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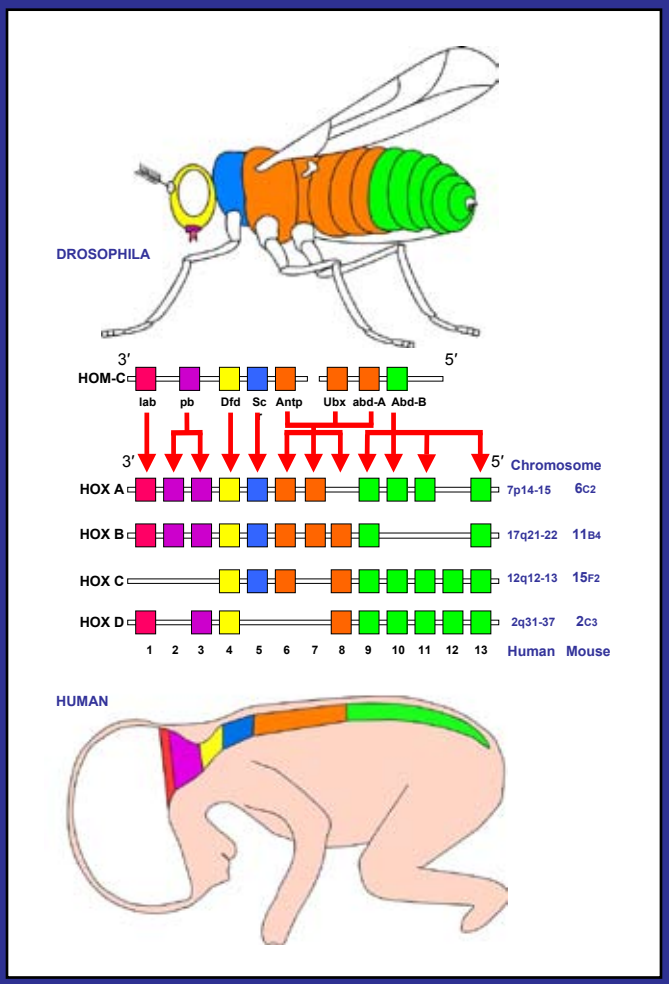

Published by

THE ULSTER MEDICAL SOCIETY

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The Ulster Medical Journal

The Journal of the Ulster Medical Society. First published in 1932.
Successor to the Transactions of the Ulster Medical Society (1884-1929), and the
Transactions of the Belfast Clinical and Pathological Society (1854-1862)

The Ulster Medical Society was founded in 1862
by the amalgamation of the Belfast Medical Society (founded 1806)
and the Belfast Clinical and Pathological Society (founded 1853)

The Ulster Medical Journal

VOLUME 75

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THE ULSTER MEDICAL SOCIETY
2006

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THE ULSTER MEDICAL SOCIETY

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President Dr Stanley Hawkins, BSc, FRCP

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"Ethical Issues Resulting from Screening for Complex Genetic Disorders"
Prof Nick Wood, Professor of Neurology and Neurogenetics, Institute of Neurology, London

Thursday 2nd February 8.00 pm — Ulster Medical Society Rooms
"Stem Cell Transplantation and the Nervous System"
Prof Neil Scolding, Professor of Neurology, University of Bristol

Thursday 16th February 8.00 pm — Ulster Medical Society Rooms
"Research and Audit in the Modern NHS"
Prof Charles Warlow, Professor of Medical Neurology, University of Edinburgh

Thursday 23rd February 8.00 pm — Ulster Medical Society Rooms
Joint meeting with the SOCIETY FOR THE HISTORY OF MEDICINE
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"Aspects of Medical Biography"
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Friday 3rd March 7.15 for 8.00 pm — Great Hall, QUB
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Thursday 16th March 8.00 pm — Ulster Medical Society Rooms
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Prof Alan Crockard, National Director, Modernising Medical Careers, London
THE ROBERT CAMPBELL ORATION

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Editorial

Colour vision

Peter: Did you hear about the Irishman* whose library burnt down?

Olivia: No - what happened?

Peter: Both books were destroyed!

Olivia: My goodness!

Peter: Worse still, one hadn't even been coloured in!

* in the interests of political correctness, substitute male or female versions of Canadian, Newfoundlander, Pole, Kerryman, and other suitable ethnic variants here to suit local conditions.

2006 is an important bicentenary for the Ulster Medical Society. In 1806, the Belfast Medical Society was founded and the later formation of the Belfast Clinical and Pathological Society in 1853, allowed amalgamation of both societies to form the current Ulster Medical Society in 1862. The vision of the early founders of the Belfast Medical Society, was far sighted, and some historical articles later this year will deal with aspects of this to commemorate the bicentenary. Dr John Logan, the Ulster Medical Societys' archivist, documents the history of the formation and publication of the 'transactions of the Ulster Medical Society' – the predecessor of the Ulster Medical Journal [1] in this issue.

The Ulster Medical Journal itself has had two changes this year – this is the first volume that has officially exceeded two issues since the shortage of paper during the war caused reduction of the four issues to two.[2] We hope that the three issues planned for this volume will become a permanent feature and we aim (costs permitting) to have some additional content available electronically on the website to enhance the paper edition. We do not know if a paper version of the journal will continue with the advent of digital flexible hand held optical reading devices (electronic books), and our colour vision (*figure*) of the future journal in 2106 is hard to predict. Professor David Hadden, a former editor of the journal outlines the interesting history of the visionary editors and assistant editors of the journal to date, and includes some personal insights illustrating their careers.[3]

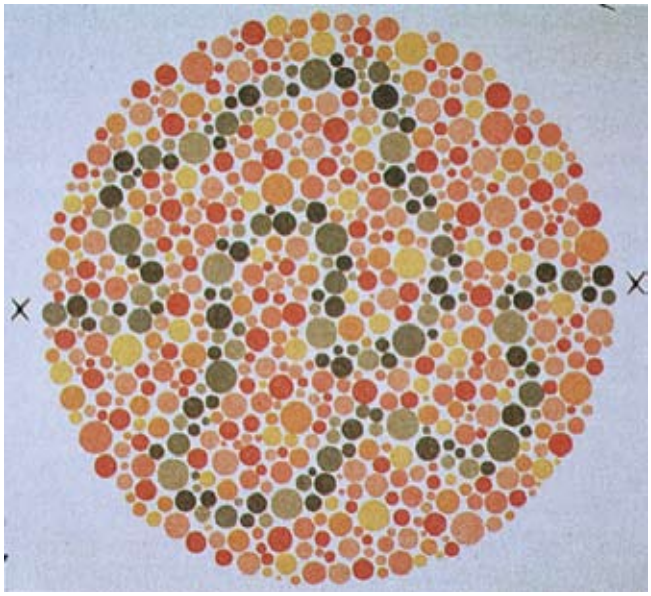

Figure. Ishihara chart showing red-green colour blindness.

The second change is the inclusion of colour for the first time throughout the journal. Cost savings in the delivery of electronic copy to the printers have allowed us to increase the number of issues and provide colour at minimal extra expense and we hope you enjoy the end result. Two colour plates appeared in the early history of the journal in a paper by TC Dodds in 1939 on the use of the recently invented Finlay colour photographic process for pathology slides.[4] The war again intervened and stopped any further advance in this direction. The next colour plate was included by Dr JA Weaver in his annual

oration in 1984 when he provided funding for a photograph of a painting by Sargent, in 1905, of the medical faculty of Johns Hopkins University.[5] The picture included William Osler, who left Hopkins shortly afterwards to become Professor of Medicine in Oxford University, England, and who helped found the Association of Physicians in 1906. The association celebrates its centenary this year.

Hopefully the changes will improve the quality and readability of the journal. Keep the good papers coming in with colour figures and illustrations and a happy and colourful new year to you all!

Patrick J Morrison, Honorary Editor.

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REFEREES CONSULTED – 2005

We thank our referees over the last year for reviewing manuscripts promptly and efficiently.

Dr D Allen
Dr P Archbold
Dr C Armstrong
Dr R Ashe
Mr P Bateson
Prof C Campbell
Mr K Chaudhari
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Dr I Cooke
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Commentary

Changes in Vocational Training for General Practice

A McKnight

Accepted 25 November 2005

The introduction of Modernising Medical Careers (MMC) and the regulatory framework being implemented by the new Postgraduate Medical Education and Training Board (PMETB) will bring about major changes for all doctors in training, not least in general practice (GP).[1,2] As there has been longstanding criticism of elements of the GP training programme, which has been set in regulation for the past 25 years, GP educationalists on the whole welcome this opportunity to develop a new training programme which is more fit for purpose.

MODERNISING MEDICAL CAREERS

The plan consists of a two-year foundation programme for all doctors some of whom will have the opportunity to spend four months in General Practice in year two. This will be followed by entry into specialist training programmes including general practice, which will lead to specialist certification. These are being referred to as run-through programmes.

POSTGRADUATE MEDICAL EDUCATION & TRAINING BOARD

The MMC changes, in addition to the change in the PMETB regulatory framework, will provide an opportunity for general practice to develop an integrated training programme with greater accessibility in the choice and length of hospital speciality posts and hopefully provide more time actually spent in general practice. In Northern Ireland we are hoping that from August 2007, in line with other deaneries in the UK, that GP trainees will commence a training programme encompassing 18 months rotating through a variety of hospital speciality posts followed by 18 months in general practice. Selection to GP speciality training will be through a national process. The programmes will be based on the new Royal College of General Practice Curriculum and Assessment process.

THE NEW ASSESSMENT FOR GENERAL PRACTICE

The PMETB is now the competent authority for certifying that doctors have achieved a level of competence to be included in the Specialist Register and the Register of General Practitioners maintained by the General Medical Council. In 2004 the PMETB published a policy statement, Principles of an Assessment system for Postgraduate Medical Training. The Royal College of General Practitioners working closely with the National Summative Assessment Board has designed a new single assessment system (nMRCGP), which should meet the requirements of PMETB. The new process will consist of three elements, an Applied Knowledge Test, a Clinical Skills Assessment and Workplace based assessment. The Applied Knowledge Test will be available locally, the Clinical Skills Assessment will be taken in the final year of training- probably at a central assessment centre in London. It is envisaged that the nMRCGP will be available from August 2007 but there will be a 2-3 year transition period when both the old and new assessments will be available to ensure that no candidate is disadvantaged. However as it is generally accepted that the new assessment will be more popular than the present Summative

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Assessment and the MRCGP examination, it is hoped then the transition period may be shortened.

In line with other speciality trainees, GP trainees will now have to pay for certification. Satisfactory completion of the new assessment will not only confer fitness to practice in the UK but also provide eligibility for membership of the Royal College of General Practice.

THE FUTURE ROLE OF THE GENERAL PRACTITIONER

The role of the GP is changing rapidly. The new general medical service contract allows GPs more flexibility over their commitment to work and what they do. The creation of GPs with a special interest must build upon vocationally trained general practitioners who have developed, or do further training to develop additional expertise. 'Caring for People Beyond Tomorrow', the new strategic framework for the development of Primary Health Care in Northern Ireland [3] has as one of its four main goals – to encompass a wider range of services in the community. We are very hopeful that development of special interests can become a significant part of a Higher Professional Education Programme for GPs in the near future.

General Practice has the potential to provide a very rewarding career for doctors in the future. It is the intention of the Northern Ireland Medical and Dental Training Agency (NIMDTA) to grasp the new opportunities created by recent changes to improve our education and training and to contribute fully to providing better health care for patients in Northern Ireland.

The author has no conflict of interest.

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Ulster Med J 2006; **75 (1)** *5-10*

Commentary

The Editors of the Ulster Medical Journal

David R Hadden

Accepted 18 October 2005

There is a long shelf of bound volumes of the Ulster Medical Journal, about four feet long, in the Council Chamber of the Society, in the Whitla Medical Building. I don't suppose anyone else has a personal set from Volume 1, but it makes interesting reading as an introduction to medicine and medical education in Northern Ireland since 1932. There is also a slim minute book recording in neat handwriting the deliberations of the editorial board from 1931 to 1939. On 4th June 1931 they agreed that *"the pages of the journal were to be open to any scientific contribution, provided it was of general interest and value"*. They hoped, then as now, *"to stimulate the younger Fellows and Members of the Society to do research work, and publish their findings in the journal"*. A quarterly editorial was suggested, written by one of the four professors on the board – Surgery, Medicine, Gynaecology and Pathology – and an abstract of each meeting of the Society. Panel practitioners from Belfast and the country regions were to produce a page on their activities and concerns. There was *"considerable discussion on the literary style and merit of articles sent in for publication, and it was agreed that the alteration of any such article was within the province of the Honorary Editor"*. In cases of difficulty, however, it was decided that such articles be submitted to Professor J. A. Lindsay, (the previous Professor of Medicine).

Our new editor and his board no doubt have similar aims and objectives, and we the readers will certainly support him. Whether the four successors to the original University Professors would agree to produce editorials on demand, and whether it would be possible on one page to discuss the business of the National Health Service general practitioner, either town or country, is debatable. But Professor Patrick Morrison has our complete confidence in making editorial alterations of literary style and merit as he sees fit – with or without an elderly retired academic as a final court of appeal on matters of taste and judgement.

Dr RH HUNTER: EDITOR 1932-1942

Volume 75 No 1 of the Ulster Medical Journal in 2006 may not seem a particularly noticeable issue – the first issue appeared on 1st January 1932 – "To inaugurate a new quarterly medical journal to replace the irregularly issued Transactions, to increase the usefulness of the Society, and to help in some small way medical advance in Northern Ireland" – a brave statement by the new editor, Dr RH Hunter, at that time Senior Lecturer in Embryology in the Department of Anatomy at the Queen's University of Belfast (*fig 1*). People of my generation probably remember him as Dickie

Figure 1. Dr RH Hunter. Editor 1932-1942.

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Figure 2. Dr RH Hunter "The man in the black hat".
Reproduced with permission of Queen's University Belfast.

Hunter, the resplendent ringmaster of Doctor Hunter's Circus, in the old Hippodrome theatre, in the late 1940's: but that was a retirement job, self selected due to his knowledge of the comparative anatomy of circus animals derived from a part-time post as consultant to the Belfast Zoo. He had also been Secretary to the University, a senior and responsible position during the war, when there were very few administrators – he is said to have presented graduates for their degrees (in the Presbyterian Assembly Hall, prior to the completion of the Whitla Hall) in the same stentorian tones he used in the circus ring across the road. That was when the well known portrait was painted, "the man in the black hat", now hung in the Great Hall (*fig 2*). Sir Ian Fraser's comment that the artist James Gunn requested him to put his overcoat, scarf, gloves and hat back on again to improve the pictorial aspect of the painting is perhaps apocryphal, but the result was memorable.

The first issue of the Journal is still worth reading: the editor requested support from the general practitioners of Northern Ireland in producing a journal worthy of the Medical School which it represents. I noted an elegant "plea for the myxoedematous" by Dr Eileen Hickey, Physician to the Mater Infirmorum Hospital – *"when myxoedematous patients arrive in the consulting room they have often surprisingly few complaints. They do not feel well, they have not much energy, they cannot walk far, they are easily tired, they feel short of breath, dizzy etc. In other words their vague complaints might be the complaints of almost anyone who had been leading a life rather too strenuous for their capabilities, physical or mental. They do not mention that their skin has become dry, their hands coarse and lined, they forget that their hair is falling out, and that they rarely feel warm – in fact they rarely mention any of the classical features of the disease".*[1] What a lovely piece of writing – present day editors yearn for doctors who can write good English! And Dr Hickey makes her important point, long before thyroid function tests or routine screening by the practice nurse. The advertisements were interesting too – "The profession demands a reliable car – buy a Ford 8 hp for £120" but the annual salary of a newly graduated House Physician was not much more than that.

Dr ROBERT MARSHALL: EDITOR 1943-1951

In 1943, in the depths of World War II, Dr Robert Marshall took on the editorship (*fig 3*). There is a short note on Ulster doctors and the war – 15 killed, 16 missing [2] including some who survived, (Dr JF Pantridge among them), and some who did not, (Dr Humphrey Thomson, son of Sir William Thomson, Professor of Medicine). Dr Marshall's own son, Dr RJ Marshall also died in the war, in an aeroplane accident in India. The Thomson Room and the Marshall Room in the Medical Library remind us of them, although the eponymous sparsely furnished computer rooms in the refurbished Mulhouse Building at the Royal Victoria Hospital are only a shadow of their former elegant oak panelled glory in the Institute of Clinical Science.

The Council accepted the resignation of Dr Hunter, noting his *"sane criticism, profound scholarship and self-effacing efficiency"*. He had earned *"the very warm thanks of Ulster doctors for his work – the fact that it has been a labour of love in no way lessens either its effort or its value".*[3] Perhaps all his editorial successors can agree with that sentiment, and hope that we have earned it as well. Robert Marshall – Bertie to his colleagues – is remembered as a punctilious, cultured and widely read doctor – a cardiologist in the days before they were subdivided into Type A or Type B. He had problems in keeping the journal going – there was a great shortage of

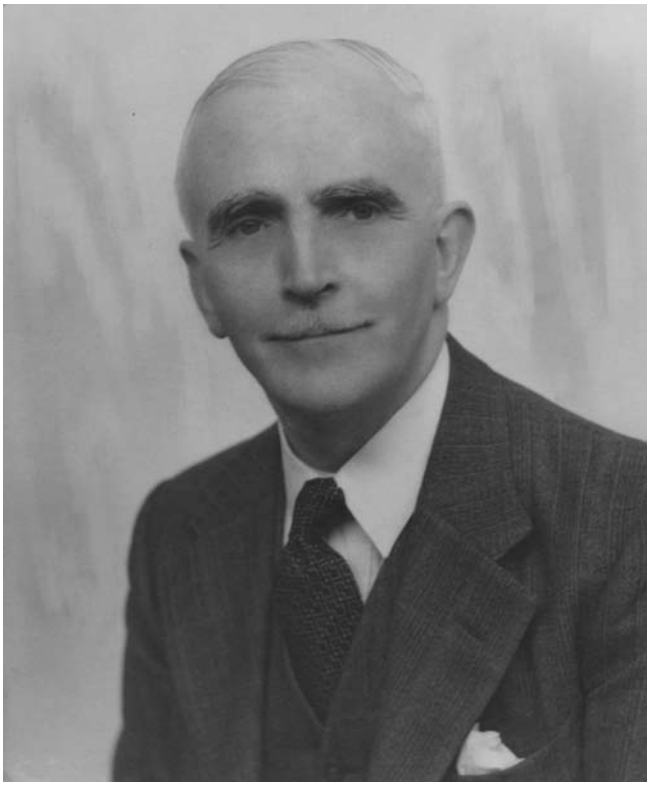

Figure 3. Dr R Marshall. Editor 1943-1951.

Figure 4. Dr RWM Strain. Co-Editor 1948-1951.

paper during the war and the number of issues was reduced from four to two per year – there were still only two issues produced every year until this volume when the number has been increased to three.[4] Perhaps it was he who encouraged a historical and literary aspect to the contents, but he also had the vision to devote a whole issue in 1944 to the scourge of tuberculosis, especially in University students. That was when compulsory health examination for students originated. He drove a large black Daimler motor car, and the House Physician in Wards 5/6 in the Royal Victoria Hospital was expected to carry his bag out to the car, parked in the small front quadrangle as was the right of corridor consultants. The story that there was a second large black Daimler coming behind to transport the large cumbersome electrocardiograph is untrue!

Dr RWM STRAIN: CO-EDITOR 1948-1951

Dr RWM (Bill) Strain, joined Robert Marshall as co-editor in 1948. He was perhaps more of a dilettante physician, with a happy cheerful smile (fig 4). He made his name as the historian of the Ulster Medical Society, and in particular with a well remembered personal account of all the occupants of University Square when it was the Harley Street of Belfast.[5] His position as Physician to the Belfast Charitable Society, Clifton House, although not particularly financially rewarding, did give him the opportunity to research and write the history of the charity and *en passant* of the early water supplies of the town of Belfast. He spent happy days exploring the old water course from the Vice Chancellor's lakes at Lennoxvale, through Conduit Street off the Ormeau Road, to Fountain Lane in the city centre, where some old wooden water pipes were found to prove his point. In his post war article on 'The Heraldry of Medicine', perhaps stimulated by the snake on the badge of the Royal Army Medical Corps he pointed out the difference between the single serpent of Aesculapius, the God of Greek Medicine, and the two serpents entwined on the caduceus of the winged herald Apollo in his guise as a healer.[6] Aesculapius was summarily executed by a thunderbolt from Zeus because his success in prolonging life on earth was reducing the population of Hades – following a complaint by Pluto, the Lord of the Underworld. Was this the first complaint about a doctor, and was the punishment justified?

