stood before him. The court was seated, and the books were opened…

Another significant character in the prophecy is the Son of Man – a title which Jesus later took for himself.

> In my vision at night, I looked, and there before me was one like a son of man, a coming with the clouds of heaven. He approached the Ancient of Days and was led into his presence. He was given authority, glory and sovereign power; all nations and peoples of every language worshiped him. His dominion is an everlasting dominion that will not pass away, and his kingdom is one that will never be destroyed.
>
> These visions in Daniel have echoes in the chapter 20 of the *Revelation (or Apocalypse) of John* where again there is a heavenly court with books being opened before an awesome figure seated upon a great throne.

Then I saw a great white throne and him who was seated on it. The earth and the heavens fled from his presence, and there was no place for them. And I saw the dead, great and small, standing before the throne, and books were opened. Another book was opened, which is the book of life. The dead were judged according to what they had done as recorded in the books.

Both visions describe the last judgement at the end of time. Newton made it his goal to understand what this meant and, in particular, when these things would take place.

One example of Newton's attempt to work out the chronology of prophecy concerns Daniel chapter 9 and the coming of the Messiah.

> Know and understand this: From the time the word goes out to restore and rebuild Jerusalem until the Anointed One, the ruler, comes, there will be ***seven 'sevens***,' and ***sixty-two 'sevens***.' It will be rebuilt with streets and a trench, but in times of trouble. After the ***sixty-two 'sevens***,' the Anointed One will be put to death and will have nothing. The people of the ruler who will come will destroy the city and the sanctuary. The end will come like a flood: War will continue until the end, and desolations have been decreed. He will confirm a covenant with many for one '***seven.***'

Newton reckoned that each of these sevens equates to seven years. Therefore, *seven sevens* equals 49 years, *sixty-two sevens* = 434 years, and one *seven* = 7 years, giving a total of 490 years. Mapping this onto historical events, king Artaxerxes issued his decree to rebuild Jerusalem in 458BC. Four hundred and 90 years later, Jesus is crucified - 'the Anointed One… put to death'. Newton also attempts to determine the date of the Apocalypse based on number sound in Daniel chapters 7 and 12. This prophecy refers to a "time, times, and half a time". Along with similar expressions found in Revelation, Newton, calculated that this referred to a period of 1,260 years. In Newton's interpretation, the 1,260 years begins with coronation of Charlemagne (king of a kingdom different to all others) in 800AD, meaning that the apocalypse and Messiah's will occur in 2060.

Even the most devout Christian believer would caution against putting too much store by Newton's calculation, for Jesus himself warns that 'no one knows the day or the hour of his return' and that the end will come as unexpectedly as 'a thief in the night'. But neither should we be dismissive of attempts to discern the meaning of prophecy. Newton's understanding from reading Daniel was that there would come a time when the Jews would return to the land promised to them by God, an event that would have remained inconceivable until the early years of the 20th century.

Reception of Whitla's book and lectures

Whitla's book was far from a best-seller and 483 copies of the original print run of 1007 were pulped. Contemporary reviews were not kind.

> 'The revived book is merely one of a hundred instances proving of what blunders the greatest intellect, seduced from its proper sphere into one strange to it, is capable. It has no other value whatever and should have been left in peace in the kindly obscurity which had covered it so long.'

Regarding Whitla's accompanying public lectures, the *Freethinker* reported these as 'so much nonsense compressed into so small a space' and expressed the 'hope that Sir William Whitla shows more intelligence in handling his patients than he does in his treatment of religion'.

Would Whitla have been disappointed? Perhaps but I don't believe he would have felt his efforts were in vain, for he writes in his preface

> *'Should the introductory portion of this volume prove an entire failure, there is left to the author of the solid consolation that he has been highly privileged in his Master's service by being permitted to restore to the Biblical student Sir Isaac Newton's valuable contribution to the study of the Babylonian prophet.'*

For Whitla, his faith was central to who he was, and this book was an attempt to counter scepticism, whether from arising

from science or textual criticism of the Bible. His hope was to encourage others in their faith as they awaited Christ's return. We more often remember Whitla as a physician, an educator, and a philanthropist, his republication of Newton's work sheds light on the motivation for these endeavours.