PROFESSOR JE MORISON. EDITOR 1952-1984

Dr John Edgar Morison – later Professor – took on the Editorship in 1952 (fig 5), the same year he and his wife were married, and he had just finished writing his major textbook on Fetal and Neonatal Pathology. John Edgar Morison is still

with us, aged 93. He did not realize then that he would remain Editor for 32 years – but his hard work and devotion set the style and appearance of the Journal, and gradually improved the scientific as well as the clinical and historical content. He is well remembered by many of us whose early efforts at medical writing would be transformed by his usually sympathetic editorial pen. The journal prospered, and became internationally recognised, with citations in Current Contents as well as the Index Medicus, the predecessor of Medline. Perhaps a pathologist is best placed to be an editor of a general medical journal – a broad knowledge of disease is less easy to acquire now, with our highly specialized training regulations.

Figure 5. Professor JE Morison. Editor 1952-1984.

PROFESSOR DAD MONTGOMERY. CO-EDITOR 1975-1984

Desmond Montgomery became co-editor in 1975, and remained in joint harness until 1984 (*fig 6*). His own joint textbook on Clinical Endocrinology had gone to two editions, and he was blessed with the ability to produce clear and concise medical prose without the need to revise and rewrite again and again. His high standards in clinical medicine were translated to the written page. I remember a wry comment that John Edgar Morison still kept much of the editorial power to himself, but the team of Morison and Montgomery continued the general advance and improvement during the decade.

Figure 6.
Professor DAD Montgomery. Co-Editor 1975-1984.

PROFESSOR DR HADDEN. EDITOR 1984-1995

When I inherited the journal in 1984 (*fig 7)* it was the time when modern computerized printing processes were starting. I explored the printing works of Dorman & Sons, who had been printing the journal in Hope Street in an old single storey mill behind Great Victoria Street. The elderly typesetter had been with them all his life, and he knew as much and more about good medical writing as I did – he could quickly demolish errors of composition and grammar, and had a quick eye for turgid medical prose. He was the one who said it was about time the journal came up to date, and he and I devised the new bright blue and white cover, with contents on the front, and a new typeface (which turned out to be somewhat cyrillic in origin, but certainly different from the previous version). Illustrations became much easier – scanning and photoreproduction was easy, and expensive blocks did not have to be cut.

A journal probably depends more on its prospective authors than it does on its readers. A good journal attracts good papers, and thus they are read by a wider audience. Francis Bacon said it all – *"Reading maketh a learned man; conference a ready man; but writing an exact man"*. I was pleased that the changes in format, and the introduction of a more definite peer review process encouraged more

Figure 7. Professor DR Hadden. Editor 1984-1995

papers, both from experienced clinicians and from junior doctors. There is a tendency to deride the wish to publish – "publish or perish", and there is a real danger of descending into a medical magazine, but the written word is a lasting expression that needs to be encouraged at all levels. By 1993, in an Editorial, I calculated our Impact Factor as 0.075, making the Ulster Medical Journal 94th in order of 123 journals listed under Medicine: General and Internal.[7] Of course, the top flight researchers will need a higher impact factor to support their grant applications, but we were at least on the map, at the 76th percentile. My plea was "send us your good papers, and improve our rating".[7]

Dr JM GIBSON. EDITOR 1995-2005

When Mark Gibson took on the task in 1995 (*fig 8*), he took the sensible decision to change the format from the original octavo size.[8] *"There are several sound reasons why the journal now appears in A4 sized paper. There is ample room for a two column format, section headings are easy to identify, and there is more scope for figures and graphs. And supplies of the old paper were running low".*[9] In 1998 he wrote *"with four issues, this has been a bumper year for the journal. Whatever one's viewpoint, all would admit that a knowledge of history is a good thing. This applies equally to our medical history and culture. The Ulster Medical Journal has published a fair number of historical articles over the years. But scientific and clinical papers rapidly become historical documents themselves. We may be surprised, amused or shocked at what was published in the past, yet can always learn from it."*[10] This was the year when the first Cumulative Index of the journal was compiled,[11] as a real labour of love by Dr John S Logan, assisted by Mrs Colette McDonald, Mrs Eilish Doran and his son Dr John I Logan. The index is an invaluable window into our first 64 years, and we owe a considerable debt to its dedicated authors. As time passes, and personal memories disappear, this index with its clear listing of authors, biographies and subjects will become the main point of entry for those wishing to find out what went on in Northern Ireland medicine during those times – the problems of infectious disease

Figure 8. Dr JM Gibson. Editor 1995-2005

before antibiotics, the disasters of the war years, the gradual development of specialist medicine and surgery, the increasing concerns for medical education, and the more recent topical aspects of ethical concepts and governmental strategies.

There are a number of people who deserve a special mention in a review of this sort. The support for the Journal by the staff of the Medical Library has been both enthusiastic and generous. Miss Jessie Webster set the scene when the new Medical Library first opened in the Institute for Clinical

Science. Mrs Eilish Doran offered considerable skills in librarianship and pointed us in several right directions as neophyte publishers: she has been followed by Ms Mary Crickard as subeditor,[12] and this remains a most responsible task, the more so as the literacy of our medical graduates becomes a matter of increasing concern. Finally, but not least, Dr Rex Wilson, in his retirement from general practice in Ballyward, County Down, has, as Assistant Editor, faithfully read and corrected most of the articles published in the past twenty or more years.

Thank you all.

PROFESSOR PATRICK MORRISON. EDITOR 2005-

In 2005 with Volume 74, No. 2, Patrick Morrison (*fig 9*) has taken the helm.[8] Those of us who have been there before will wish him, and the Journal, well. Perhaps he will be able to persuade those professors to write the editorials – or the general practitioners, city or country, to contribute their thoughts on the organization of practice in Ulster: they were brave ideals in 1931.

Figure 9. Professor PJ Morrison. Editor 2005 -

CONFLICT OF INTEREST

The author was editor of the Ulster Medical Journal from 1984-1995.

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Presidential Address

The History of Neurology in Belfast: The first hundred years

Presidential Address to the Ulster Medical Society, 13th October 2005

Stanley A Hawkins

I would like to tell the story of the development of neurology in Belfast. I wish to concentrate on the first century. Why do I say the first century? Having researched the beginnings, I was surprised to discover that the first physician with special training in neurology to practice in Belfast set up his brass plate as long ago as 1888. From 1888 to the late 1980's comprises the first hundred years of neurology in Belfast. This takes us up to the closure of Claremont Street Hospital, and in-patient beds in Belfast City Hospital, with concentration of acute neurology beds at the Royal Victoria Hospital. I am not going to say much about my contemporaries or myself. I also feel more comfortable describing the talents and accomplishments of my predecessors whose lives have run their full course. There are many precedents for this.

PEOPLE AND PLACES

The story is essentially one of people and places. The people were pioneering individuals who formed teams and fruitful collaborations. The story concentrates on three very influential men – their publications were read and quoted extensively in the world of medicine and neurology. Two of them served as presidents of the Association of British Neurologists, Sydney Allison and Harold Millar. The third, Louis Hurwitz, surely would also have been accorded that honour, had he not died at the age of forty-five. All were gifted researchers, writers, clinicians and teachers. The places were the hospitals where they worked, and the stories of their development.

Dr Hugh Calwell succeeded Sydney Allison as honorary archivist at the Royal Victoria Hospital. He wrote an article on the initiation of neurology in Belfast based on Sydney Allison's collected papers.[1] The paper covers the foundation of the clinics in Great Victoria Street and of Claremont Street Hospital, extending up to 1948, the foundation of the National Health Service. I want to move the account forwards by forty years.

Sydney Allison published extensively on a wide range of topics but did not publish much concerning his personal feelings and experiences, when he was active professionally. I am grateful to John Allison his son, who copied some extracts of his father's extensive private diaries to help me with my background research. The papers contain frank personal views of hospital politics of his time. These have been quoted sensitively. I am also indebted to Mrs Sheila Millar who gave me collections of papers, slides and books belonging to Harold shortly after his death in 1993. Dr Natalie Hurwitz also gave me Louis' slide collection in the mid 1990's following a guest lecture in his honour given in 1996 by their close friend Prof P K Thomas, a past editor of Brain.

THE FIRST BELFAST NEUROLOGIST

The first physician in Belfast with specific neurological training was John McGee McCormac of Banbridge (*fig 1*). He entered Royal Belfast Academical Institution in 1860 and after two years there went on to Queen's College Belfast, as a medical student. In 1867 he qualified in Edinburgh with LRCP & S, and proceeded to gain his MD degree in Durham in 1885. He spent some time in London studying neurology and attended the National Hospital, Queen Square as a post-graduate student. This institution had been founded only a few years

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Figure 1. John McGee McCormac

earlier in 1860. Before he left London, he became one of the original members of the Neurological Society of London.

McCormac, on his return to Belfast in 1888, practiced from his own home at 29 Great Victoria Street. This was a location popular among other members of the medical fraternity, being on the then outskirts of the expanding city. The current layout of this part of Belfast is dramatically different, being the site of a modern commercial arcade leading to Glengall Street bus station. His neighbours included future eminent physicians such as HL McKissack and JA Lindsay, who later became professor of medicine. By 1889 McCormac's house had become "The Belfast Institution for Nervous Diseases, Paralysis and Epilepsy". In 1893 McCormac moved to the house next door leaving number 29 to the patients and in 1897 he and the institution moved to numbers 71 and 73 where they remained until his sudden death in 1913.

Active in Belfast medical and intellectual society, on his return to Belfast in 1888, he was a member of the Natural History and Philosophical Society. It is recorded that he read neurological papers at the Northern Ireland Branch of the British Medical Association. It is of interest that within one year of Roentgen's discovery of X-ray apparatus in the session 1896-7 he gave a detailed account of the physics of the production of X-rays and described their use in examining bones, liver, kidneys and heart.

CLAREMONT STREET HOSPITAL

McCormac was also instrumental in the establishment of Claremont Street Hospital (*fig 2*) in 1896. It was initially called the "Victoria Hospital for Diseases of the Nervous System, Paralysis and Epilepsy" and was opened at number 14 Claremont Street. It was endowed and sponsored by a Miss Farrell, the daughter of a former rector of Dundonald, Co. Down. McCormac was its first physician. Miss Farrell suffered from a neurological illness, but it is not recorded what the nature of this illness was. The new hospital had male and female wards containing 15 beds altogether. The hospital was supported by a committee of management drawn from the members of the Belfast establishment. For example Lieutenant-General Geary presided over the Committee of Management during the year 1899 and Sir James Henderson DL succeeded him. The first surviving annual report covers the year ending 1904. Thirty-five in-patients were admitted. According to McCormac "31 were cured, 18 much benefited and 2 unchanged". In the 1909 report it is recorded that "cases of paralysis, melancholia, hypochondriasis, rheumatic neuritis, sciatica and chorea were treated with complete success and epileptics have been so greatly benefited that for years they have not suffered from any recurrence of attacks". I am sure our contemporary outcome statistics would not better that!

When John McGee McCormac died in 1913 he was described as the founder of the hospital, but credit was also given to Miss Farrell. Following McCormac's

Figure 2. Claremont Street Hospital

death John Thompson MD (RUI) LRCP London originally of Lisburn was appointed to succeed him. Thompson had been a student in Queen's College Belfast. He also studied in Dublin, London and Vienna. It was not unusual for undergraduate students in those days to migrate between several medical schools before graduation. This phenomenon was described in detail in Prof Richard Clarke's "Gary Love Lecture", delivered during the last year. Thompson's interests lay more in what we would now call functional disorders rather than organic nervous diseases.

In 1927 when the hospital was amalgamated with the Killowen Colony for Epileptics in Lisburn (*fig 3*), the title of the combined institutions was changed to the "Nervous Diseases Hospital and Epileptic Colony". Thompson reported good results "in treating epilepsy and most functional diseases were much improved by electrical treatment and the

Figure 3. Killowen Hospital

use of ultra-violet rays." The use of ultra-violet rays in medicine was controversial. He is recorded as deploring the "unscientific attitude" of the Medical Research Council in a report that cast doubt on the value of treatment of nervous diseases using ultra-violet light. He wrote that the report would "have the tendency to disturb the mind of the large number of patients receiving the treatment, and even if there were a psychological or faith healing element in the treatment, they have no right to criticise one of the most recent advances in medical science and shake the confidence of the public".

In 1926 Thomas Howard Crozier was appointed assistant physician to Claremont Street. He worked in Claremont Street for only 2 years before moving on to the staff of the Royal Victoria Hospital. He remained on the staff of the Royal as a physician until his retirement. Crozier later recalled that when Thompson was interviewing him for the appointment in Claremont Street the conversation concerned religious and theological belief rather than medicine. In some of Sydney Allison's later writings, he recalled the liberal distribution of biblical texts throughout the hospital. Little remains in the archives of Thompson's time. By all accounts he was a diligent and caring physician. The Killowen Colony for Epileptics in Lisburn was housed in a property belonging to the Thompson family, which later was passed to the Health Service.

DR HILTON STEWART

In 1929 Howard Hilton Stewart (*fig 4*) was appointed assistant physician. He had been a registrar in the Hospital for the Paralysed and Epileptic in Maida Vale, London, where he had undergone neurological training. He was later appointed to the Ulster Hospital. In 1930 he applied for the post of assistant physician at the Royal Victoria Hospital. The book containing testimonials for his application is still preserved (*fig 5*). He received letters of support from Wilfred Harris, the Senior Physician in Maida Vale, Douglas MacAlpine and Russell Brain. Hilton Stewart was a son of Andrew William Stewart, a former editor of the Belfast Telegraph. His special interest lay in the follow up and control of patients suffering from epilepsy. Another particular interest was the management of psychoneurosis. After the National Health Act in 1948 he gave up general medicine and became a consulting neurologist. In 1956 he was appointed Clinical Lecturer and Examiner in Medicine in Queen's University in Belfast and joined the staff of the Royal. His publications include works on epilepsy, the mental consequences of head injuries and on Sydenham's chorea.[2-5]

Figure 4. Dr and Mrs Hilton Stewart

CONTENTS.

1. Letter of Application.
2. Testimonials from :—
   (1) W. W. D. Thomson, Esq., B.A., B.Sc., M.D., D.P.H., F.R.C.P. (Lond.)
   Professor of Medicine, Queen's University of Belfast.
   Physician, Royal Victoria Hospital, Belfast.
   (2) Foster Coates, Esq., B.A., M.D., D.P.H.
   Physician, Royal Victoria Hospital, Belfast.
   Consulting Physician, Forster Green Hospital, Belfast.
   Member of Senate, Queen's University, Belfast.
   (3) Robert Marshall, Esq., M.D., D.P.H., F.R.C.P.I.
   Physician, Royal Victoria Hospital and Ulster Hospital for Children and Women.
   (4) C. G. Lowry, Esq. M.D., F.R.C.S.
   Professor of Midwifery, Queen's University, Belfast.
   Gynaecologist, Royal Victoria Hospital, Belfast.
   Senior Consulting Surgeon, Belfast Maternity Hospital.
   Consulting Surgeon to Ulster Hospital for Children and Women, Belfast.
   (5) S. T. Irwin, Esq., B.A., M.Ch., F.R.C.S.
   Surgeon, Royal Victoria Hospital, Belfast.
   Consulting Surgeon, Ulster Hospital for Children and Women, Belfast.
   (6) Wilfred Harris, Esq., M.D., F.R.C.P. (Lond.).
   Senior Physician, Hospital for Epilepsy and Paralysis, Maida Vale.
   Senior Physician, St. Mary's Hospital, London.
   (7) Douglas McAlpine, Esq., M.D., M.R.C.P. (Lond.).
   Physician, Hospital for Epilepsy and Paralysis, Maida Vale.
   Neurologist, Middlesex Hospital, London.
   (8) W. Russell Brain, Esq. M.A., M.D., M.R.C.P. (Lond.).
   Assistant Physician, Hospital for Epilepsy and Paralysis, Maida Vale.
   Assistant Physician, The London Hospital.

Figure 5. Testimonials for Dr Hilton Stewart 1930

His South American wife, May Clara Dos Santos whom he married in 1930 pre-deceased him by 6 years in 1958. He never fully recovered from this loss. A very kind woman, she devoted her life to the welfare of the patients and staff in Claremont Street Hospital. The entry on Hilton Stewart in Munk's Roll (a record of particularly distinguished deceased fellows of the Royal College of Physicians of London) records that he was "a man of deep religious faith and an Elder of the Kirk. Religion was in his heart rather than his tongue. Throughout his life his friends were drawn to him by his wit and his consideration for others." Following his death in 1963 a library was founded in Claremont Street Hospital as a tribute to his memory, based on his personal collection of books and journals. This remarkable occasion was well attended. Photographs of the occasion still exist, as does a collection of autographs of those who attended, including Dr MacDonald Critchley, who had travelled from London for the occasion. The dean of the medical school at Queen's Professor (later Sir) John Henry Biggart, was also present. As a young man he published a textbook on neuropathology.[6]

DR SYDNEY ALLISON

Dr Sydney Allison was born on 15th May 1899 (*fig 6*) in 7 Wellington Park Avenue, Belfast. His father, William Locock Allison, an Englishman from Bradford was a fashionable society photographer. He had a studio in Donegall Place in Belfast opposite the City Hall. Sydney was educated at the Royal Belfast Academical Institution and then at Queen's University Belfast, qualifying with Honours in 1921. In 1922 he became a house physician and house surgeon in the Royal in Belfast. In 1923 he was appointed house physician at the West London Hospital in Hammersmith and later became a registrar in the same hospital. He engaged in postgraduate study at the National Hospital for Paralysed and Epileptic in Maida Vale, the National Hospital Queen Square, St. George's, St Bartholomew's and Charing Cross Hospitals. In 1924 he obtained the degree of Doctor of Medicine with commendation and was elected a member of the Royal College of Physicians of London. He was a young man in a hurry and after just 4-5 months working for Dr Grainger Stewart in Maida Vale having had time to obtain his MD degree and his MRCP he went to a private hospital in North Wales called Ruthin Castle run by Dr (later Sir) Edmond Spriggs. There were only four to five on the medical staff and Dr

Figure 6. Dr Sydney Allison

Allison was appointed as an assistant physician. This hospital received only very wealthy patients. Many of them had neurotic conditions. Some had neurological illnesses.

During his time in North Wales he obtained a grant from the Medical Research Council to investigate "The incidence, frequency, distribution and other aetiological factors of the patients with disseminated sclerosis in North Wales". This led to a publication in "Brain". This was the first population-based study ever published on multiple sclerosis.[7]

In 1930 he was appointed to the medical staff of Royal Victoria Hospital in Belfast and became a visiting physician to Claremont Street Hospital in 1939. It is interesting that he competed with Hilton Stewart and Howard Crozier for the position on the staff of the Royal Victoria Hospital. Sydney Allison in his private diaries wrote that the obvious candidates were Stewart and Crozier. A female relative of one of the members of the board of the Royal Victoria Hospital, Henry Berrington had been unwell and had been treated in Ruthin Castle by Spriggs. John Allison remembers his father saying he was particularly attentive and solicitous to the well-connected lady from Belfast.

In those days it was expected that applicants for positions on the staff of the Royal Victoria Hospital would canvas support. Though we do not know the details of Sydney Allison's approaches to members of the Board of Management, an amusing account of this process is detailed in the recently published biography of Sir Ian Fraser.[8] Though Henry Berrington supported Allison's application, Spriggs at the time was in the USA and the resourceful Allison got him to send a telegram of support. In any case, Sydney Alison was appointed, and Hilton Stewart had to wait for 26 years until 1956 before he was appointed to the visiting staff of the Royal. Sydney enjoyed working with his colleague Hilton Stewart. He was more of an organic neurologist than Stewart. Hilton Stewart was what we would now call a neuro-psychiatrist. He was interested in neurosis, psychosis and depression, treating middle class patients who felt they would have been stigmatised by attending psychiatry clinics. Sydney writes that his friend Hilton Stewart had a flair for administration, and he gladly left that to him.

Sydney Allison was always interested in the sea and the navy. As a medical student he spent a year in the Royal Navy as a surgeon probationer on a destroyer. A book detailing his memories was published based on his diaries.[9] The great influenza epidemic wiped out many of the crew and made a profound impression on him. Before becoming a houseman in the Royal Victoria Hospital he spent a year at sea in the merchant navy with the Blue Funnel Line in the Far East. He became a Surgeon Lieutenant in the Royal Naval Volunteer Reserve (RNVR) – Ulster Division on HMS Caroline in 1925.

EARLY NEUROSURGERY AND CECIL CALVERT

From the time of his appointment to the Royal, Allison conducted teaching demonstrations in neurology for students attending the hospital. There was no specialist appointment in neurology, nor was there a specialist neurosurgeon. Mr GRB Purce was a general surgeon in the Royal with an interest in thoracic and neurosurgery. In the Royal in 1930 the list of neurosurgical operations performed contains the following: removal of brain tumours, 2 (died 2); removal of cerebral cyst, 1; cerebral abcess, 1 (died 1); laminectomy, 1 (died 1). Purce gradually abandoned neurosurgery.

During the 1930's Cecil Calvert was developing an interest in neurosurgery. Sydney Allison and Cecil Calvert got on well. Cecil Calvert spent his days practising general surgery in nursing homes to earn his living. He also practised general surgery in the Royal. It was his preference to operate on neurosurgical cases at night. He was a careful, meticulous surgeon, but memorably slow. In those days haemostasis within the head was difficult. Sydney Allison frequently assisted at operations. Beginning at 8.30 to 9.30pm, the operations invariably went on into the small hours of the night. The surgical outcomes gradually improved. It must be remembered that in those days none of the modern diagnostic aids were available. The preoperative assessment was based almost entirely on the bedside methods, using the clinical history and the careful consideration of the neurological examination.

THE WAR AND POST-WAR PERIOD

At the start of the Second World War the admiralty called up Sydney Allison employing him as a medical specialist. His wartime experiences are recorded in a paper published after his death by his son John based on his diaries.[10] At Barrow Gurney near Bristol he was placed in charge of a 40-bed neurology ward. In 1944 he was appointed senior medical officer in command Royal Naval Neurological Hospital at Stonehouse, Plymouth, carrying the rank of Surgeon Captain RNVR (one of just three reservists to achieve that rank). Early

in the war, during quieter postings, he studied for a qualification in psychiatry, the DPM.

After discharge from the Navy, on his return to Belfast he found that his colleagues were "still in the mind-set of 1939". Those who had not been to the war, and were in powerful positions in medicine felt that things would settle down and return to the pre-war state. Sydney Allison found this attitude infuriating. He was approached to become honorary secretary of the medical staff in 1947. At that time Professor WWD Thomson was chairman of the medical staff. There was a mutual regard. They were also near neighbours in University Square. Allison lived at number 27 and Thomson at number 25. Before the inauguration of the National Health Service, this was Belfast's equivalent of Harley Street. Incidentally, Cecil Calvert lived at number 8 University Square. An interesting account of the medical occupants of University Square is to be found in Dr Strain's presidential address to the Ulster Medical Society in 1968.[11]

Sydney Allison expressed a desire to Prof WWD Thomson that he wished to become a full time neurologist. Thompson initially was against this but later actively facilitated him. He writes "many of my friends thought I was being foolish, and to stake all on the success of a new venture such as neurology was courting disaster. It did not seem proper or justifiable to take over one of the general medical wards and stuff it with neurological cases," and "neglecting other aspects of medicine". He was also convinced that neurological cases required specialist nursing. He felt such patients would be better gathered under the care of nurses skilled and practised in the care of neurological diseases.

Cecil Calvert joined the Royal Army Medical Corps in 1940. His expertise in neurosurgery resulted in a posting to Oxford, attached to St Hugh's Hospital for head injuries. This pioneering unit was run by Sir Hugh Cairns, later Nuffield professor of Neurosurgery in Oxford.

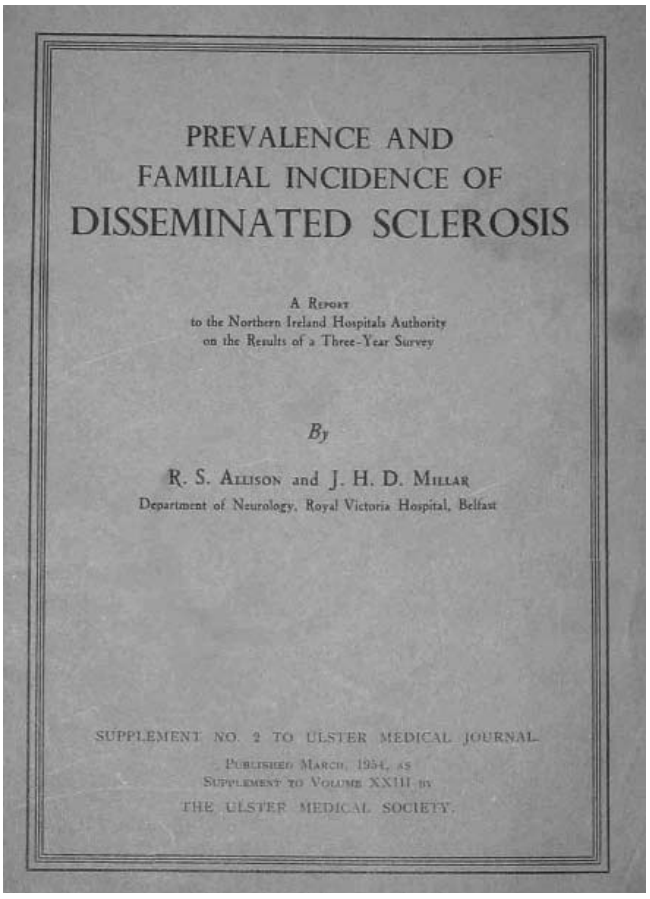
While he was the honorary secretary to the staff Sydney Allison actively promoted the concept of neurology and neurosurgery working more closely together. There was no neurosurgery unit. He also became interested in the development of the hospital. Two tours of European hospitals were made. The first was to France and Switzerland in May 1947, and the second to Denmark and Sweden in June and July. These countries had escaped the worst ravages of World War II.

Cecil Calvert, before the war, had developed an interest in neurosurgery. A year before the introduction of the Health Service, in 1947 he was appointed a full time neurosurgeon with a salary of £1,500 per year. This freed him of the necessity to earn his living practising general surgery. He was also permitted to see private neurosurgical cases. 25 beds were allocated to him in wards 11 & 12 in the old Royal corridor. In 1948 there was a further development. A decision was made to establish a department of neurology in the Royal with Sydney Allison as physician in charge, the appointment being on the same terms as Calvert's. Allison and Calvert brought their needs to the hospital Management Committee, which was chaired by Senator Herbert Quin. The upshot of this planning was that Quin House was to be redeveloped to accommodate neurology and neurosurgery. On the ground floor were thirty-five beds, a theatre suite, and an X-ray department run by Dr Harold Shepherd, who had been appointed in 1950. There was also a room for EEG equipment. On the second floor were sixteen beds for neurology. The advantage of having a special unit was the development of a team of specialised nurses. The close collaboration between medical, nursing and physiotherapy staff greatly benefited the patients, after the unit was opened.

Sydney Allison continued his interest in MS by involving Harold Millar in a major epidemiological study. This was published in a supplement (*fig 7*) to the Ulster Medical Journal in 1954.[12] It is perhaps the most frequently cited paper ever published in the journal. The reason for this is that the simple diagnostic criteria that they proposed were not superseded for twenty years. All papers on the epidemiology of MS for nearly thirty years quoted the Allison and Millar criteria.

In 1950 it was clear that a new matron of Claremont Street should be appointed. Sydney Allison went to Queen Square and forged a formal link with the National Hospital for Nervous Diseases. The matron of Queen Square, Miss Marjorie Ling was appointed matron of Claremont Street Hospital and despite the distance visited Belfast regularly. Many of the nurses from Claremont Street benefited from periods of training in Queen Square. Miss Ruby Moore was her deputy, and acting matron.

Also in 1950, Belfast City Hospital advertised sessions for consultant neurologists. Sydney Allison


PREVALENCE AND
FAMILIAL INCIDENCE OF
DISSEMINATED SCLEROSIS

A Report
to the Northern Ireland Hospitals Authority
on the Results of a Three-Year Survey

By

R. S. Allison and J. H. D. Millar
Department of Neurology, Royal Victoria Hospital, Belfast

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Figure 7. Cover, Ulster Medical Journal supplement on MS

and Hilton Stewart were appointed. There were 15 beds, and a neurological presence twice a week.

The extension to Quin House was opened 1953 when Sydney Allison was on sabbatical in London. Sydney spent the months from September to December of 1953 working with Dr McDonald Critchley in the National Hospital, Queen Square. Incidentally Critchley also served in the RNVR during the war. The fact that they were both naval men no doubt helped their friendship. The collaboration resulted in a book called the "Senile Brain", published in 1962.[13] Allison's presidential address to the Ulster Medical Society in 1969 was heavily influenced by Critchley's researches on the parietal lobes.[14]

Cecil Calvert died tragically as the result of a car accident at Ballygawley in1956. At that stage there was one other neurosurgeon on the staff – Mr Alec Taylor, a Scot, had been appointed in 1952. Mr Campbell Connolly had been appointed in 1950 but resigned in 1952 to take up a post in Birmingham. Mr Colin Gleadhill, an Englishman who had trained in Dublin was appointed to succeed Cecil Calvert in 1957. Mr Derek Gordon a very young man at the time of Cecil Calvert's death was appointed in 1960. Before his appointment as a consultant he gained further surgical experience in Boston.

During 1957 Sydney Allison went to the USA at the request of Dr Leonard Kurland who was working at the NIH in Bethesda at the time. The invitation came after a chance meeting at a conference in Chicago in 1956 where Sydney had presented the results of his survey of MS in Northern Ireland. He was encouraged to study the prevalence of MS in Charleston, South Carolina and Halifax, Nova Scotia, assisted by a young Dr Milton Alter. Milton Alter still has fond memories of his association with the Allison family, and recalls visiting Belfast in the late 1950's. In September 1957 Dr and Mrs Allison set off on board a liner to New York. Derek and Mavis Gordon happened to be on the same ship en route to Boston. This cemented a lasting friendship. Louis Hurwitz who was in New York at the time went to

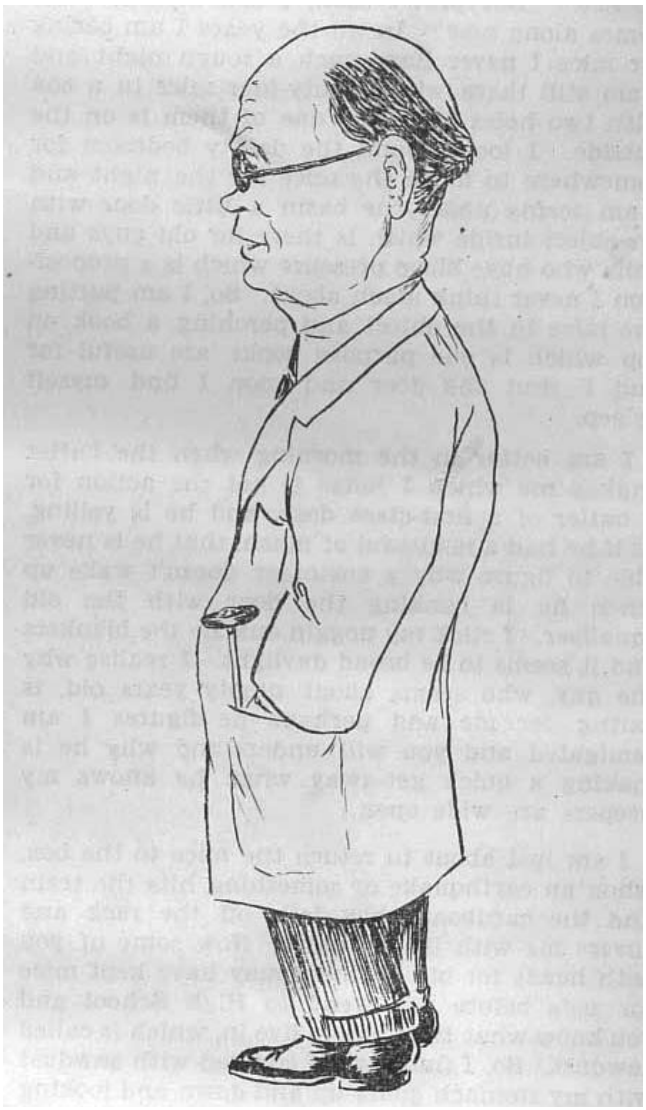

Figure 8. Cartoon from 'Snakes Alive' 1957

visit him in Charleston. Later the Allisons spent four days in New York over Christmas with Louis and his boss Dr Wolff in Cornell before returning home by air to London on Boxing Day. In 1957 Sydney was honoured by a tribute in "Snakes Alive", the usually disrespectful journal of the Belfast Medical Students Association. (*fig 8*)

From 1966-1968 Allison served as President of the Association of British Neurologists. During his presidency he hosted a meeting of the association in Belfast. Following his retirement he worked as Honorary Archivist in the Royal Victoria Hospital, publishing an extensive history of the hospital "The Seeds of Time".[15] (*fig 9*)

Derek Gordon was a gifted surgeon, who in his maturity was a great ambassador for Belfast. He was to serve as the President of the Society of British Neurological Surgeons. In the 1970's and 1980's he, Colin Gleadhill, Ian Bailey and three young registrars – Alan Crockard, Tom Fannin and Dermot Byrnes put Belfast neurosurgery on the map. The fact that Quin House was adjacent to the casualty department and the intensive care unit was influential in their pioneering work on head injuries in the early days of the civil war (in all but name) on the streets of West Belfast.

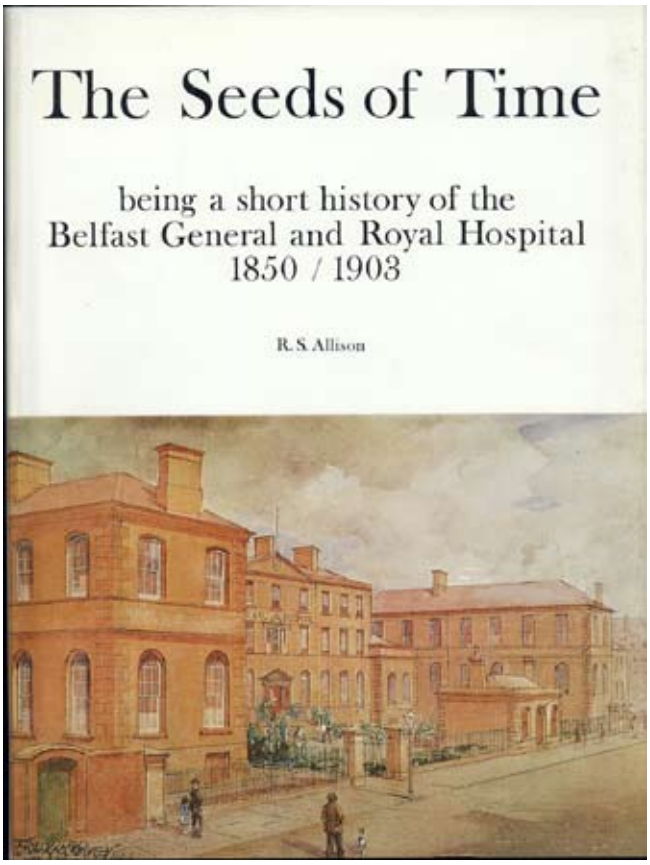

Figure 9. Cover, "The seeds of Time"

DR HAROLD MILLAR

Harold Millar was born in Belfast, the eldest son of Samuel Dundee Millar, a resident of Bangor, and a jam manufacturer and company director. Sheila Millar told me his friends on the Bangor train called Samuel "Lord Preserve-Us". Harold was educated at Elm Park Preparatory School in County Armagh and from the age of fourteen at Campbell College, Belfast. He studied medicine at Queen's University Belfast 1935-1940. After qualifying he became house physician at the Royal Victoria Hospital for six months, (*fig 10*) and could have become fully registered on the strength of that, but he then moved to be a house surgeon at Plymouth General Hospital where one of his friends was working in Greenbank Hospital. His friend told him they were short of doctors there at the time. As a consequence he experienced at first hand the effects the blitz of the naval base. Images of that remained etched on his memory for the rest of his life.

Harold had three brothers and one sister. Along with all his brothers he volunteered for His Majesty's Forces in 1941. He served as surgeon lieutenant in the Royal Naval Volunteer Reserve until 1946. His first experience was in minesweepers and destroyers

Figure 10. Dr Harold Millar

in the Atlantic, then in the artic convoys. The arctic convoys helped to supply the Russian allies with munitions and were particularly hazardous. U-boats lay in wait in Norwegian fjords. If a ship was torpedoed in winter, sailors overboard faced almost certain death from hypothermia.

Having survived several arctic convoys, he told me he applied for a course in tropical medicine. His application was successful and he spent the last two years of the war in the Far East, based in Ceylon. He had happy memories of "sundowners" in Trincomalee. Late in his life, shortly before he died, he received a campaign medal from the Soviet Government in recognition of his wartime service. This pleased and amused him for he carried with him all his life the memory of harrowing experiences on the Murmansk convoys.

After the war he returned to Belfast to pursue post-graduate education. He quickly obtained the MD with commendation and the MRCP in London, one of the first of his generation following the war. As a registrar at the Royal Victoria Hospital he became interested in neurology. He went to the National Hospital for Nervous Diseases, Queen Square, London in 1947-1948, as a supernumerary registrar to study electro-encephalography (EEG). In 1950 he married Sheila who had trained as a nurse in the Middlesex Hospital, and later trained as a social worker. She was the daughter of Robert Hugh Clay, Regional Director of the Post Office in Northern Ireland. They had three sons and two daughters of whom one son and one daughter qualified as doctors.

In 1952 he was appointed Consultant Neurologist at the Royal Victoria Hospital and Claremont Street Hospital for Nervous Diseases in Belfast. He was also visiting neurologist at the Belfast City Hospital, Thompson House (home for the long-term disabled at Lisburn) Killowen Hospital for Epilepsy (Lisburn), Tyrone County General Hospital, Omagh and the Erne Hospital, Enniskillen, – a heavy and greatly dispersed clinical commitment. He was the senior neurologist in Belfast for over 25 years, and continued to work full time until he was sixty-five.

Harold Millar was a gifted clinical neurologist who greatly enhanced the reputation of neurology in Northern Ireland. His clinical acumen was remarkable. Ward rounds started in Quin house on Monday mornings on the dot of nine o'clock. They were conducted at considerable speed, frequently being completed by nine thirty, when he would travel down the main corridor of the Royal to perform consultations in other wards, and thence to the medical library. His house staff were frequently astonished at his mercurial ability to spot significant clinical signs from the end of the bed. His diagnostic skill was legendary, rather like a gifted mathematician who could leave out several lines of a complex calculation and still end up with the correct answer.

His abiding passionate interest in multiple sclerosis (MS) remained with him until he died. Between 1948 and 1952 he carried out an epidemiological survey of MS in Northern Ireland with Sydney Allison.[7] This was one of the first studies of its kind to be performed anywhere and was regarded as a model for other subsequent studies. He founded a register of MS in Northern Ireland that he maintained.

In 1971 he was invited to write the monograph on MS on the "American Lecture Series" published by CC Thomas in Springfield, Illinois.[16] To this he gave the sub-title "A Disease Acquired in Childhood". This arose out of the interest at that time in a possible relationship between MS and measles, following the discovery of measles virus in cases of subacute sclerosing panencephalitis. He had a conviction that MS will eventually turn out to be an infectious disease.

Harold Millar felt that specialists should not lose touch with general medicine. His breadth of interests was apparent in the range of his papers on many aspects of general medicine, in addition to his many contributions to the neurological literature. He produced papers on platelet stickiness in cerebrovascular disease in diabetes, the neurological manifestations of systemic carcinoma, amino-aciduria and the EEG, on epilepsy, subarachnoid haemorrhage and cerebral tumours. In 1956 with colleagues he described for the first time in Britain a family with Refsum's Disease, a rare autosomal recessive enzyme defect resulting in failure to metabolise phytanic acid, presenting clinically with a mixed polyneuropathy, blindness and deafness.

He was a benign teacher who preferred to guide by example. If there were an occasion when something did not please him, he would merely chuckle and say "How extraordinary!" At academic meetings he was less benign and did not hesitate to pursue a debatable point with vigour but again with good humour. In 1977 he was appointed Honorary Reader in Neurology at Queen's University. He was elected President of the Association of British Neurologists from 1979-1980. Harold Millar was a modest man

who did not tolerate pretension. He had a warm outgoing personality with a great sense of humour. He was gregarious, a generous host, a fisherman and a former captain of the Royal Belfast Golf Club at Craigavad.

When he retired from the National Health Service in 1982 he kept up his active interest in research on MS and although his health was deteriorating continued to live life to the full at his farm in the County Down countryside. At all times he was supported by his wife Sheila, his constant companion and together they continued visiting MS patients in their homes as well as holding annual tea parties, fund raising, barbecues and barn dances (*fig 11*).

Of all his many clinical attachments he was particularly fond of his work at Claremont Street

Fig 11. Barbeque in Dr Millar's garden from left to right, Dr M Swallow, Dr T Beringer, Dr S Hawkins, Fiona Hawkins, Dr H Miller.