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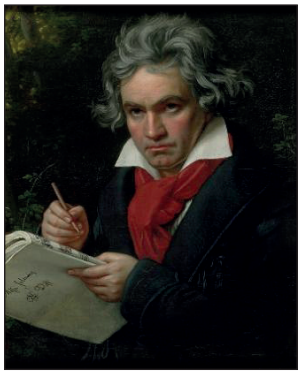
Ulster Med J 2025;**94(1):**53-54

Curiositas - Gastrointestinal Celebritas

QUIZ 1



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1. **Who is this?**
2. **What condition did they die of?**

Eoin Leggett (Internal Medicine Trainee, Belfast Health and Social Care Trust); Jane Bryden (Internal Medicine Trainee, Belfast Health and Social Care Trust); Ciara McAuley (Hepatology Registrar, Belfast Health and Social Care Trust)

QUIZ 2

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1. **Who is this actress?**
2. **What was her cause of death?**

Eoin Leggett (Internal Medicine Trainee, Belfast Health and Social Care Trust); Jane Bryden (Internal Medicine Trainee, Belfast Health and Social Care Trust); Ciara McAuley (Hepatology Registrar, Belfast Health and Social Care Trust)

CONSIDER CONTRIBUTING TO CURIOSITAS?

Please refer to *'Curiositas: Guidelines for contributors'* http://www.ums.ac.uk/curiositas.html and email curiositas@ums.ac.uk with your ideas and submissions.

QUIZ 3

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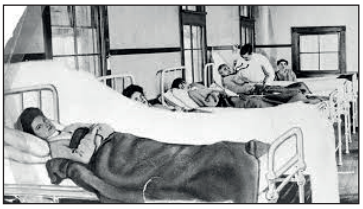
1. **Who is this military leader?**
2. **What inherited condition is it hypothesised that he may have suffered from?**
3. **What is the usual mode of inheritance of this condition?**

Jane Bryden (Internal Medicine Trainee, Belfast Health and Social Care Trust); Eoin Leggett (Internal Medicine Trainee, Belfast Health and Social Care Trust); Ciara McAuley (Hepatology Registrar, Belfast Health and Social Care Trust)

QUIZ 4

A



B

These images (**A** and **B**) are licensed under CC BY-NC-ND

1. **What historical figure is depicted in the above picture?**
2. **Which Northern Irish town was she from?**
3. **What is she famous for?**

Jane Bryden (Internal Medicine Trainee, Belfast Health and Social Care Trust); Eoin Leggett (Internal Medicine Trainee, Belfast Health and Social Care Trust); Ciara McAuley (Hepatology Registrar, Belfast Health and Social Care Trust)

Curiositas: Answers

QUIZ 1

1. Ludwig van Beethoven; a pivotal figure in Western classical music, who suffered from a protracted illness culminating in his death in 1827.

2. While his musical genius is undisputed, the precise aetiology of his terminal illness has been a subject of ongoing scholarly debate. Contemporary accounts and post-mortem findings point towards decompensated liver disease as the primary cause of death. His final months were marked by clinical manifestations including jaundice, ascites, peripheral oedema, and abdominal pain, strongly suggestive of end-stage liver disease. Multiple paracenteses were performed in an attempt to alleviate the ascites, a common practice at the time.

Given the invasive nature of these procedures in the pre-antiseptic era, the likelihood of iatrogenic infection is substantial. The development of either spontaneous bacterial peritonitis (SBP), arising from bacterial translocation within the ascitic fluid, or secondary bacterial peritonitis (due to contamination during paracentesis) is highly plausible. The presence of abdominal pain, a key symptom in Beethoven's final days, further supports this hypothesis. The underlying cause of Beethoven's liver cirrhosis remains a matter of speculation. Alcohol-related liver disease is considered the most probable aetiology, given contemporary accounts of his alcohol consumption. However, other contributing factors have been proposed, including chronic hepatitis, and lead poisoning from contaminated wine or medical treatments. Recent analysis of Beethoven's hair revealed elevated lead levels, lending credence to the lead poisoning theory. However, whether these levels were sufficient to cause significant hepatic damage is unclear.

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3. Adams P. Historical hepatology: Ludwig van Beethoven. J Gastroenterol Hepatol, 1987; 2(4):375-79.

QUIZ 2

1. Audrey Hepburn

2. She died on 20th January 1993 aged 63 from pseudomyxoma peritonei (PMP). PMP is a rare cancer with an incidence of approximately 1-4 per million annually. It is a condition characterised by the implantation of neoplastic cells on the peritoneum, resulting in the production of large volumes of mucin. It most commonly arises from the appendix. Due to its insidious nature, PMP often presents in the later stages of disease with appendicitis-like symptoms or increased abdominal distension with ascites. The mucinous ascites is gelatinous and widespread, and so PMP has been coined "Jelly belly". Management options are difficult however cytoreductive surgery with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) has become the treatment of choice. As the name suggests, HIPEC differs from traditional chemotherapy as it is delivered directly into the peritoneal cavity. This allows for higher dosages and improved cytotoxic effect with reduced systemic complications compared to conventional intravenous use.