Hospital, in a warm friendly and efficient atmosphere with small band of dedicated nurses. He was very upset when Claremont Street Hospital was closed a short time after his retirement. Claremont Street was based on a row of Victorian terrace houses. It became increasingly difficult to provide modern medical and nursing care. It was under threat of closure for ten years. The highly skilled band of nurses helped to postpone the inevitable through their dedication. Sydney Allison in his diaries wrote in the 1960's that it was difficult at times to practice modern medicine there.

DR LOUIS HURWITZ

Lewis John Hurwitz (*fig 12*) was born on 9th February 1926. In later life he always signed his name and was known to most of his friends as Louis. The youngest child of Barney Hurwitz, for many years president of the Jewish community in Belfast, he went to school at Belfast Royal Academy where he showed academic and athletic promise. He won the Girdwood Cup (for a best all-round performance in track events) on two occasions. He entered Queen's University medical school graduating in 1949.

His first appointment was House Physician to the newly formed Department of Neurology at the Royal Victoria Hospital under Dr Sydney Allison. He showed a remarkable aptitude for the careful clinical assessment of neurological cases. Sydney Allison encouraged this. He subsequently held a house physician post at Claremont Street Hospital and Killowen Hospitals. Later he held appointments in Liverpool and Bradford in general medicine. In 1951 he spent a year in the Department of Pathology of the Queen's University Belfast gaining a BSc in 1952 and an MD in 1953. In 1954 he became registrar in the Department of Neurology and passed the MRCP of Edinburgh in 1955.

Having decided to make his career in neurology he went to London and spent two years as Resident House Physician at the National Hospital for Nervous Diseases, Queen Square. In 1957 he was awarded a scholarship to work on cerebral vascular disease at Bellevue Hospital, New York and became Assistant Director of the Neurological Services at Cornell University with John Foster Kennedy who was from Belfast and was a student at the Belfast Medical School. Returning to Queen Square in 1959 he spent a year as Senior Registrar in the outpatient department. In 1960 he won a Ciba Travelling Fellowship that took him to Paris where he worked with Professor Garcin at the Hôpital de la Salpêtrière. He absorbed much of the clinical expertise of the French neurologists and took to his heart their style of clinical demonstrations in teaching. In 1961 he was appointed Lecturer at the Institute of Neurology in London. During this time he worked with Dr Purdon Martin on cases of post-encephalitic Parkinson's disease in the Highlands Hospital where 130 patients were resident. A publication in Brain resulted from this collaboration.[17] The following year he returned to Belfast as Consultant Neurologist to the Royal Victoria Hospital, Claremont Street Hospital and Belfast City Hospital.

Figure 12. Dr Louis Hurwitz

Louis had infectious enthusiasm and boundless intellectual energy. This is exemplified by the work on subacute sclerosing panencephalitis. It was his conviction that measles was to blame. The young Ingrid Allen had confirmed the diagnosis in three cases of SSPE. He pursued the virologists. Fortuitously the techniques of immunofluorescence and immunohistochemistry had been recently introduced to Belfast. Measles antigen and antibody were discovered, resulting in one of the most cited papers ever.[18] John Connolly talked with pride of a special note to that effect in Excerpta Medica in the 1980's. The contribution of Dame Ingrid Allen to Belfast neurosciences is legendary. The full account of her achievements is beyond this short paper. She was awarded the DBE as a result of her original research and her contributions to national and international committees.

Louis Hurwitz was a member of the Association of British Neurologists, The Association of Physicians of Great Britain and Ireland and the Louis Rapkine Association. He was Honorary Secretary of the Ulster Neuro-Psychiatric Society from 1962-1971 and a founder member of the Irish Neurological Association. He served on the council of the section of neurology of the Royal Society of Medicine of London and the Royal Academy of Medicine in Ireland.

During the last two years of his life he experienced a series of heart attacks. He was encouraged to curtail his clinical activities, but his research work continued with unabated enthusiasm. He held several grants from the Medical Research Council, for work on diabetic neuropathy, amino-aciduria in relation to myopathy and to establish a register of muscular dystrophy in Northern Ireland.

He was an inspirational enthusiastic teacher. The students elected him President of the Belfast Medical Students' Association (1965-1966). His contributions to neurology in Belfast and his keen interest in teaching, particularly of undergraduates, were rewarded by an appointment as Honorary Lecturer at Queen's University shortly before his death in 1971. His wife, Natalie was also medically qualified. They had two sons and a daughter. Following his death Dr Natalie Hurwitz returned to England to work in Leeds in the student health service. After his death, Michael Swallow published a volume of selected papers with a complete bibliography.[19]

He died when I was a medical student in my final year. In those days clinical demonstrations in neurology and neurosurgery for students were conducted on Thursday afternoons, Friday afternoons at 5pm in Claremont Street and on Saturday mornings in the Royal. These classes were attended by an enthusiastic band of students even on Saturdays. Students from the country would postpone trips home so as not to miss the classes.

Dr Michael Swallow was appointed to succeed Sydney Allison in 1964. A graduate of the University of London and the Westminster Hospital he had been inspired to adopt a career in clinical neurology by Dr Swithin Meadows, a consultant neurologist with an interest in neuro-ophthalmology. While he was a house physician to MacDonald Critchley, Dr Sydney Allison was at Queen Square on sabbatical. Michael was impressed. Louis Hurwitz was also at Queen Square at the time. Friendships were formed, so when the post in Belfast became available, he applied. Michael Swallow graced the department until his retirement in 1988. A gifted teacher of undergraduate and postgraduate students, he developed interests in neuro-ophthalmology, rehabilitation, Parkinson's disease, and muscle disease. His clinical practice included the Royal, Claremont Street, Belfast City Hospital, and units for chronically disabled in Musgrave Park and Thompson House in Lisburn. He also travelled to

Altnagelvin and Coleraine hospitals to conduct regular outreach clinics. A facet of neurology that particularly interested him was the assessment and management of disabled children and adults with multiple handicaps.

As a boy, Michael was a chorister in the choir school of Westminster Abbey. At the start of the Second World War, the choir school was evacuated to Christ's Hospital School at Horsham. After two years when it was obvious the war was going to be prolonged, the choir was temporarily disbanded. Michael applied for a place in the choir school in Magdalen College School, Oxford. At the end of his schooling, Michael was torn between a career in music and a career in medicine. He became a medical student, but has had a passion for music all his life. In Belfast, he has enjoyed leading amateur musical productions in a wide range of styles from oratorio to jazz. The choirmaster of the Royal Victoria Hospital Choir for many years, he has also been associated with the St George's Singers and the Ulster Orchestra. He has enriched the cultural life of Belfast in very many respects, serving on the Arts and the Environment Committee in the Royal and the Northern Ireland Arts Council. An interest in music therapy has enabled him to combine neurology, rehabilitation and music.

Figure 13. Dr Jo Lyttle's retirement party 1996

Dr John (Jo) Lyttle (*fig 13*) was appointed to succeed Dr Louis Hurwitz after his premature death. A son of the manse, he was brought up in rural setting in Ballyroney, Co Down, and was educated at Campbell College and Queen's University. Having obtained an MD in cardiology, Jo switched to neurology. Then he spent some time in Queen Square before returning to Belfast, where he developed a large practice. Jo developed an interest in cerebral vascular disease, and participated in international therapeutic trials of transient ischaemic attacks and stroke. He retired in 1996, and was replaced by two neurologists, Dr Tom Esmonde and Dr Michael Watt.

I joined neurology in 1974 as a registrar. Mrs Ruth Baker, a daughter of Sydney Allison, published a contemporaneous account of Claremount Street Hospital in that year.[20] Claremont Street was closed in early 1986, and at the same time the inpatient beds in Belfast City Hospital. Beds for acute inpatient neurological investigations were all aggregated in Quin House. Thus ended the first century of neurology in Belfast. It will be for someone else to write the next chapter.

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Review

HOX GENES: Seductive Science, Mysterious Mechanisms

Terence RJ Lappin,[1] David G Grier,[2] Alexander Thompson,[1] Henry L Halliday [2,3]

Based on an Invited Lecture "Physiology and Pathophysiology of *HOX* genes in embryonic development" given by Professor Terry Lappin to the British Association for Perinatal Medicine at their Annual Scientific Meeting in Belfast on 9th September, 2005.

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ABSTRACT

***HOX* genes are evolutionarily highly conserved. The HOX proteins which they encode are master regulators of embryonic development and continue to be expressed throughout postnatal life. The 39 human *HOX* genes are located in four clusters (A-D) on different chromosomes at 7p15, 17q21.2, 12q13, and 2q31 respectively and are assumed to have arisen by duplication and divergence from a primordial homeobox gene. Disorders of limb formation, such as hand-foot-genital syndrome, have been traced to mutations in *HOXA13* and *HOXD13*. Evolutionary conservation provides unlimited scope for experimental investigation of the functional control of the Hox gene network which is providing important insights into human disease. Chromosomal translocations involving the MLL gene, the human homologue of the Drosophila gene trithorax, create fusion genes which exhibit gain of function and are associated with aggressive leukaemias in both adults and children. To date 39 partner genes for MLL have been cloned from patients with leukaemia. Models based on specific translocations of MLL and individual *HOX* genes are now the subject of intense research aimed at understanding the molecular programs involved, and ultimately the design of chemotherapeutic agents for leukaemia. Investigation of the role of *HOX* genes in cancer has led to the concept that oncology may recapitulate ontology, a challenging postulate for experimentalists in view of the functional redundancy implicit in the *HOX* gene network.**

INTRODUCTION

It is a fascinating thought that the single cell zygote contains all the information required for the development of the adult organism. Understanding how this information is encoded and deciphered is a major uncompleted scientific challenge. A group of genes known as homeobox genes has emerged as important master regulators of development. These genes have been highly conserved throughout evolution. They are expressed during embryonic development in a highly co-ordinated manner and continue to be expressed in virtually all tissues and organs throughout adult life.

Homeobox (*Hox)* genes were discovered following the observation of two striking mutations in the fruit fly, *Drosophila melanogaster*. In the *antennapedia* mutation the antennae are changed into legs, whereas in the bithorax mutation, the haltere (a balancing organ on the third thoracic segment) is transformed into part of a wing. These changes were described as homeotic transformations from the Greek word homeosis, signifying a change of a

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complete body structure into another. *Drosophila* geneticists devised the term 'homeotic selector gene' to encapsulate the concept that a master regulatory gene could control the development of each segment of the fly. Subsequently *Drosophila* was found to contain a cluster of genes consisting of the *bithorax* complex with three homeobox genes (*Ubx, Abd-A*, and *Abd-B*) and the *antennapedia* complex with five homeobox genes (*Lab, Pb, Dfd, Scr and Antp*). The relationship between the chromosomal arrangement of *Hox* genes and the localisation of their expression was established by Lewis in 1978. In effect, these genes specify positional identity of the body segments of the fly along the anterior-posterior axis.[1]

EVOLUTION OF *HOX* GENES

Homeobox genes are present in the genomes of all animals which have so far been mapped as well as in the genomes of plants and fungi, indicating that the origins are ancient and precede the divergence of these kingdoms. Plants, fungi and unicellular animals do not, however, have clustered homeobox genes. Shortly after the origins of animals the primordial homeobox gene duplicated to form a protohox cluster of two genes which are still present in *cnidara* such as *hydra* (*Figure 1*). Sponges do not have clustered homeobox genes, suggesting that this duplication occurred before the divergence of the parazoa. This is also reflective of the very simple body structure of sponges compared to other multicellular animals.

The nematode *Caenorhabditis elegans* has a single cluster of at least five homeobox genes.[2] *Amphioxus* is a vertebrate-like chordate which has a notochord and segmental muscles derived from somites but does not develop a true vertebral column. It has only one *Hox* cluster which contains ten *Hox* genes and this cluster is regarded as being homologous to the ancestral cluster from which all vertebrate *Hox* clusters were derived. Two duplication events,

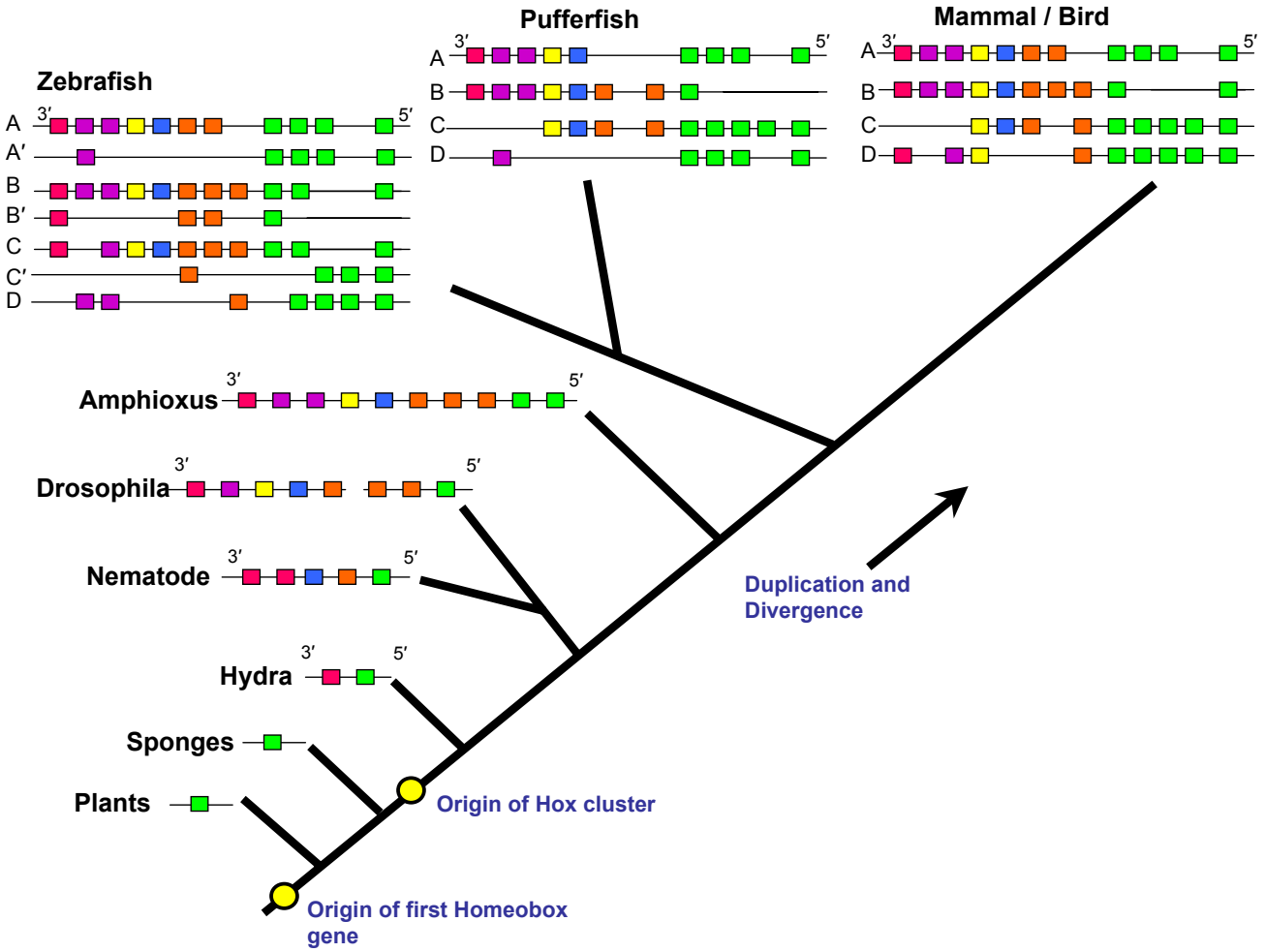

Fig 1. A representative dendrogram illustrating the evolution of *Hox* clusters.
Hox gene clusters are thought to have developed by a process of duplication and divergence from a primordial homeobox gene estimated to have arisen about 1,000 million years ago.

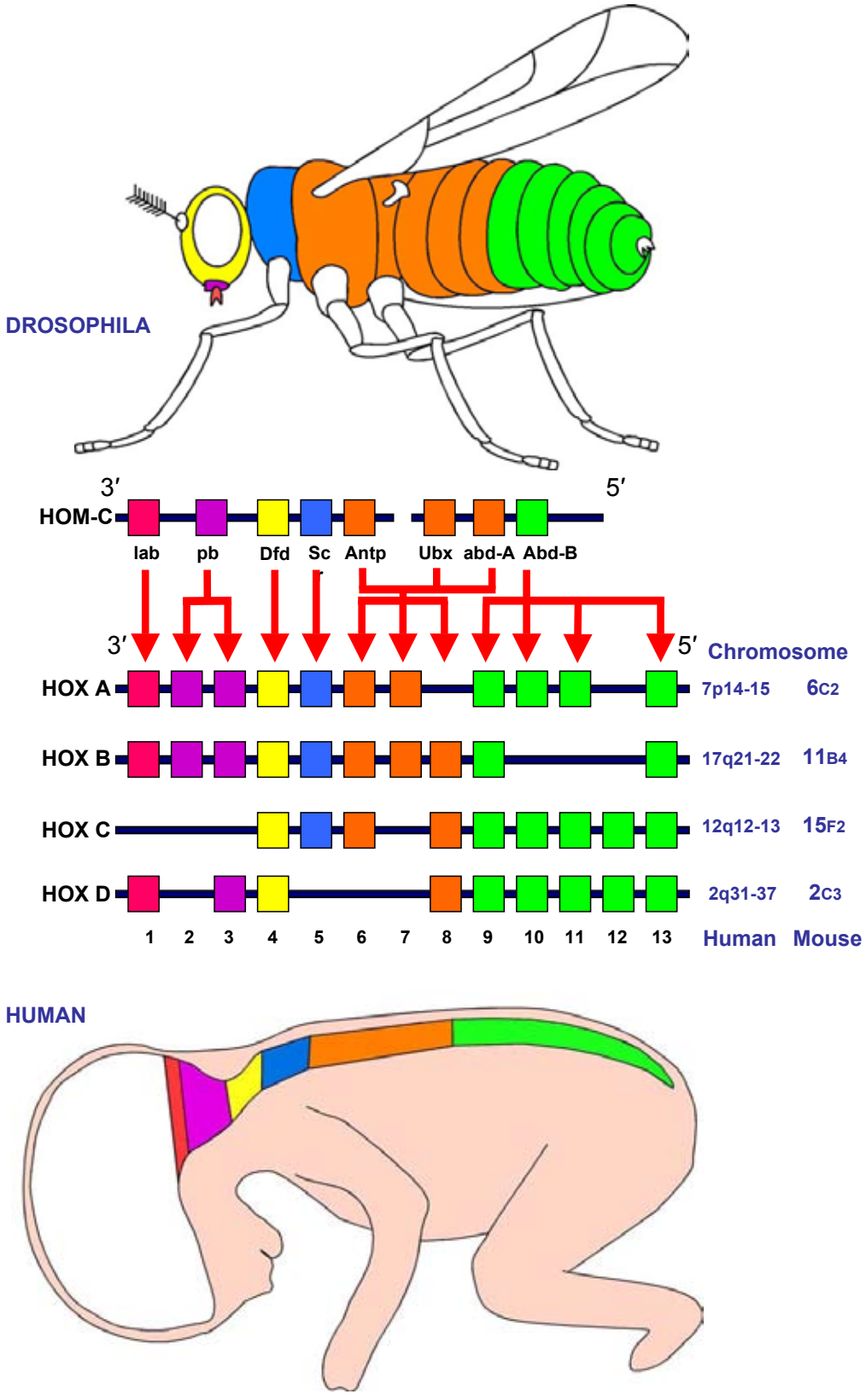

Fig 2. Conservation between the *HOM-C* and *HOX* gene clusters.
The four *Hox* gene clusters found in mammals are conserved from the *Drosophila Hom-C* complex in terms of nucleotide sequence and colinear expression. During embryonic development, the genes are expressed in a pattern that correlates with the chromosomal positioning, depicted here for human and mouse. The 3` genes are expressed both earlier and more anteriorly than the 5` genes.

early in vertebrate evolution, resulted in the four clusters seen in mammals and birds. Loss of some of the *Hox* genes in each cluster has also occurred with the result that not every primordial vertebral *Hox* gene is represented in each of the four clusters. Interestingly in some fish, such as zebrafish, a further duplication has occurred resulting in seven clusters.[3]

Hox GENES IN VERTEBRATES

The vertebrate counterparts of the *bithorax/ antennapedia* cluster are the *Hox* genes, usually found in four clusters (reviewed by Duboule[4]). In man the four *HOX* gene clusters (A-D) are located on different chromosomes, at 7p15, 17q21.2, 12q13, and 2q31. Each cluster consists of 13 paralog groups with nine to eleven members assigned on the basis of sequence similarity and relative position within the cluster. A high degree of homology is evident between the human *HOX* genes and the *Hom-C* genes of *Drosophila*, (*Figure 2*). Thus the human paralog groups 1-8 are more closely related to antennapedia (Antp), with groups 9-13 more closely related to *abdominal-B* (abd-B).

Hox STRUCTURE

Mammalian *Hox* genes are small, each containing only two exons and a single intron which varies from less than 200 bases to several kilobases (*Figure 3*). The homeobox is always present within the second exon in *Hox* genes and shows a high degree of homology among these genes, especially within paralog groups. The structures of non-Hox homeobox genes are more variable, frequently having the homeobox bridging an exon splicing site.

Hox proteins have an acidic tail at the C-terminus and a pentamer upstream of the homeodomain that binds the TALE (three amino acid loop extension) proteins which act as cofactors. The homeodomain is a highly conserved motif of 60 amino acids. The function of the homeodomain was suggested by its similarity to the sequence of several prokaryotic gene regulatory proteins which contain a helix-turn-helix DNA binding motif. The homeodomain can be divided into three helical regions. Helix 3 contacts the major groove of DNA while helices 1 and 2 lie above the DNA.[5] Further contact of the homeodomain to the DNA is made by the sequence which proceeds helix 1, the N-terminal arm. The binding of Hox cofactors, (*exd* in *Drosophila*, *Meis* or *Pbx* in mammals) increases the stability of *Hox*-DNA binding.

Hox GENES AND DEVELOPMENT

The order of expression of *HOX* genes within a cluster is co-ordinated during development, so that the low number, 3` genes, are expressed more anteriorly and earlier than the high number, 5` genes. During embryogenesis, cells require positional information to ensure that uncommitted cells differentiate into tissue appropriate for its location within the developing embryo. Thus groups of cells, known as functional domains, become committed to form body structures such as limbs and organs. There is growing evidence that it is the combination of *Hox* genes expressed within the functional domains along the AP axis which results in specifying the development of structures within these domains. The possible mechanisms by which this occurs have been reviewed by Kmita and Duboule.[6] In both Drosophila and man the spatial patterning corresponds to the relative position on the chromosome, thereby conforming to the "principle of colinearity".

In the developing vertebrate *Hox* genes are first expressed during early gastrulation at a stage when the embryo generates its major body axis.[7] In a pattern which correlates with the spatial expression of *Hox* genes, 3` genes are expressed earlier than 5` and as the embryo develops more progressively 5` genes are expressed. This pattern is termed "temporal colinearity" and is evident in other models of development such as haematopoiesis.

HOX GENES AND LIMB DEVELOPMENT

Hox genes define patterns of development in vertebrate limbs. In the chick, at least 23 *Hox* genes are expressed during limb development, with *Hoxa9* expressed in the proximal part of the limbs where the humerus or femur develop. *Hoxa9, Hoxa10* and *Hoxa11* are expressed in the forelimb where the radius and ulna (or tibia and fibula) develop. *Hoxa9* to *Hoxa13* are expressed in the wrist (or ankle) and the digits. A similar pattern of expression was found for the *Hoxd* genes whereas the expression of the *Hoxc* cluster was more complex. These observations illustrate that complicated networks of gene expression are involved in organ development, and suggest that functional redundancy among the *Hox* genes may mask the effects of under-expression or mutations in individual *Hox* genes. However a number of abnormalities in human limb

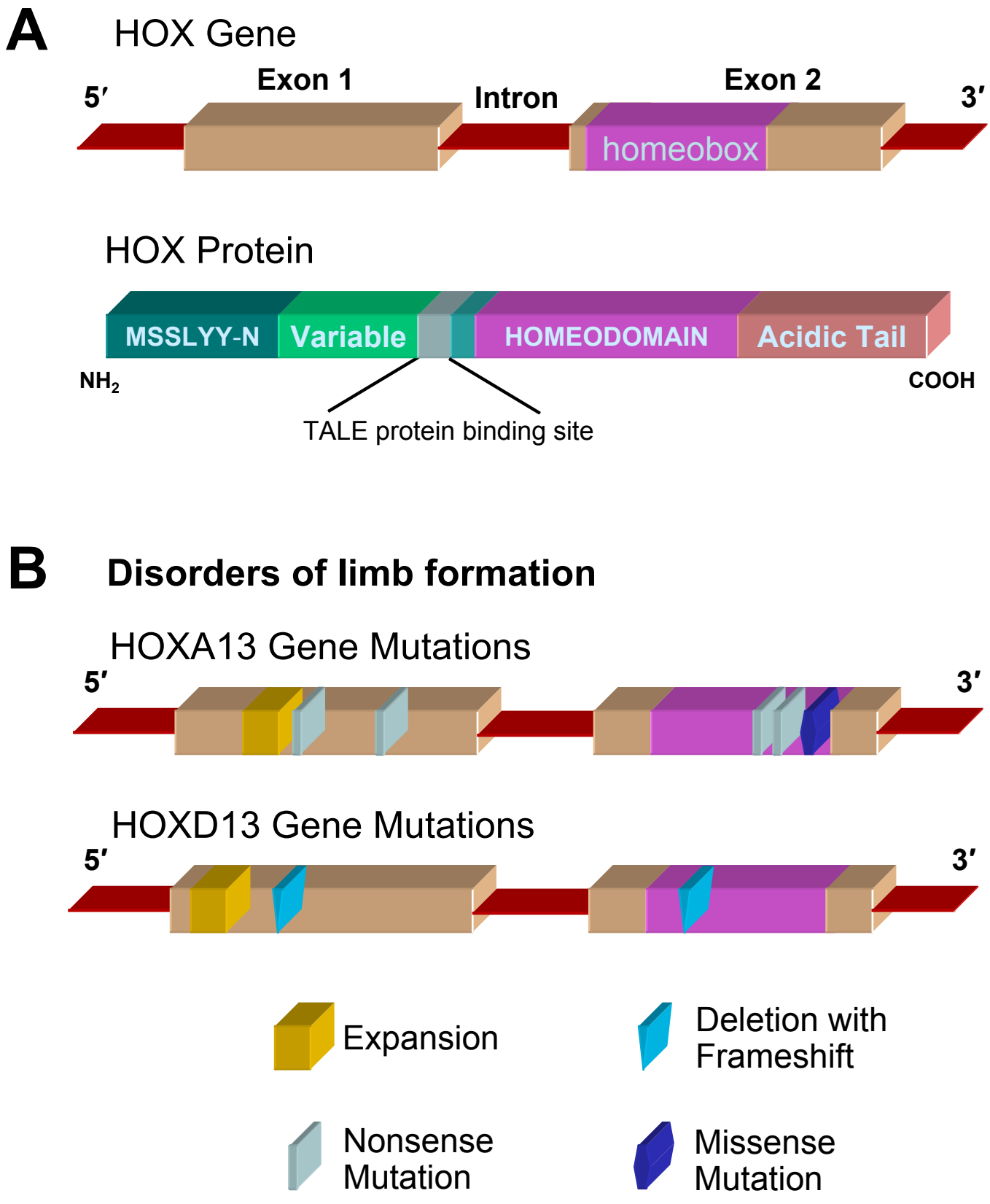

Fig 3. *HOX* gene/protein structure and mutations found in limb malformation.
(A) *HOX* genes consist of two exons and one intron. Exon 2 contains a 180-nucleotide sequence, termed the homeobox, that encodes a 60-amino acid helix-turn-helix motif, termed the homeodomain, which has DNA-binding activity.
(B) Mutations in *HOXA13* and *HOXD13* are found in disorders of limb formation, such as hand–foot–genital syndrome (HFGS), synpolydactyly (SPD), and brachydactyly.

formation have been described and recently these have been linked to specific *Hox* genes.

Synpolydactyly (SPD), a rare, dominantly inherited limb malformation with a distinctive combination of syndactyly (fusion of digits) and polydactyly (extra digits), is caused by mutations in *HOXD13*. SPD typically consists of 3/4-finger and 4/5-toe syndactyly, with a duplicated digit in the syndactylous web. Affected family members often show variable expression of the disorder due to incomplete penetrance. The molecular basis of SPD was identified during a study of affected individuals in an isolated Turkish village.[8] The SPD locus was mapped to chromosome 2q31, where the *HOXD* gene cluster is located.[9] In normal individuals exon 1 of *HOXD13* contains an imperfect trinucleotide repeat sequence encoding a 15-residue polyalanine tract, and in subsequent studies each affected family displayed an expansion of this repeat, resulting in 7, 8 or 10 additional residues being expressed, see Figure 3B.

Brachydactyly, in which there is shortening of the digits, is rare in patients who are homozygous for SPD.[10] Two patients out of 128 screened for unselected congenital limb abnormalities requiring reconstructive surgery, were found to have a novel mutation within the *HOXD13* homeodomain (Ile314Leu). In further investigations specific mutations in *HOXD13* were linked with different combinations of limb disorders.[11]

Hypodactyly, a semi-dominant syndrome of loss of digit development, has been studied in mice. Animals with homozygous hypodactyly have a profound deficit in digital arch formation associated with a deletion in exon 1 in *Hoxa13*.[12] This leads to a translational frame-shift resulting in the loss of wild-type Hoxa13 protein and the production of a novel, stable protein in the limb buds of mutant mice. Mortlock and Innis have linked hypodactyly to a strikingly similar human disorder – hand-foot-genital syndrome (HFGS), which differs from SPD because the deformities of the hands and feet are fully penetrant, bilateral and symmetrical, and uniform in their severity.[13]

The first *HOXA13* mutation associated with HFGS was a nonsense mutation in exon 2 which leads to the conversion of a tryptophan residue in the homeodomain to a stop codon, truncating the protein by 20 amino acids.[13] Some patients with HFGS also harbour expansions of the polyalanine tract of HOXA13, similar to those found in HOXD13 of SPD.[14,15] A missense mutation in exon 2 is associated with an exceptionally severe form of HFGS.[14] Two unrelated boys had deletions at 2q24.1-q31 and 2q31.1-q32.2, regions that include *HOXD3* and *HOXD13*, associated with severe limb and genital abnormalities.[16] Other patients, in whom the entire *HOXD* cluster is deleted, have a mild SPD phenotype attesting to the inherent redundancy in the *HOX* gene network.

HOX GENES AND LUNG DEVELOPMENT

Lung development is dependent upon the coordinated expression of a large number of genes in a manner tightly controlled both in time and space. Expression studies in fetal human and rodent lungs have demonstrated high expression of 3` *Hox* genes in clusters A and B.[17, 18] There is a marked decrease in expression of most of these genes as lung development progresses suggesting that they are involved in the early stages of lung morphogenesis, such as airway branching. However some *Hox* genes, for example *Hoxa5*, continue to be expressed at high levels throughout development and may be required for pulmonary maturation.[19]

Abnormal expression of *HOX* genes is associated with several congenital lung abnormalities e.g. *HOXB5* is over-expressed in both bronchopulmonary sequestration[20] and congenital cystic adenomatoid malformation.[18] These disorders are characterised by deregulated patterns of morphogenesis in primordial lung tissue. Persistent high levels of *HOXB5* expression, beyond the early stages of lung development, result in primitive lung morphology. Altered patterns of *HOX* gene expression have also been demonstrated in several acquired disorders including emphysema, primary pulmonary hypertension and lung carcinomas.[21,22]

Murine models in which *Hox* gene expression has either been reduced or deleted provide strong evidence for the role of these genes in structural development of the respiratory system and regulation of pulmonary surfactant production. The degree of branching morphogenesis is decreased following reduction in *Hoxb5* levels by antisense oligonucleotides.[23] Furthermore, *Hoxa5* knock-out mice develop to full term but die in the early neonatal period due to tracheal occlusion, reduced expression of surfactant proteins and lung pathology similar to surfactant-deficient respiratory distress syndrome in preterm human neonates.[24]

HOX GENES AND LEUKAEMIA

Multiple *HOX* genes of clusters A, B and C, but not D, are expressed in haematopoietic stem cells. Down-regulation or many *HOX* genes occurs as cells within a given lineage differentiate. For example, Care *et al*. demonstrated that peripheral T lymphocytes which were stimulated to proliferate using phytohaemagglutinin showed a rapid induction wave of *Hox* genes from *Hoxb1* to *Hoxb9*, *i.e.* in the 3` to 5` direction.[25]

Perturbation of the process of cell differentiation by reciprocal chromosomal translocations can lead to the development of leukaemia. Such translocations lead to the creation of fusion genes, and may involve individual *HOX* genes or regulators of *HOX* gene activity. Thus translocations involving t[(7;11)(p15;p15)] or t[(2;11)(q31;p15)] have been described in which the *HOXA9* or *HOXD13* genes, respectively, are fused with the NUP98 nucleoporin gene in rare cases of acute myeloid leukaemia (AML). More frequently rearrangements of the mixed-lineage leukaemia gene *MLL1*, a positive regulator of cell specific *HOX* gene expression, have been found associated with aggressive acute leukaemias in both children and adults. Both types of translocation lead to gain of function, affecting the normal processes of differentiation of the pluripotent stem cells or the committed lymphoid or myeloid progenitors by deregulating the *HOX* gene expression patterns.

Rearrangements involving *MLL* and its 39 partner genes identified to date, are associated with approximately 5% of patients suffering from AML and 22% of those with acute lymphoblastic leukaemia (ALL).[26] To investigate the t[(11;19)(p22;q23)] translocation which gives rise to the MLL-ENL fusion protein, commonly found in infant acute leukaemias of both myeloid and lymphoid lineage, Horton *et al,* established a tetracycline-regulable system of MLL-ENL expression in primary haematopoietic cells.[27] Utilising a real-time quantitative PCR system[28] they were able to measure the expression of all 39 murine *Hox* genes and showed for the first time that reduced *Hox* gene expression is specific to loss of MLL-ENL and is not a consequence of differentiation. They concluded that MLL-ENL is required to initiate and maintain immortalisation of myeloid progenitors and may contribute to the development of leukaemia by aberrantly sustaining the expression of a *"Hox* code*"* consisting of *Hoxa4* to *Hoxa11*.

HOX GENES AND CANCER

Numerous studies have been undertaken to examine the differences in *HOX* gene expression between normal and neoplastic tissue, but the functional relationship with the malignant phenotype has remained elusive as reviewed by Abate-Shen.[29] Some investigators have explored the postulate that *Hox* genes expressed during embryogenesis but down-regulated during adult life are re-expressed in neoplasia- the so called "oncology recapitulates ontology" hypothesis. During embryogenesis a fine balance exists between cell proliferation and differentiation which is essential for normal development of the fetus. In contrast in cancer the balance between the two processes goes awry as reviewed by Grier *et al*.[30]

Neoplastic growth in mammary epithelial cells is associated with increased expression of human growth hormone (hGH). Utilising human mammary carcinoma cells, Zhang and colleagues found that hGH production increased the expression and transcriptional activity of *HOXA1*.[31] Furthermore overexpression of *HOXA1* in mammary carcinoma cells resulted in up-regulation of Bcl-2, an anti-apoptotic factor, and increased total cell numbers. Interestingly *HOXA1* also enhanced anchorage-independent cell proliferation and caused oncogenic transformation of the cells, rendering them capable of aggressive tumour formation. Furthermore overexpression of *HOXA1* abrogated the response of the mammary carcinoma cells to daunorubicin. Taken together these observations serve to exemplify the effect of overexpression of a single gene *HOXA1*, and indicate that changes of expression of multiple *Hox* genes may substantially dysregulate cellular processes in neoplasia.

Epithelial ovarian cancers (EOCs) arise from the simple epithelium lining the ovarian surface. Major EOC subtypes show morphological features that resemble müllerian duct-derived epithelia of the reproductive tract. Recently Cheng and colleagues presented strong evidence that lineage infidelity of epithelial ovarian cancers is controlled by *HOXA* genes that specify regional identity in the reproductive tract.[32] They found that the *HOX* genes which normally regulate müllerian duct differentiation are not expressed in normal ovarian surface epithelium, but are expressed in EOC subtypes according to the pattern of müllerian-like differentiation of the cancers. Furthermore overexpression of *Hoxa9, Hoxa10* and *Hoxa11*

gave rise to papillary tumours resembling serous, endometrioid-like and mucinous-like EOCs respectively. These observations support the contention that alteration of expression of genes in the *HOX* network that controls the patterning of the reproductive tract could explain the morphological heterogeneity of EOCs.

CONCLUSIONS

Attempts to understand the role of *HOX* genes in both normal and abnormal development and malignant transformation will be enhanced by the identification of their upstream regulators and downstream target genes. Whereas *MLL* fusion genes have provided some useful insights in the molecular mechanisms involved in leukaemogenesis much work remains to be done to identify specific gene products involved in the *HOX* network which might ultimately become feasible targets for therapeutic intervention. More research is also needed to explore the role of *HOX* genes in developmental processes.

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One hundred years ago

The foundation of the British Museum

Does the British public, or even the medical profession, fully realize that the nation owes that magnificent institution, the British Museum, to the liberality of a doctor? Its true begetter was Sir Hans Sloane, a fashionable physician of the eighteenth century. . . . Hans Sloane, who was of Scottish descent, was born in County Down in 1660. Even in boyhood he collected specimens, and the taste grew upon him till it became the ruling passion of his life. Natural history led him to medicine, which in those spacious days comprehended all science within itself. . . . With a rapidity that seems enviable to us whose professional lot lies in more arduous times, Sloane was elected a Fellow of the Royal Society in 1685, and was admitted to the Fellowship of the College of Physicians in 1687. In that year there came to him an offer to go to Jamaica as physician to the Duke of Albemarle, who had been appointed Governor of that island. . . . Within eighteen months the Duke died, and his physician's nominal occupation was gone. Sloane's real occupation, however, had been the gathering of materials for the museum which was his lifework. He returned to England in 1689, loaded with the spoils of his expeditions . . . and became a highly prosperous physician. The Court and the aristocracy, we are told, had the "greatest confidence in his prescriptions." Queen Anne took counsel of him; George the Second made him the keeper of the royal constitution; George the First had previously made him a baronet and appointed him Physician-General to the Army. The University of Oxford gave him its doctor's degree in 1701, and he was President of the College of Physicians for sixteen years. He was appointed Secretary of the Royal Society in 1693, and succeeded Isaac Newton in the Presidency of that body in 1727. . . . Throughout his life Sloane went on adding to his museum, and he accumulated a vast collection, which included books, manuscripts, pictures, medals, and coins, as well as objects of natural history. He retired from practice in 1721, and died in 1753 at the age of 93 leaving in his will directions that his museum, which was valued at £50,000, should be offered to the nation for the sum of £20,000. The offer was accepted by Parliament, and the collection formed the nucleus of the British Museum, which was opened to the public in 1759. During the greater part of his professional life Sloane lived in Bloomsbury Square, close to the site of the future British Museum. Towards the end of his life he retired to Chelsea, where be had purchased a manor house and land, which is now covered by the stately mansions of the Cadogan estate. One of his daughters became the wife of the second Lord Cadogan, and the physician's own name is perpetuated in Sloane Street and Hans Place. If Sloane was wealthy, he was also liberal. He gave the Apothecaries' Society their famous Physic Garden at Chelsea; he took part in the establishment of the Foundling Hospital, and he was never deaf to any deserving appeal made in the name of charity.

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Review

Non-variceal upper gastrointestinal bleeding

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INTRODUCTION

Non-variceal upper gastrointestinal bleeding (UGIB) remains a common and challenging emergency for gastroenterologists and general physicians. The annual incidence is 50 to 150 per 100,000 of the population, and, even though there have been significant improvements in endoscopic and supportive therapies, the overall mortality stubbornly remains around 10%, and may even reach 35% in hospitalised patients with serious co-morbidity. Patients aged over 80 years of age now account for around 25% of all UGIB and 33% of UGIB occurring in hospitalized patients and therefore tend to account for much of the poor outcome of this condition.[1]

The causes of non-variceal UGIB are shown in (*Table I*), although the commonly quoted figure of 50% for peptic ulcer bleeding may be overestimated. In a recent large CORI (Clinical Outcome Research Initiative) study of UGIB, peptic ulcer was the probable cause of UGIB in only 20% of cases.[2] The incidence of peptic ulcer disease is expected to continue to decline with more widespread helicobacter pylori eradication and proton pump inhibitor (PPI) usage.

RISK ASSESSMENT AND INITIAL MANAGEMENT

Several clinical scoring systems e.g. Rockall score, the Baylor bleeding score, the Cedars-Sinai Medical Centre Predictive Index and the Blatchford score, have been developed to direct appropriate patient management and enable cost effective use of resources. These systems weigh a combination of clinical, laboratory and endoscopic variables to produce a score that predicts the risk of mortality, recurrent haemorrhage, need for clinical intervention or suitability for early discharge. Factors commonly associated with poor outcome from UGIB may be related to the patient's presentation and co-morbidities, or to the behaviour of the ulcer (*Table II*). Risk stratification using non-endoscopic parameters has the advantage that it can be performed readily on initial presentation in the emergency department, and appropriate initial risk assessment is still possible, even if early endoscopy, which requires skilled staff and resources, is not always available.