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QUIZ 3

1. Napoleon Bonaparte, who is said to have experienced multiple periods of jaundice, especially when unwell or under stress.

2. Gilbert's syndrome is a benign hereditary condition. It was first described by French physician Augustin Nicolas Gilbert in 1901 as "cholémie simple familiale" (benign hyperbilirubinaemia) and included Napolean and his mother as proof of a hereditary disease.

3. The condition is usually inherited in an autosomal recessive manner and is caused by a mutation in the UGT1A1 gene, leading to the reduced activity of the enzyme UDP-glucuronosyltransferase. This results in impaired conjugation of bilirubin, causing mild, intermittent hyperbilirubinaemia which is often exacerbated by stressors such as fasting, illness or physical exertion. In most cases it is asymptomatic and typically requires no medical intervention.

Napolean was exiled to the Island of St Helena after the defeat at the battle of Waterloo. He died 6 years later. There have been many theories about his cause of death including poisoning by arsenic. However, his personal physician Dr Francesco Antonmmarchi performed an autopsy which showed a large gastric cancer extending from the cardiac orifice to the pylorus and a perforated gastric ulcer (6-7mm) at the pylorus which was covered by adhesions between the liver and the stomach.

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QUIZ 4

1. Mary Mallon, otherwise known as "Typhoid Mary"

2. She was born in Cookstown, Co. Tyrone in 1869 before emigrating to the USA as a teenager.

3. She was infamously responsible for the direct contamination of at least 120 people with typhoid fever, which at the time was fatal in approximately 10% of cases. Typhoid fever is caused by the bacterium *Salmonella typhi* and is spread via contaminated food and water. Mary worked in various domestic roles, primarily as a kitchen cook, and was the first documented asymptomatic carrier of the disease in the United States.

Today, the incidence of typhoid is low within the UK but remains prevalent throughout South Asia and can be found in recently returned travellers. Studies have shown that up to 10% of untreated patients will continue to shed the bacteria for up to 3 months - wash your hands.

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Ulster Med J 2025;**94(1):**55-60

Medical History

From Rennes To Belfast: Angus Hedley-Whyte, DSO, FRCS

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

SUMMARY

The authors have previously described the contribution of the RAMC's 31st General Hospital and its successor, Harvard's 5th General Hospital at Musgrave Park, under commanding officer Angus Hedley-Whyte, DSO, FRCS (AHW), in providing medical treatment to Allied troops in Northern Ireland during World War II years 1940-1942[1,2,3,4]. In this Medical History they recount AHW's experience in Operation Aerial, the post-Dunkirk evacuation of the British Expeditionary Forces (BEF) from France in June 1940. In the summer of 1940 AHW was awarded the DSO for outstanding service, and shortly thereafter appointed Commanding Officer of the 31st General Hospital, Musgrave Park, Belfast. He served in this capacity until the hospital's handover to the U.S. Army in June 1942.

INTRODUCTION

Angus Hedley-Whyte was born in South Shields on 23 May 1897, the only son of General Practitioner Dr. John Whyte, JP and his wife, the former Helen Hedley (Fig. 1).

Figure 1. Angus Hedley-Whyte (1897-1971)**,** DSO, TD, MRCS 1919, FRCS 1924, FRCS Ed 1924, MB BS Durham 1919, MS 1925, LRCP 1919.

Photograph by H.R. Hembry, Belfast, ca. 1940-41.
From the personal collection of John Hedley-Whyte.

After attending Ackworth School he entered the University of Durham College of Medicine, and graduated in 1919 as the first winner of the Phillipson Prize. He became a Fellow of the Royal College of Surgeons of Edinburgh and England in 1924. At age 29 he was appointed Honorary Assistant Surgeon to the Newcastle Infirmary in 1926. This position was followed by AHW's 1938 appointment as Honorary Surgeon to the Royal Victoria Infirmary, Newcastle-upon-Tyne—an appointment he held until his 1962 retirement[5,6,7]. Beginning in 1927 he held a concurrent appointment as a Medical Officer in the Territorial Army[6].