Inclusion of endoscopic stigmata of recent haemorrhage (SRH) that relate to increased risk of re-bleeding and death into scoring systems increases the sensitivity for predicting patients at high or low risk compared to non-endoscopic assessments.[3-5] High risk lesions such as actively bleeding ulcers, non-bleeding visible vessels (NBVV) and adherent clots (*Table III*) require effective aggressive intervention to reduce re-bleeding which is associated with a 5-16 fold increase in mortality.[6,7] The re-bleeding rate of ulcers with a clean base or red or blue spots are low and endoscopic intervention is usually not recommended.[8-10] In fact, early endoscopy-based triage may permit safe and early discharge of "low risk" patients with no increased rate of re-bleeding or mortality.[11]

Endoscopic SRH, particularly NBVV and flat pigmented spots, can be difficult to differentiate.[12] Doppler assessment is unlikely to be widely available for some time because of technical and resource

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TABLE I

Causes of non-variceal UGIB

Diagnosis	*Incidence [%]*
Peptic ulcer	20 – 50
Mallory-Weiss tear	15 – 20
Erosive gastritis/ duodenitis	10 – 15
Oesophagitis/ oesophageal ulcer	5 – 10
Malignancy	1 – 2
Angiodysplasia/ vascular malformations	5
Other	5

TABLE II

Predictors of adverse outcome from UGIB

Patient:	Shock
	Melaena
	Significant fresh blood in vomit, gastric aspirate or rectum
	Sepsis
	Anaemia at presentation
	Cardiac/ liver/ renal disease
Ulcer:	Large ulcer size
	Persistent bleeding despite endoscopic therapy
	Recurrent bleeding

TABLE III

Forrest classification of peptic ulcers in UGIB

Forrest class	*Type of lesion*	*Risk of rebleed if untreated [%]*
Ia	Arterial spurting	100
Ib	Arterial oozing	17-100
IIa	Visible vessel	8-81
IIb	Sentinel clot	14-36
IIc	Haematin covered flat spot	0-13
III	No stigmata	0-10

limitations, but may be effective at differentiating between patent vasculature and pigmented spots.[13] In this study there was agreement between the endoscopic Forrest classification and Doppler assessment in only 58% of cases, suggesting that Doppler was more sensitive at detecting high-risk lesions. Re-bleeding, requirement for surgery and mortality rate were all significantly lower in the Doppler-assessed endoscopically treated group.

Resuscitation and management of medical co-morbidities, often in intensive care or high dependency, remains the mainstay of the initial management of patients prior to endoscopy. The presence of blood-stained nasogastric aspirate can be used to predict the presence of high risk lesions and nasogastric tube insertion should be considered for some patients.[14] The role of endotracheal intubation remains controversial; the benefits are easier endoscopy and reduced risk of massive aspiration in patient with a reduced level of consciousness, but evidence of a reduction in acquired pneumonia or cardiopulmonary events is lacking.[15,16]

ENDOSCOPIC MANAGEMENT

Endoscopic intervention reduces the rate of re-bleeding, need for surgical intervention and mortality in high risk patients with UGIB.[17] The optimum timing of endoscopy remains a balance between clinical need and resources, but endoscopy performed within 24 hours of hospital admission has been shown to reduce the length of hospital stay and may reduce the likelihood of re-bleeding or surgical intervention in the highest risk patients.[18] Not infrequently, excessive blood in the upper GI tract may preclude an accurate endoscopic diagnosis in a small number of patients. These patients have a significantly higher rate of complications, rebleeding, need for surgery and mortality.[19] Bolus administration of intravenous erythromycin prior to endoscopy has been shown to clear the stomach of blood, increase the likelihood of successful haemostasis and reduce the need for subsequent interventions.[20,21]

Most haemostatic techniques are equally effective when used alone, although doubt has been cast on the value of "stand alone" therapy with adrenaline injection. Recent focus has been directed towards combination therapies and mechanical means of homeostasis. Injection of dilute (1:10 000) adrenaline in 1ml aliquots around the bleeding points has traditionally been the main method of haemostasis in Europe, whereas application of heat is the preferred strategy in the United States. Adrenaline injection results in haemostasis in up to100% of patients with bleeding peptic ulcers, probably by a combination of vascular tamponade and vasoconstriction, with a concomitant reduction in re-bleeding rates from 40 to 15%.[22,23] The dose of adrenaline required to achieve haemostasis is variable but larger volumes (13-20ml vs. 5-10ml) in high risk patients (Forrest type I or IIa lesions) results in less re-bleeding (15.4% vs. 30.8%).[24] Although injection with adrenaline is successful in achieving initial haemostasis, 15-36% of patients rebleed, a figure that is unacceptably high.[25,26]

Sclerosants such as ethanol, polidocanol and ethanolamine are equally effective as adrenaline but carry more risk.[25,27-29] In one study, ethanol injection alone was shown to have a re-bleeding rate as low as 4%;[30] however, most other published studies have achieved similar haemostasis to adrenaline alone. Combination therapy with adrenaline and ethanol may improve haemostasis and shorten hospital stay for patients with spurting haemorrhage.[28]

The evidence for thrombin injection is mixed with differing reports of effect on clinical outcomes.[31-33] Repeated daily injection of fibrin glue following treatment with dilute adrenaline in patients with active bleeding or NBVV until the ulcer base is clean or covered is expensive but reduces re-bleeding although not mortality rates.[34]

N-butyl-2-cyanoacrylate (Histoacryl) injection has been shown to be effective for control of variceal bleeding,[35] but its role in non-variceal UGIB remains uncertain. In a small study of 32 patients with bleeding ulcers, Histoacryl injection was no more effective than injection with dilute adrenaline.[25] More recently, Lee *et al* demonstrated significantly lower re-bleeding rate for patients with Forrest type Ia lesions treated with Histoacryl compared to injection with hypertonic saline-adrenaline injection.[36] However, there was no overall benefit in the use of Histoacryl with regards to haemostasis rates, emergency surgery or mortality. Arterial embolisation is a recognized complication of this treatment and means that this therapy is recommended as a measure of last resort because of potentially fatal adverse effects.

In contrast to injection techniques, thermal haemostasis is achieved by compression of the artery during heating (coaption) and/or the

effect of heat on tissue. The only non-contact thermal techniques currently available are Argon Plasma Coagulation (APC) and laser (Nd:YAG). APC involves conduction of a high frequency electrical current through a beam of ionized argon gas, resulting in superficial tissue damage and coagulation. A prospective observational study of APC in 254 patients with non-variceal UGIB revealed initial haemostasis rates of 75.9% and re-bleeding rates of 5.7%.[37] The addition of a second haemostasis technique increased successful haemostasis to 99.6%. The only comparative randomised trial involving APC alone with heater probe was underpowered, although rates of haemostasis, rebleeding, emergency surgery and 30 day mortality were similar for the two techniques.[38] A larger prospective randomised study of dual therapies for bleeding peptic ulcers showed no significant difference in primary haemostasis, procedure duration, re-bleeding, requirement for surgery, 30-day mortality or ulcer healing at 8 weeks between treatment with adrenaline and heater probe versus adrenaline and APC.[39] ND:YAG laser therapy has been shown to be as effective than injection with adrenaline-polidocanol,[40] but, due to technical constraints of the technique, laser therapy is not routinely used in the management of non-variceal UGIB.

In contrast to APC and laser, Bipolar Electrocoagulation (BPE) and Heater Probe Thermocoagulation (HPT) use thermal contact to achieve haemostasis by compression of the vessel and coaption. BPE devices sometimes include an injector/irrigator component (e.g. Gold probe, Boston Scientific, MA), which allows injection of adrenaline or irrigation of the lesion. BPE reduces the re-bleeding rate when compared with normal saline injection in high risk bleeding ulcers,[41] and compared to medical therapy when used in combination with adrenaline in Forrest IIb ulcers.[42] Combination therapy with HPT and adrenaline in the treatment of actively bleeding peptic ulcers resulted in haemostasis in up to 98.6%, with re-bleeding in 8.2%,[43] although added benefit is confined to high risk lesions.[26] When used alone, HPT was not superior to combination treatment with adrenaline and polidocanol in patients with Forrest type I, IIa and IIb ulcers.[44] There is no incremental benefit of adding thrombin to HPT in patients with bleeding peptic ulcers with regards to haemostasis, re-bleeding rates, requirement for surgery, adverse events or mortality.[45]

Mechanical haemostasis with endoloops or clips, e.g. the Hemoclip (Teleflex Medical, PA), has an increasing role in the control of non-variceal UGIB. Endoclips are deployed on a visible vessel to achieve vascular compression and can achieve homeostasis in up to 100% of cases.[46] Comparative studies suggest lower re-bleeding rates than adrenaline injection,[47] ethanol[48] or saline/adrenaline injection.[49] The additional benefit of adrenaline with a mechanical method is unclear,[50] although one randomised comparative study of combination epinephrine-polidocanol injection and Hemoclip versus Hemoclip alone for bleeding peptic ulcers showed clipping to be inferior to combination therapy.[51] Two small studies have evaluated Hemoclips for control of bleeding due to Dieulafoy's lesion, demonstrating a trend towards reduction in the need for repeat procedures.[52,53] Hemoclips can be technically difficult to apply if the ulcer is relatively inaccessible, for instance high on the gastric lesser curve or on the posterior duodenal wall. In fact, application of a clip with successful haemostasis in either of these locations has been as low as 30% in published series. Rotatable, versatile endoclips that can deploy multiple and/or stronger clips are needed.

Endoscopic band ligation (EBL) is currently technically easier to use than endoclips and has been shown to be safe and effective for control of small lesions in a small series of acute peptic ulcer bleeding[54] and with bleeding due to Dieulafoy's lesions.[55]

ADHERENT CLOTS

Subgroup analysis of patients with adherent clots in early endoscopic studies demonstrated little or no benefit of endoscopic therapy for ulcers with adherent clots.[56-59] However, a subsequent meta-analysis showed significant benefit in the group of patients with active bleeding or NBVV.[17] To further address this issue, a recent controlled trial in patients with severe UGIB and adherent clot randomised 32 patients to "medical" or combination endoscopic therapy following clot removal.[42] Endoscopic therapy consisted of adrenaline injection, shaving of the clot with cold guillotine and BPE of the underlying ulcer SRH. Combination endoscopic therapy was safe and associated with less early re-bleeding compared to medical therapy, although the small sample size, unexpectedly low re-bleed rates in the combination therapy group [0%] and unequal distribution of confounding

factors in the two groups means that caution needs to be taken when extrapolating the results. Also, even in clinical trials there tends to be significant intra-observer variation in the labelling of SRH and the degree clot "adherence" depending on the method of removal employed.[60,61] For instance, in one study five minutes of irrigation via a bipolar probe was found to remove clot in 43% of patients, whereas irrigation with a syringe via the endoscope channel only removed 9% of clots.[62] Placement of a transparent irrigating hood over the endoscope tip that allows forceful irrigation yet maintains a reasonable endoscopic view may prove useful for clot removal and may reduce total procedure time.[63,64] Although the optimum technique for clot removal is unclear, clot removal should be attempted as high risk SRH may be exposed in the underlying ulcer in around a further 30% of patients. Current practice among experienced endoscopists involves targeted irrigation and possibly snare guillotine of an adherent clot followed by treatment of the underlying lesion.[42]

Finally, a variety of endoscopic suturing devices have been developed primarily for gastroplication in patients with gastro-oesophageal reflux. Endoscopic suturing for UGIB management is an attractive prospect, but further development of new devices is required before endoscopic suturing for UGIB can be widely adopted.

"SECOND-LOOK" ENDOSCOPY AND ENDOSCOPIC RE-TREATMENT

Routine "second look" endoscopy, in the absence of established rebleeding or patient instability, has gone out of vogue after studies showed no benefit with regards to clinically significant outcomes for unselected patient populations,[65] although there may be a role in high risk patients.[66,67] Repeat therapeutic endoscopy may be indicated (depending on local endoscopic and surgical expertise) if there is clinical evidence of re-bleeding or if the initial therapeutic procedure was unsuccessful or partially successful.[10,68] In expert hands, endoscopic re-treatment is associated with fewer complications and no increased mortality risk compared to surgery.[69]

ACID SUPPRESSION

In vitro studies of the effect of gastric pH on platelet aggregation and coagulation provide the rationale for acid suppression in UGIB. If gastric pH is maintained above pH6 (by infusional PPI), platelet aggregation is optimized and fibrinolysis relatively inhibited, thereby potentially improving the likelihood of clot stability at an ulcer site. Individual trials of H2 receptor antagonists (H2RA) have generally failed to demonstrate a clinical benefit in UGIB,[70] although one meta-analysis has suggested a weak effect.[71] A recent consensus statement suggested that the available data on H2RAs does not support their use in ulcer bleeding.[10]

Several studies have evaluated intravenous proton pump inhibitors (PPI) for non-variceal UGIB; unfortunately, these trials are heterogeneous in terms of patient population, regimen of PPI and timing/type of endoscopic intervention, making comparisons difficult. However, meta-analyses of PPIs in non-variceal UGIB have now shown a benefit in terms of re-bleeding and need for surgery, but not for mortality.[2,72-75] The usual intravenous regime for omeprazole therapy in the more robust studies was an 80mg intravenous bolus of omeprazole followed by a continuous infusion of 8mg/hour for up to 72 hours. This regimen resulted in a reduction of rebleeding from 22.5% to 6.7%, representing a NNT of 6 to prevent one person bleeding within 30 days.[74] Subsequent studies using lower intravenous doses of omeprazole[76] or high dose oral omeprazole[77-79] also demonstrated a reduction in rebleeding rate. Further study is required to determine the optimum dose, route of administration and dosing schedule of PPI in UGIB. In the meantime, and with the evidence currently available, it seems appropriate to treat patients with high risk peptic ulcers with intravenous or high dose oral PPI after endoscopic therapy has been administered.

FUTURE DIRECTIONS IN ENDOSCOPY

Endoscopic suturing has already been mentioned earlier in this article. Currently available suturing devices are somewhat awkward to use and are not suitable for management of bleeding, although the principle of suturing peptic ulcers to control bleeding is well established in surgery. Further development is required before suturing becomes possible in the endoscopic sphere.

The risks associated with application of heat to bleeding lesions are due to the requirement for tissue contact, lack of control of depth of injury and difficulty in treating multiple or diffuse lesions. Gastric freezing to achieve haemostasis during variceal and non-variceal bleeding has been possible for several decades although evidence of therapeutic

benefit from the original techniques was lacking and delivery systems were clumsy.[80] However, recent delivery of new liquid nitrogen or nitrous oxide delivery systems has made endoscopic cryotherapy feasible although still experimental.[81-83] Cryotherapy using nitrous oxide relies on the Joule-Thompson effect: rapid expansion of compressed gas results in a drop in temperature of the gas. The resultant "no contact" therapy has been tested in proctitis and may also be possible in upper gastrointestinal lesions.

CONCLUSIONS

Non-variceal UGIB remains a significant cause of morbidity and mortality. Patients at high risk can be identified by risk assessment scoring systems that include clinical and endoscopic variables. Adequate resuscitation, aggressive endoscopic therapy and PPI therapy are effective for achieving haemostasis and preventing adverse clinical outcomes, although the effect on mortality is low. Multidisciplinary care, including endoscopists, surgeons, intensivists and radiologists early in the assessment and decision stages, is vital to optimise care.

CONFLICT OF INTEREST

The authors have no declared conflict of interest.

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Review

Goblet Cell Carcinoids of the Appendix

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INTRODUCTION

Carcinoid tumours are rare, but are the most common gastrointestinal neuroendocrine tumours. We review the diagnosis, pathology and management of goblet cell carcinoid of the appendix using an illustrative case history.

ILLUSTRATIVE CASE HISTORY

A 21-year-old man was admitted with a 24-hour history of right iliac fossa abdominal pain associated with nausea and vomiting. There was no history of diarrhoea or weight loss, and no family history of inflammatory bowel disease. He described a one-year history of right iliac fossa pain, colicky in nature, lasting for three to four days at a time and recurring every three months. This was his second hospital admission, the first episode settling with conservative management. On retrospective questioning he denied any symptoms suggestive of carcinoid syndrome.

On examination he was apyrexic with rebound tenderness in the right iliac fossa. Blood investigations revealed a white cell count of $19.3x10^9$/L and a C-reactive protein of 260mg/L. Abdominal sonography was performed in view of the recurrent nature of the pain and the possibility of Crohn's disease. This showed multiple fluid filled loops of bowel in the right iliac fossa but no direct visualisation of the appendix and no thickened loops of small bowel. Following a short period of observation we proceeded to appendicectomy, which confirmed an acutely inflamed appendix with purulent free fluid in the pelvis. There were no post-operative complications.

Histopathology confirmed acute appendicitis. In addition, within the tip of the appendix there was a 4mm tumour composed of small glandular acini and individual cells with eosinophilic and focally granular cytoplasm (*figs 1* and *2*). The tumour extended through the muscularis propria of the appendix into serosal fat, reaching 1.5mm from the serosal surface. The tumour was positive with the epithelial markers CAM 5.2, CEA and neuroendocrine marker Neurone Specific Enolase. The tumour cells failed to stain with the neuroendocrine marker Chromogranin. Overall the histological and immunohistochemical features were those of a goblet cell carcinoid tumour of the appendix tip with co-existing acute appendicitis.

Post-operatively a plasma neuroendocrine profile, including plasma Chromogranin A, and urinary levels of 5-hydroxyindoleacetic acid (5-HIAA) and 5-hydroxytrptyphan (5-HT) were within normal limits. A CT scan of abdomen and pelvis and an octreotide radioisotope scan did not reveal any metastatic disease (*Fig 3*). Despite our patient having a tumour size of less than 1 cm, it was felt that in view of the presence of mesoappendiceal extension and his younger than average age at presentation, a right hemicolectomy was justified to decrease his risk of delayed local and distant recurrence, and to study the regional lymph nodes. He proceeded to a laparoscopic right hemicolectomy, the pathology of which did not reveal any residual disease and at twelve month follow up he remains disease free.

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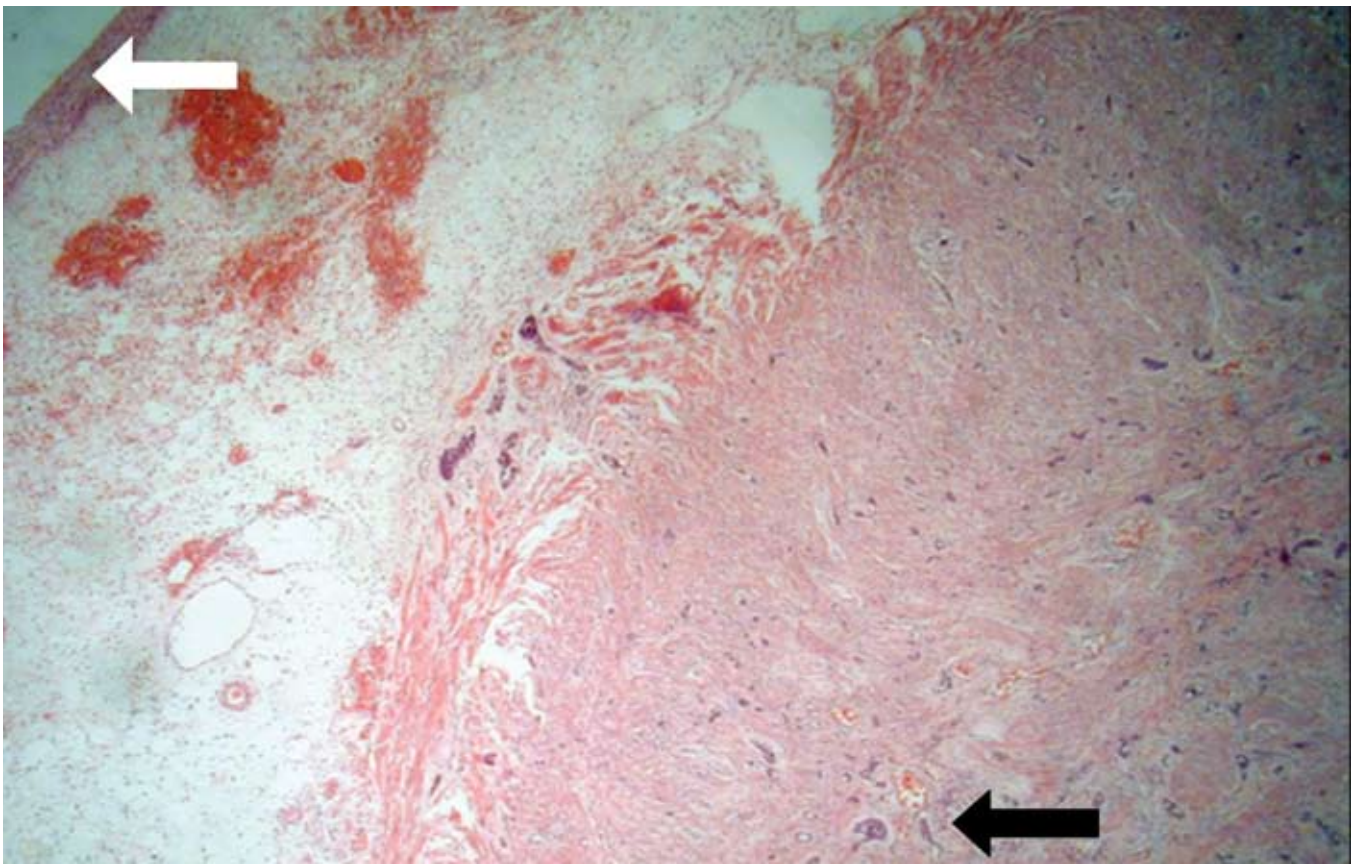

Fig 1. Haematoxylin-eosin slide showing tumour infiltrating wall (dark arrow) and a serosal reaction (white arrow).