TERRITORIAL ARMY AND THE RAMC

On 8 November 1936, AHW was promoted to Major in the British Territorial (Reserve) Army. In 1937, he was assigned to command the 149th (N) Field Ambulance Unit which he led to France in September 1939 with the British Expeditionary Force (BEF)[7]. His son, John Hedley-Whyte, reports that in September 1939 the entries in his father's Newcastle clinical appointment diary came to an abrupt halt.

The RAMC's 8th General Hospital arrived at Lesneven northeast of Brest between 7 and 14 September 1939, and opened on 2 October. AHW was tasked with management of the Surgical Division of this hospital under Commanding Officer Col. J.B. Grogan[8,9,10]. On 7 April 1940 the 8th General Hospital relocated to Rennes (Table 1)[9].

OPERATION AERIAL

Following the evacuation from Dunkirk in May 1940, the remaining BEF was ordered to leave France in a campaign beginning 14 June 1940, known as 'Operation Aerial' led by Admiral William Milbourne James, Commander-in-Chief, Portsmouth[11]. Admiral James was responsible for organizing the evacuation but had too few vessels at hand to organize a convoy. He arranged for an improvised succession of

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troopships, storeships and motor transport ships to sail from Southampton to the French ports. Coasters were to sail from Poole Harbor, and Dutch barges known as *schuyts* from Weymouth[11].

The ports to the south on the Bay of Biscay were to be cleared by naval operations under Admiral Sir Martin Dunbar-Nasmith, Commander-in-Chief Western Approaches, at Plymouth (Fig. 2). As a Lieutenant Commander during the First World War, Dunbar-Nasmith had been awarded the Victoria Cross for outstanding accomplishments in the Sea of Marmara, the Dardanelles and Turkey. In June 1940 he ordered the assembly of a large group of ships including the destroyers *Havelock, Wolverine* and *Beagle,* the liners *Georgic, Franconia, Duchess of York, and Lancastria*, the Polish ships *Batory* and *Sobieski,* as well as additional cargo ships[11].

Figure 2
Admiral Sir Martin Eric Dunbar-Nasmith, VC, KCB, KCMG, (1883-1965), oil on canvas, 101.6 x 76.2 cm, by Arthur Douglas Wales Smith (1888- 1965), No. BHC2667. Credit: © National Maritime Museum, Greenwich, London.

On 15 June 1940 the 8th General Hospital was ordered to evacuate[9]. On 17 June 1940, under Commanding Officer Col. J.B. Grogan, AHW organized an emergency ambulance train to transport hospital patients and medical staff southward to St. Nazaire, where they were to board ships

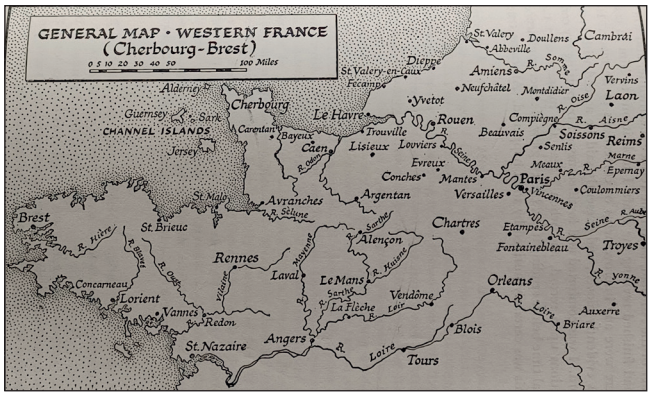

Figure 3
General Map – Western France (Cherbourg-Brest)
AHW evacuated patients and staff from the 8TH General Hospital in Rennes toward St. Nazaire beginning 17 June 1940, a distance of approximately 76 to 93 miles depending on the route selected. He departed from St. Nazaire on the *Glenaffric* on 18 June and arrived in Plymouth on 19 June 1940. From *Their Finest Hour*, by W.S. Churchill[12] © Winston S. Churchill/Portland Ltd. *Reproduced with permission of Curtis Brown, London on behalf of Portland Churchill Ltd.*

to return them safely to England (Fig. 3). The Luftwaffe attacks on western France were increasing and the number of soldiers and airmen who were then passing through St. Nazaire was estimated to be about 47,000[13].