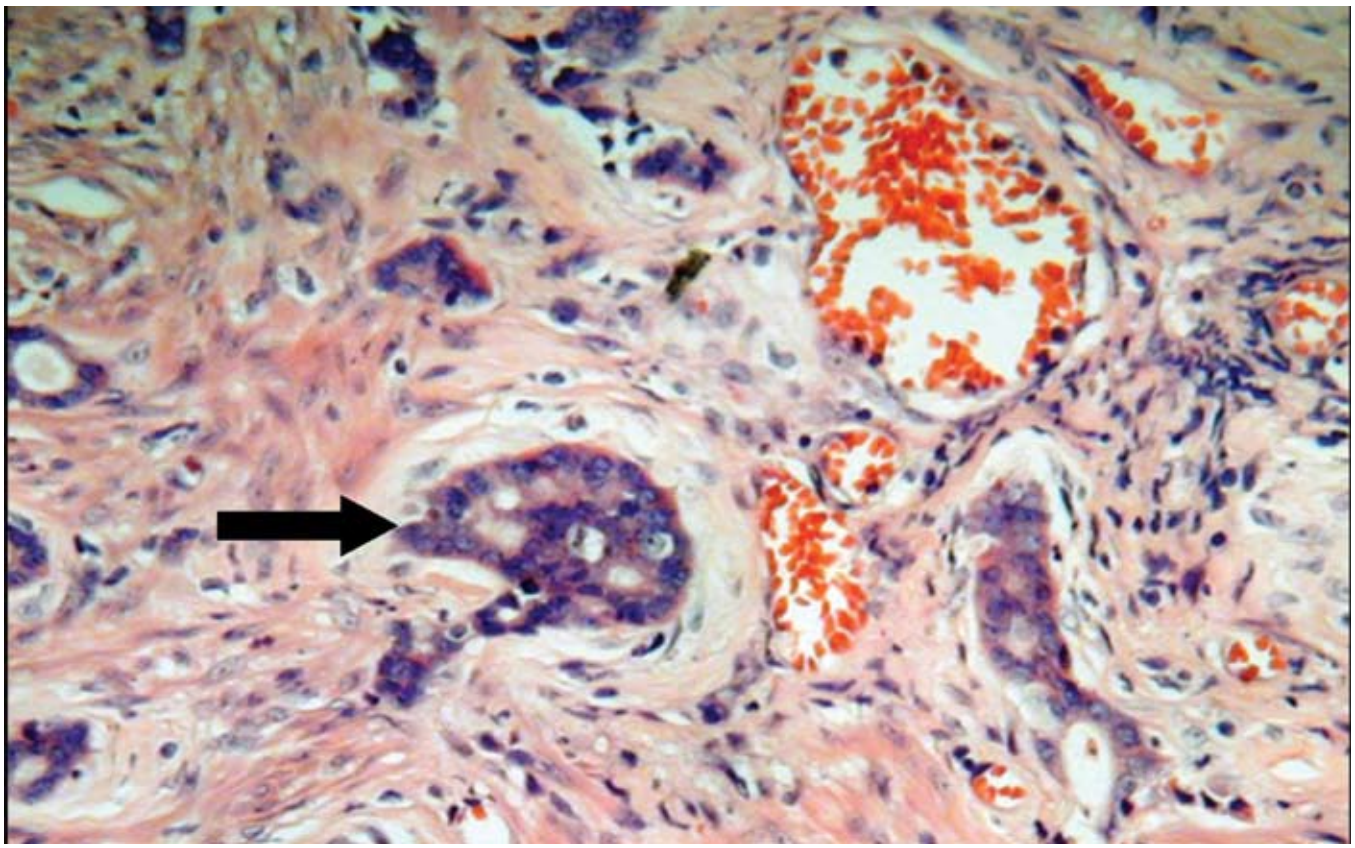

Fig 2. Haematoxylin-eosin slide showing tumour cells infiltrating through the muscularis propria (black arrow).

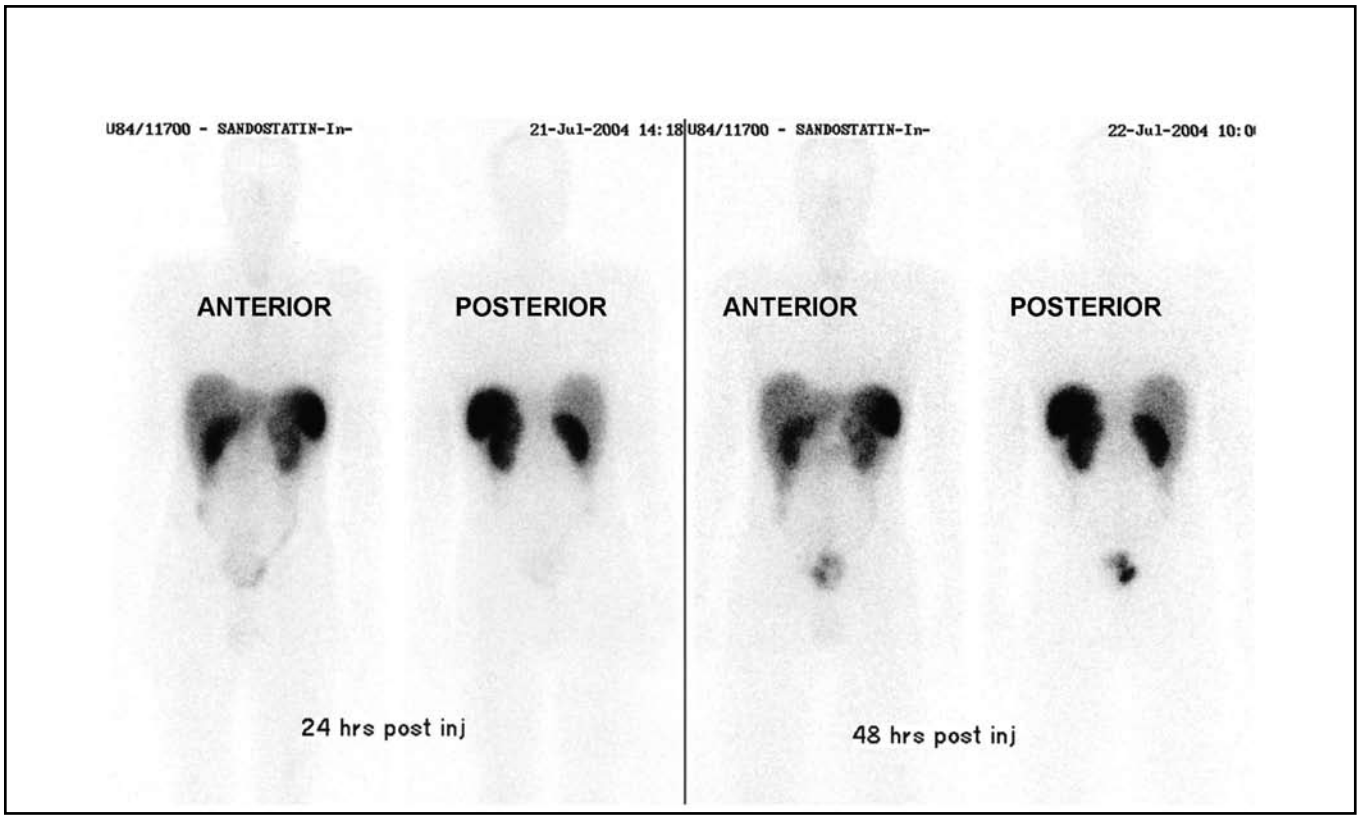

Fig 3. The normal octreotide scan of the patient looking for evidence of metastatic disease. Normal uptake is seen in the liver, kidneys and spleen, 24 and 48 hours post injection of radioisotope.

EPIDEMIOLOGY

Carcinoid tumours are rare, but are the most common neuroendocrine tumours.[1,2] In a series of 13,715 carcinoids reported to the Surveillance, Epidemiology, and End Results programme of the National Cancer Institute, the majority were located in the gastrointestinal tract (67.5%) and in the bronchopulmonary system (25.3%).[3] Carcinoid tumours are the most common neoplasms arising in the appendix, accounting for about 85 per cent of all appendiceal tumours seen in surgical pathology. The prevalence of appendiceal carcinoid is between 0.3% and 0.9% in patients undergoing appendicectomy. The recent study of McCusker *et al*,[4] reported 227 goblet cell carcinoids (13.8%) among 1645 appendiceal malignancies, along with 613 cases (37%) of mucinous adenocarcinoma, the most frequent diagnosis. These epidemiological studies suggest an average diagnostic age of between 38 and 49 years for malignant lesions, although goblet cell carcinoids tend to present at a later age of about 52 years.

Data from the Northern Ireland Neuroendocrine Database (*Table I*) includes 517 carcinoid tumours of the appendix, midgut and lung diagnosed since 1975. 114 of these were appendiceal carcinoids, 16 of which were goblet cell in nature. The age at diagnosis and the presence of metastatic disease is shown in the table below. The mean age at diagnosis was 54.75 years ±4.57 SEM. Four of the 16 patients have since died. The only patient with hepatic metastases died from recurrent goblet cell carcinoid tumour, ten years following her appendicectomy and subsequent right hemicolectomy.

MALIGNANT CHANGE

Tumour characteristics of all appendiceal carcinoids that predict aggressive behaviour include tumour size, histological subtype and mesoappendiceal involvement. Moertel *et al*[5] first indicated in 1968 that metastatic disease from lesions smaller than 2cm was unlikely and consequently considered that the risk of metastatic disease in tumours less than 2 cm was sufficiently low to treat them by appendicectomy alone. In one study mesoappendiceal extension correlated with nodal metastases and tumour size.[6] In a series of 92 appendiceal carcinoids they reported two patients with 1cm tumours with nodal spread, both of

TABLE I

Patients diagnosed with appendiceal carcinoid from the Northern Ireland Neuroendocrine Database

Patient	*Age at Diagnosis*	*Metastases*
1	78	No
2	73	Yes - mesentery
3	39	No
4	56	No
5	62	Yes - small bowel
6	46	No
7	15	No
8	65	No
9	22	No
10	74	No
11	59	No
12	60	No
13	47	No
14	67	Yes - hepatic
15	43	No
16	70	No

which had mesoappendiceal involvement. Serosal involvement is present in about 70% of malignant carcinoid tumours but this has been shown to be unrelated to outcome in several studies.

DIAGNOSIS

The diagnosis of goblet cell carcinoid of the appendix is essentially made on histological examination after surgery, which is one of the clinical hallmarks of appendiceal carcinoids. This neoplasm has also been described as an adenocarcinoid, crypt cell carcinoma and goblet cell carcinoma. The preferred term, goblet cell carcinoma, was first coined in 1974 by Subbuswamy *et al*.[7] As the nomenclature implies, these tumours possess morphological features suggestive of both carcinoid and glandular differentiation. Appendiceal carcinoids are usually divided into three histological patterns; the typical argentaffin enterochromaffin (EC)-cell carcinoid, the non-argentaffin L-cell carcinoid and the more recently described goblet cell carcinoid. The goblet cell carcinoids show striking differences in histology from the other two varieties but more importantly, they are biologically more aggressive lesions.[8]

Goblet cell carcinoids behave differently biologically and their outcome is similarly different. In the study by McCusker *et al*[4] only 17% of 227 patients with goblet cell carcinoma had positive lymph nodes, but in 65% there was spread through the serosa, invasion of the mesoappendix, or involvement of peritoneum or adjacent organs. Serosal involvement and mesoappendiceal extension are therefore more predictive of outcome than lymph node status in goblet cell carcinoids. In the Surveillance, Epidemiology, and End Results programme of the National Cancer Institute, patients with malignant carcinoid had a better overall survival rate of more than 80% at 10 years compared with goblet cell carcinoids which had a 60% 10 year survival rate. The survival rate for goblet cell carcinomas was not significantly worse than that for malignant carcinoid when adjusted for age and extent of disease at presentation.[4]

INVESTIGATION

Most patients do not require any further procedure or investigations relating to an appendiceal carcinoid. Those patients with tumours larger than 2cm, incomplete resections, metastatic disease or goblet cell carcinoids require estimation of plasma Chromogranin A concentration and 24-hour urinary levels of 5-hydroxyindolacetic acid along with CT scanning and octreotide scintigraphy.[111] In-labelled octreotide scintigraphy is the most sensitive imaging modality in the diagnosis and staging of metastatic disease. The isotope scans are performed more than eight weeks after initial surgery to avoid false positives and therefore any unnecessary further surgery.[9]

Chromogranin A is a secretory protein present in vesicles of neuroendocrine cells and its ubiquitous presence in these cell types makes it a suitable circulating marker of neuroendocrine neoplasms, the levels being raised in 80-100% of patients with these neoplasms.[10] It is currently the most important blood marker available for carcinoid tumours, with levels corresponding to tumour load and levels above 5000 µg/l predicting a poor outcome.[11]

PROGNOSIS AND SURGICAL MANAGEMENT

Patients with appendiceal carcinoids have a good prognosis overall with the vast majority cured by

TABLE II

Indications for right hemicolectomy

1. All lesions larger than 2cm in diameter
2. Histological evidence of mesoappendiceal extension
3. Tumours at the base of the appendix with positive margins or involvement of the caecum
4. High-grade malignant carcinoids
5. Goblet cell carcinoids.[13]

simple appendicectomy as the definitive procedure. In at least 70% of the cases encountered by most general surgeons, patients with a tumour less than 1 cm will almost certainly have no future problem from the lesion. Patients with goblet cell carcinoid tumours however fall into a different category, as these tumours are more aggressive than classic appendiceal carcinoids. They are characterized histologically by wide invasion of the mesoappendix, and clinically by delayed local recurrence and distant metastases. As the vast majority of these tumours are detected post-operatively, management centres on the need for re-operation as a right hemicolectomy is often curative.[12] In patients with goblet cell carcinoids relative indications that may favour further surgery are: (1) angioinvasion as an isolated finding, (2) tumours at the base of the appendix with clear margins, greater than 1cm but less than 2cm in diameter and (3) mucin-producing tumours.[13]

CONCLUSIONS

When considering appendiceal carcinoids as a whole, acceptable indications for a right hemicolectomy are shown in Table II. Careful diagnosis and management of goblet cell carcinoid tumours will hopefully improve prognosis in patients with this rare entity.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

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Paper

The evolution of sites of surgery

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SUMMARY

The shift to ambulatory surgery has taken decades. The history and causation of the move are complex. Key enablers are recounted. The complex interchange of ideas, and physicians, between Belfast and Boston was important in the development of relevant facilitating standards. US and UK governmental and hospital statistics in the increase of ambulatory surgery are presented. The transition of surgery away from hospitals was not all plain-sailing. Insurance companies, governments and hospital administrators hindered and then acquiesced. The shift to ambulatory surgery has not resulted in increased patient morbidity and mortality.

INTRODUCTION

Five cities, Belfast, Boston, Los Angeles, Phoenix, and Washington, DC have been the sites of major successful efforts to change the vast majority of surgery and anaesthesia from requiring the patient's use of hospital beds (*Fig. 1*). The enabling causes are political, including patient and family preference, legislation, improvement in surgical and anaesthetic equipment and the advent of new drugs. We will recount the key enablers.

HISTORY

Milne Barbour, President of the Royal Victoria Hospital, Belfast, at social events in 1940-1942, described the work of Robert Campbell and Andrew Fullerton. These accounts were of great interest to the surgeons of Harvard's 5th General Hospital, especially Thomas Lanman from Boston's Children's Hospital, stationed at Musgrave Park.[1,2]

Elected honorary assistant surgeon to the Belfast Hospital for Sick Children in 1897 and full surgeon one year later, Robert Campbell did much to reinstate the role of ambulatory surgery especially in the treatment of inguinal hernia. His results and commentaries as published in the British Medical Journal in 1899[3] and five years later in the Lancet[4] led to Nicoll's description of his outpatient surgical results in Glasgow in 1909.[5,6] Campbell's successor, Andrew Fullerton, in 1913, reported to the Board of the hospital that in the previous fifteen years there "had never been a death following an operation in the extern department."[7]

In the 1950s and for the next thirty-five years, John Dundee and his co-workers, chiefly in Belfast, followed on the work of John Lundy of the Mayo Clinic[8] and Ralph Waters of the University of Wisconsin[9] in facilitating the introduction, and understanding of intravenously administered, short-acting anaesthetics.[10,11] Dundee, for intellectual and family reasons, often visited Boston and lectured at Harvard.

BOSTON'S MISSED OPPORTUNITY

In 1919, Ralph Waters reported the successful experience of a downtown anaesthesia clinic in Sioux City, Iowa.[9] From Kansas City, where he described a free-standing outpatient surgical

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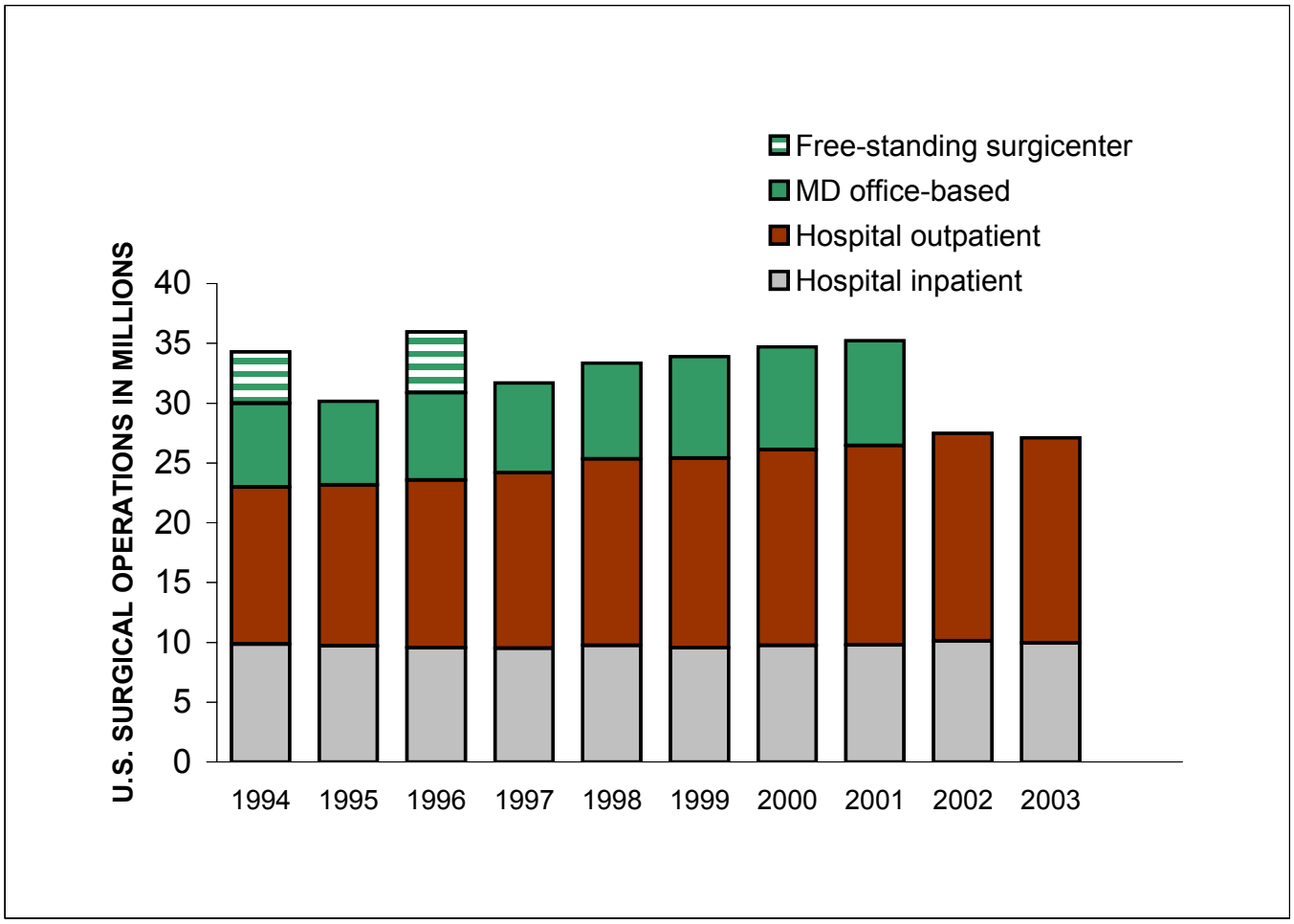

Fig 1. The total number of U.S. surgical operations has continuously increased. The rate of surgical procedures performed on hospital inpatients has slowly declined among the US resident population as this population has increased over the last decade. Hospital-based ambulatory surgery, MD office-based and free-standing surgicenter surgery continue to increase in volume. US Federal Statistics for surgicenter surgery only exist for 1994 and 1996; their collection will be resumed in 2006. In the US there are currently about 4,600 free-standing ambulatory surgicenters in operation, an increase of about fifty percent over the past five years. Almost nine million surgicenter operations (not represented in fig. 1) are projected for the US in 2005; the US federal figure was 5.1 million in 1996 (see "striped" data). Reliable data for MD-office based surgery are not yet available for the years after 2001.

service in 1923,[12] Waters was called to establish the first autonomous academic department of anaesthesia in a University at Madison, Wisconsin. This department was so successful that a Harvard Search Committee to fill the Henry Isaiah Dorr Chair in Anaesthesia Research called Waters to the Massachusetts General Hospital. While Professor Elliott Cutler,[2] Surgeon-in-Chief, Peter Bent Brigham Hospital, was showing Waters around, a chance encounter in the corridor with the in-situ Surgeon-in-Chief, Professor E (Pete) Churchill eventually led to Harry Beecher's appointment to the Dorr Chair.[12] Beecher was no champion of free-standing anaesthesia, and on more than one occasion threatened to fire a colleague who was planning to moonlight on such an enterprise. Neither Beecher nor his department was interested in the development of short-acting anaesthetics. He did, sometimes, in his required departmental lectures, mention Morton's advice on outpatient anaesthesia.[13]

In 1966, Beecher asked John Hedley-Whyte if he would like to be nominated as a United States delegate to the International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC). At the Inaugural meeting of ISO Technical Committee 121 on Anaesthetic and Respiratory Equipment in London the shortcomings in performance and

lack of standardization were cataloged and a start made on writing performance standards for equipment used in anaesthesia, intensive therapy, ENT surgery and chest medicine. The US efforts had begun in 1956 with the formation of American National Standards Institute Committee Z79. The Z79 Committee, because of need for insurance coverage, metamorphosed by 1983 to American Society for Testing and Materials International (ASTM) Technical Committee F29 on Anesthetic and Respiratory Equipment. A similar committee for surgical instruments and equipment, ASTM Technical Committee F4, was founded in 1962, and continues its work today.[14,15] By October 1968, a disposable anaesthesia system and swivel Y-connector to the tracheal tube or facemask meeting ANSI Z79 and ISO TC121 specifications was in use for ambulatory surgery.