AHW's official citation reads that "they were attacked with high explosive bombs and machine guns. Over 200 British casualties, 43 of whom had urgent operations, were treated and evacuated, in addition to many French military and civilians. He [AHW]improvised an Ambulance convoy which, together with the personnel of the Unit, proceeded to St. Nazaire where they came in for further bombing but were safely embarked [aboard the *Glenaffric*], including a further 51 cases from *S.S. Lancastria*."[8]

BOMBING OF THE *S.S. LANCASTRIA*

The 'further bombing' includes the catastrophic bombing on 17 June 1940 in St. Nazaire of the luxurious *Lancastria,* the largest and best known of the ships dispatched by Admiral Dunbar-Nasmith to expedite the evacuation of the BEF. Her engines were oil-fired and the bombing and subsequent explosions resulted in a massive oil spill with the sea engulfed in flames[12,13].

Churchill forbade reporting of this event at the time and did not lift the ban[1,12,13]. On 26 July 1940, an account appeared in the New York Times[14] which then briefly appeared in British newspapers on that date[15]. Estimates of the death toll varied, with Churchill later reporting more than 3,000[12,13]. There were at least 6,000 individuals aboard the *Lancastria* at the time of the bombing, and there were thought to have been about 2,500 survivors[13].

The *Lancastria* casualties were sent to a French auxiliary hospital staffed by nuns, and a reception center staffed by

mostly female civilian volunteers. Most of the ambulatory survivors were transferred to ships waiting at the dock[16]. Local citizens organized a first-aid centre which provided hot water and soap, donated clean clothing, food and tea, in addition to assistance with removal of wet and oil-soaked clothing[16].

AHW and his party were able to board the trawler *H.M.T. Glenaffric*, sometimes spelled "*Glenaffaric*" or "*S.S. Glen Afric*", at St. Nazaire (Fig.4). According to the War Diary for the 8th General Hospital, "15th June all patients evacuated to the United Kingdom by Ambulance Train, Hedley Whyte CO of rear party. 17th June to St. Nazaire and embarked casualties and staff. Embarked aboard SS *Glen Afric* at 2300 hrs."[10]

An account attributed to the *Glenaffric's* assistant steward recounts how the

> "M.O. [Medical Officer] asked me if we could put up about 80 survivors from the "*Lancastria*" …I told them the only space we could put them was the saloon and smokeroom but that they were already full of officers. The M.O. asked me if we could manage to put them up… and I wouldn't ask you if I knew there was another ship coming up, but I think you are the last one…" [17]

Figure 4
H.M.T. Glenaffric, ex Machaon, undated, photographer unknown. Credit: National Maritime Museum, Liverpool, object no. MCR/41/212. This ship, launched 1920, was originally named *S.S. Machaon*, and renamed *Glenaffric* (sometimes referred to as *Glenaffaric or Glen Afric)* in 1935. AHW's 1940 DSO refers to 51 casualties from the bombing of the *Lancastria* evacuated home aboard this vessel. Other estimates, including that of the ship's Assistant Steward, vary[17]

While AHW was not named, his actions were lauded. The author of the account describes assisting with treatment of back and other orthopaedic injuries on patients still coated in oil post-rescue. Hot water, soap, sheets and other supplies were provided. The ship's captain W.W. Harrison, and others were recognized for effective management and bravery by Brigadier H.C. Cole, CBE. [17].

Upon arrival at Plymouth on 18 June 1940, AHW telephoned his wife, Nancy, to inform her of his safe return, after he had been missing for a few days (Table 1)[18] . Patients from the *Glenaffric* with severe burns were transported for treatment by Sir Harold D. Gillies, OBE, FRCS at Rooksdown House. This formerly private wing of Park Prewitt Hospital, Basingstoke, Hampshire, had opened in February 1940, as the last of the new Plastic Surgery units established in the South of England[4,19].

TABLE 1. LOCATIONS OF THE RAMC'S 8TH GENERAL HOSPITAL IN WORLD WAR II[9]

DATES	LOCATION
***7 Sept 1939-7 April 1940**	**Lesneven, France**
***7 April 1940-18 June 1940**	**Rennes, France**
***18 June 1940-7 Aug 1940**	**Leeds, England**
15 Sept 1940-25 Sept 1940	Port Tewfik (Suez), Egypt
25 Sept 1940-8 Jan 1944	Alexandria, Egypt
8 Jan 1944-19 Jan 1944	Taranto, Italy
19 Jan 1944-4 March 1944	Casenta, Italy
5 March 1944-6 April 1944	Unspecified
7 April 1944-15 July 1944	Bogside Racecourse, Scotland
15 July 1944-16 Aug 1944	Watford, England
16 Aug 1944-11 Sept 1944	Bayeux (Normandy) France
***AHW served at these locations**	

AHW was awarded an immediate DSO which was reported later in the London Gazette[8,20]. Churchill took note and was consulted about AHW's next assignment.

EMERGENCY MEDICAL SERVICE HOSPITALS

A surge in the number of casualties treated in England resulted from the evacuation of the BEF from Dunkirk and other French ports in May-June 1940[21]. While many of the casualties arrived in South Coast towns, during the latter weeks of this period, casualties were landed in Liverpool and other northern points of entry.

The EMS was assigned the responsibility of providing transport of war-related casualties to hospitals whether they were military personnel or civilians[21]. In situations where the Service branches had their own stretcher bearers and transport services available, these were to be utilized[21].

8TH GENERAL HOSPITAL RELOCATED TO LEEDS; 31st TO BELFAST

Upon its return to England the 8th General Hospital was relocated to Leeds from 18 June to 7 August 1940 (Table 1)[9]. AHW continued to serve until the hospital's departure upon reassignment to Egypt and North Africa.

As of 7 August 1940 the 31st General Hospital was relocated from Hallston Hall Camp to Belfast, with AHW appointed as its Commanding Officer (Table 2)[9]. John Hedley-Whyte recalls accompanying his mother on a visit to AHW in Leeds during July 1940. Plans for the family's move to Belfast later that year were discussed in Leeds, and his family joined AHW at Musgrave Park near Belfast in time for Christmas[18].

EPILOGUE

After the handover of the RAMC 31st General Hospital to the U.S. Army Medical Corps, it became known as the U.S. Army's 5th General Hospital (Harvard Unit). The RAMC 31st General Hospital was relocated from Belfast to Hatfield House in June 1942 at the invitation of the 4th Marquess of Salisbury for its use as a military hospital[1,9](Table 2). The 4th Marquess's son, Lord David Cecil, later wrote:

> "The effect was strange. In the great state rooms planned for 'feasts and triumphs', the narrow iron hospital beds lay side by side against the carven panelling and beneath the sculptured ceilings. Stranger still …the odour of disinfectant replaced that of beeswax and wood smoke."[22]

TABLE 2. LOCATIONS OF THE RAMC'S 31st GENERAL HOSPITAL IN WORLD WAR II[9]

Dates	Location
7 Jan 1940-7 Aug 1940	Hallston Hall Camp then to Belfast
***7 Aug 1940-7 June 1942**	**Belfast-Campbell College (Musgrave Park)**
***7 June 1942-7 Oct 1942**	**Hatfield, England**
7 Nov 1942-7 Dec 1942	Alexandria, Egypt
8 Dec 1942- 30 June 1944	Unspecified
1 July 1944-1 Aug 1944	Cancello, Italy
1 Aug 1944-7 Aug 1944	Arezzo, Italy
***AHW served in these locations**	

During the 19th Century, the Cecils had intermarried with the American Vanderbilts who had endowed the Clarence Barker Memorial Hospital near their renowned Biltmore Estate in Ashville, North Carolina[23].

The Hedley-Whyte family was greeted upon arrival at Hatfield by the 4th Marquess who suggested young John might like to go into the garden while his parents were given a tour. A heron was feeding in the pond, and in order to watch, John attempted to climb Queen Elizabeth I's oak stump. He pushed through the guard rail with its allusion to half-sister Bloody Mary. After watching the heron catch fish for a few minutes a roar of "Get down!" issued from the house and John cut himself while descending. " Even our queen in detention here was not so bold," John was told in Gascoyne Cecilian rebuke, and AHW added that he hoped John would soon be able to become a boarder at the Dragon School at Oxford. John Hedley-Whyte's letter of apology to the 4th Marquess is not in the Hatfield Archives.

AHW returned as a Brigadier to Newcastle-upon-Tyne and served as consulting surgeon to Northern Command during World War II years 1942-1945[5,6,]. In preparation for the D-Day landings he inspected British Troops with Ulsterman General Montgomery[24,25]. AHW co-authored a Handbook of War Surgery with Major-General Mitchiner[26]. Post-war he served on the Court of Examiners and on the Council of the Royal College of Surgeons. Angus Hedley-Whyte, D.S.O., F.R.C.S. died on August 2, 1971, aged 73.

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Cover Image:

The front cover image shows the late Dr John Geddes (front left) with other staff from the world's first Mobile Coronary Care Unit at the Royal Victoria Hospital in 1966.

A tribute to Dr Geddes appears in the Letters section of this issue.