THE HARVARD MEDICAL SCHOOL

In 1967, Hedley-Whyte became the second, to Beecher, tenured Harvard Anaesthesia Professor. He was moved from the Massachusetts General Hospital to Boston's Beth Israel Hospital by the President and Fellows of Harvard College, at least in part to help recovery from a scandal involving anaesthesia-associated brain death during childbirth (the fictionalized account by Barry Reed, *The Verdict,* and motion picture produced by Sidney Lumet, which starred Paul Newman, is almost entirely accurate).

Subsequently the father of the brain-dead mother threatened members of the anaesthesia department with retribution. His gun license was eventually revoked. In 1967, when Hedley-Whyte, during his visit to Musgrave Park and the Royal Victoria Hospital, Belfast, reported these events to John Dundee, he promised to help with physician recruitment. The result was that Hedley-Whyte was able to appoint four Ulster doctors as Director or Co-director of Clinical Anaesthesia, Outpatient Anaesthesia and Obstetric Anaesthesia: Dorothy M Crawford, Doris Cole, Nial M Murray and T Gordon McNabb. The first of the quartet subsequently married a surgeon expert in outpatient surgery,[16] the second an expert on transportation policy and the third, the Executive Assistant of Obstetrics.

In 1966, in planning the Harvard Anaesthesia Research Center Grant Proposal, Henrik Bendixen, the Principal Investigator, and co-investigators Myron Laver and John Hedley-Whyte, decided that there must be an Engineering Unit for the Department of Anaesthesia of Harvard. This was funded by the National Institutes of Health at $50,000 per annum for the period 1967-1972.

In 1969 Beecher was succeeded by Richard J Kitz as Dorr Professor and Head of Anaesthesia at the Massachusetts General Hospital. The Harvard Executive Committee on Anaesthesia started to hold regular meetings. The new committee and Harvard Department were to be patterned after the academic departments of Medicine and Surgery with a rotating presiding Secretary. Membership was to be limited to the professorial heads of hospital departments with separate approved anaesthesia residency training programs. Milton Alper (Children's Hospital), John Hedley-Whyte, Richard Kitz and Leroy Vandam (Peter Bent Brigham Hospital) were therefore the sole members. Kitz became Principal Investigator of the U.S. federally funded Harvard Anaesthesia Research Center, then in its second year, and Hedley-Whyte, Secretary of the Harvard Faculty of Medicine. The Committee met monthly for several hours and held retreats. "Each of us reported information that could be shared", wrote Kitz, and the problems of all aspects of the delivery of surgical care, intensive therapy, politics related to medicine, medical and surgical equipment, pain, insurance, economics, simulations and examinations were considered frequently, with outlines and handouts. According to Kitz,[17] "gossip was also a prime ingredient". Academically the committee and its appointed subcommittees functioned harmoniously and effectively. This organization was the genesis of monitoring guidelines, many equipment standards and the rediscovery of the patient safety concept initially promulgated by Codman in 1912 while working at the Massachusetts General Hospital.[18] The Executive Committee felt that the time had come to expand outpatient anaesthesia and surgery, whether hospital-based or at free-standing locations. This suggested the appointment of Ben Covino, an expert on local anaesthesia[19] to succeed Leroy Vandam. Covino had finished his residency at the Massachusetts General Hospital only two years before his call back to Harvard. Hedley-Whyte was subsequently appointed Chairman of a Harvard Medical Institutions Committee on Outpatient Surgery with Debra R Milamed as Secretary.[20] The election of two Harvard Faculty Members, Jess Weiss (1979) and Ellison C Pierce, Jr. (1984) as Presidents of the American Society

of Anesthesiologists, was a great facilitator for advances in patient safety, equipment standards and insurance and governmental negotiations.[21]

In 1972 Jeffrey Cooper was recruited by Dick Kitz to assume control of the Harvard Bioengineering Research Unit. The evolution of this Bioengineering Unit has been called the DNA of the Patient Safety Movement;[17] if so, International Standards writing must be the RNA. Since 1966 the interchange of information between the US and British and other national standards writing bodies, International Organization for Standardization (ISO) Committee ISO TC121 on Anaesthetic and Respiratory Equipment and the International Electrotechnical Commission (IEC) Technical Committee 62 on Electrical Equipment in Medical Practice, has been invaluable for evaluation of medical equipment used in both inpatient[22] and outpatient surgery.[16] As a result equipment standards for both inpatient and outpatient surgery are now the same.[23,24] The development of the US Food and Drug Administration (FDA) and the German Bundesinstitut füer Arzneimittel und Medizinprodukte (BfArM) medical equipment function data bases and the engineering skill of Harvard and the Massachusetts Institute of Technology (MIT) provided, starting in the early 1970s, very beneficial feed-back and cross-fertilization of equipment design and both pre- and post-market assessment of devices.[20,24]

About 1973 it became obvious that there needed to be both a code of conduct for anaesthesia and its monitoring and a set of performance-based international standards for life support equipment involving most equipment used in anaesthesia and critical therapy.[21,25] Meanwhile under Cooper's leadership there was a revival of critical incident analysis.[26] Such work received support from both the insurance and aeronautics industries. The US FDA lead on the anaesthetics committees was Pete Carstensen, an aeronautics engineer, and his input was seminal in advising John Eichhorn and his subcommittee of the Executive Committee that developed the Harvard Monitoring Standards for Anaesthesia.[27]

The Massachusetts General Hospital opened its Surgical Day Care Unit in 1974, and the other Harvard hospitals soon followed. The major reimbursement for medical care at the Massachusetts General Hospital was from Blue Cross/Blue Shield of Massachusetts. This insurer refused to pay for surgical or anaesthetic professional services unless the patient was admitted to hospital. After numerous visits of teams of administrators, surgeons, and anaesthesiologists, this insurance carrier agreed to reimburse the hospital for outpatient surgical and anaesthesia care on a trial basis.[28] The Harvard experience with insurance payments thus mirrored the Phoenix experience, but five years later.

PHOENIX, ARIZONA

In 1970 the Phoenix Ambulatory Surgicenter opened as a free-standing ambulatory unit.[29] Preliminary planning with 101 insurance companies, the project architect, representatives of the local hospital and community and with the Arizona State Legislature and the state's executive governor were initiated in 1968 and took almost two years to be successful. The Phoenix Surgicenter's records of these negotiations, their fiscal reports and their careful surveys of patient and health care provider feedback were of inestimable value in alleviating the worries of hospital staffs, trustees and politicians in subsequent negotiations at other sites world-wide.[29,30] These worries were substantial because revenue loss to hospitals was considerable, often in the order of thirty percent of hospital gross. All was not smooth sailing. In 1971, C Rollins Hanlon, Director of the American College of Surgeons discussing the recent Duke University experience noted that the Phoenix Surgicenter had not been approved for reimbursement under Part A of Medicare. The reason free-standing surgical facilities had not been approved by the National Blue Cross Plan was because of a $60 million deficit in their Federal Employees Program to cover surgery without hospitalization. This deficit was allegedly due to overordering of outpatient perioperative laboratory tests and radiographs. The move from inpatient to outpatient surgery for Federal employees had not saved money. Hanlon continued, "In Phoenix the controversy is submerged, whereas... in Providence, Rhode Island the facility has not been accepted by "the profession" nor by local Blue Cross". Further speakers referred to the need for inspection and accreditation and for standards for surgery and anaesthesia to be equivalent to those required in hospitals accredited by the US Joint Commission on the Accreditation of Hospitals, now the Joint Commission on the Accreditation of Health Care Organizations.[31]

WASHINGTON, DC, LOS ANGELES AND CANADA

The Department of Surgery/Anesthesiology at the University of California at Los Angeles reported on their experience from 1962 in a "properly equipped and staffed outpatient surgical unit"; the conclusion was that there were cost savings and safety.[32] Insurance companies frequently would not reimburse because the relevant policy required admission to hospital for at least 18 hours.[32] In 1967, the first year of "in and out" surgery at George Washington University in Washington DC was reported to the US Southern Medical Association.[33] The patients approved, despite 73 percent reporting postoperative nausea and 40 percent headache. Nausea, vomiting and sore throat were common, occurring in approximately a quarter of outpatient surgical patients, but only one in fifty required admission to hospital.[33,34] During the same period, the conduct of one surgical and two dental outpatient operating rooms in the city of Vancouver, British Columbia was described.[35]

US FOLLOW-UP THIRTY AND FORTY YEARS ON

The US Health Care Financing Administration (HCFA), has established standards for ambulatory surgical services for Medicare and Medicaid patients.[36] The designation of specific procedures as appropriate for outpatient status does not preclude government coverage in an inpatient hospital setting, usually the preferred location for procedures requiring operating time and/or general anaesthesia of 90 minutes or more and four or more hours of recovery.[36]

The Joint Commission on Accreditation of Health Care Organizations (JCAHO)[37] and the American Association for Accreditation of Ambulatory Surgery Facilities[38] accredit sites where ambulatory surgery is performed and review personnel. Both organizations reappraise staff annually or biannually.[37,38] The American College of Surgeons' *Guidelines for Optimal Ambulatory Surgical Care and Office-based Surgery* includes all aspects of ambulatory surgical care,[39] and has been cross-

Fig 2. The different states of the United States differ considerably in the proportion of surgery performed without admission to hospital. These figures provided by the American Hospital Association include only hospital-based surgery. Free-standing surgicenter and MD office-based surgery are excluded (see fig. 1). The differences between states may reflect different state laws and regulations, county and other local ordinances, as well as demographic factors and variations in physician practice patterns. US presidential electoral voting results for each state are indicated as red for Republican candidates and blue for Democratic Party candidates. The 1993 panel is mapped to the 1992 presidential election (GHW Bush versus WJ Clinton), the 1998 to the 1996 election (WJ Clinton versus R Dole) and the 2003 to the presidential election of 2000 (A Gore versus GW Bush). There appears to be no association between a state's political orientation and the percentage of surgery performed without admission to hospital.

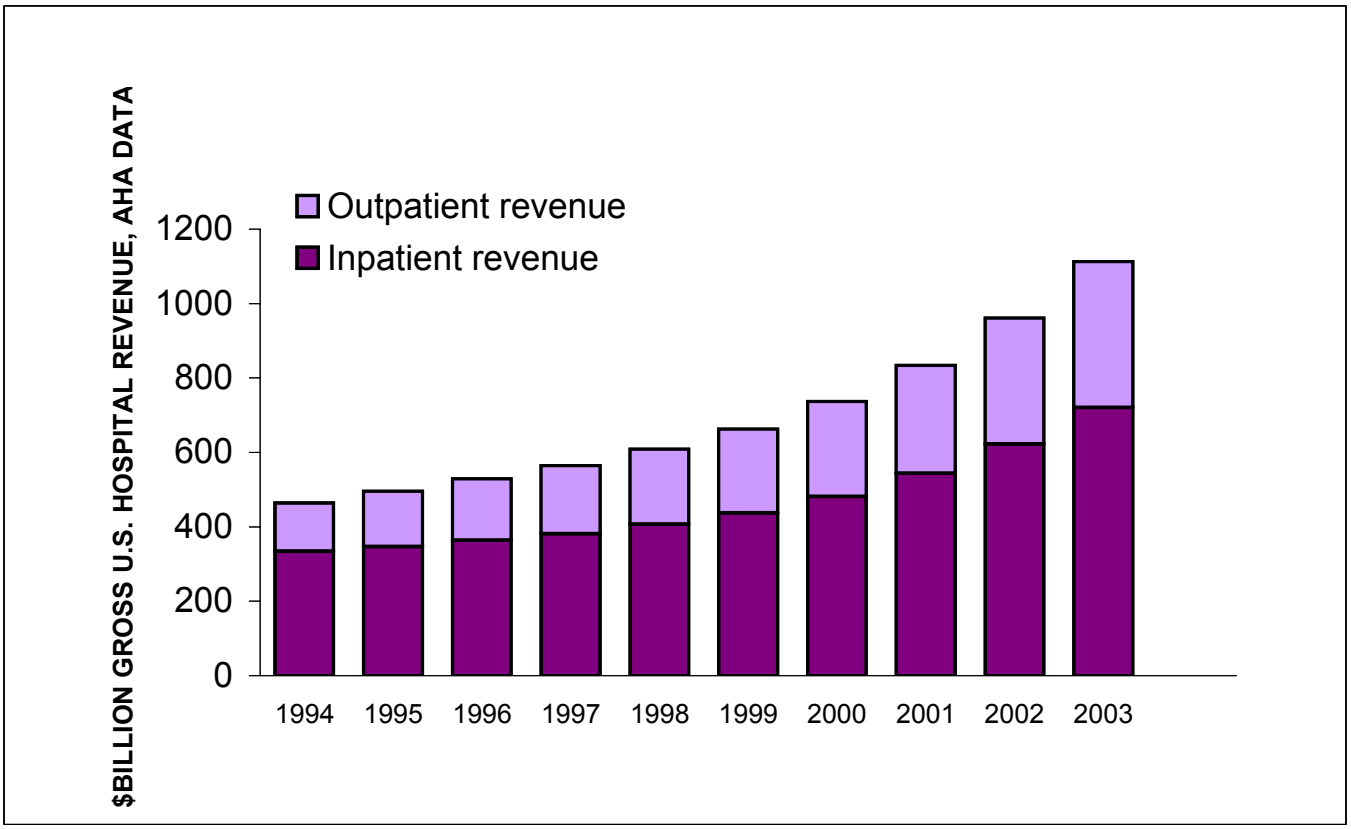

Fig 3. According to the American Hospital Association over the decade from 1994 through 2003, the gross revenue of US acute care hospitals increased from approximately 450 billion dollars to just over one trillion, or doubled in the first nine years using constant dollars. During this decade, US Gross Domestic Product (GDP) increased 32% in constant dollars. Outpatient revenue as a percentage of total gross hospital revenue has shown a small but steady increase (28-35%) during the same decade.

referenced by the JCAHO to its accreditation requirements.

The American Society of Anesthesiologists has approved guidelines for office-based anaesthesia, standards for basic anaesthetic monitoring, pre-and post-anaesthesia care and guidelines for ambulatory anaesthesia and surgery, as well as non-operating room anaesthetizing locations.[40] If exceptions are made to these standards and guidelines, the reasoned justification shall be documented in writing.[40] The American Association of Nurse Anesthetists has developed standards for Certified Registered Nurse Anesthetists (CRNAs) which address responsibilities in perioperative care.[41] The Anesthesia Patient Safety Foundation has promulgated twenty-two questions to ask before accepting office-based anaesthesia.[42]

Recently the US Department of Health and Human Services, Centers for Medicare and Medicaid Services has issued an "Update of Ambulatory Surgical Center List of Covered Procedures: Interim Final Rule."[36] While it may be a reasonable list for 2005, it may hinder advances in endoscopic surgery and in hip and knee replacement. The US Federal government has agreed to reinstitute its information gathering of 1994 through 1996 on ambulatory surgery, beginning again in 2006.

The acceptance internationally of the Harvard anaesthesia monitoring guidelines[27] has been guided by their success in reducing complications and lessening the cost to insurance carriers for surgeons and anaesthesiologists.[43] Most carriers now are reluctant to insure physicians who do not follow relevant guidelines and standards.[43]

Variations in results for individual institutions with differing practices may be hidden in national statistics and important local changes may be obscured.[44-49] Certainly it is not immediately apparent why the rate of outpatient surgery is so different between countries and states[45,47] (*Fig 2*).

The number of free-standing ambulatory surgery centers in the US had increased to over 3,700 by

2004,[45] and according to the New York Times of June 14, 2005, about 4,600 by mid-2005. These surgicenters are neither physically nor financially connected to hospitals and are generally physician-owned. Claims and settlements for anaesthetic malpractice have recently shown a marked decrease. This trend supports the surveys of outpatient surgical patients, which show appreciation. Less than one percent of patients undergoing ambulatory or office-based surgery require hospitalization.

Hospital revenues, at least in the US seem to have compensated for the loss of revenue caused by the shift to ambulatory surgery (Fig 3).[45,50,51]

POLITICS AND FINANCE

In the United States the pressure to change from inpatient to outpatient surgery appears to have come largely from patients and the more entrepreneurial members of the medical profession. This change was impeded and delayed, at least in the earlier stages, by insurance companies' financial restrictions and concern about safety. In the United Kingdom, the pressure was from the British government to reduce the requirement for surgical beds and thereby save expenditure. Much of the rest of the world has yet to make this change.

What is striking about this change in the United States is how hospital revenue has been compensated for the loss of hospital-based surgery (*Figure 3*). Surgical revenue is approximately five percent of the US Gross Domestic Product (GDP), so hospitals were losing three percent of US GDP. The sporadic, but often vehement and legalistic, opposition of local hospital trustees and state government to the setting up of free-standing surgicenters is thus understandable but misplaced.

Are patients overall receiving value for money? The advances in medical equipment safety and cost have been enormous in the last forty years.[52-54] Even the principal author of former President Clinton's proposed health plan, Harvard's Otto Eckstein Professor of Applied Economics, David Cutler, thinks the benefits of medicine are worth what is now paid. As a participant in the Harvard University Technology Assessment Group and present Dean of Social Sciences, his is an interesting epiphany.[55]

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Paper

Comparison of Laparoscopic-assisted Vaginal Hysterectomy, Total Abdominal Hysterectomy and Vaginal Hysterectomy

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INTRODUCTION

Hysterectomy is one of the most commonly performed major operations. Approximately 600,000 hysterectomies are performed in the United States each year[1] and 20% of women in the UK undergo hysterectomy before the age of sixty.[2] Historically the uterus has been removed by either the abdominal or vaginal route. The vaginal operation is preferable when there are no contraindications because of lower morbidity and quicker recovery.[3] The VALUE Study[4] suggested that 67% of surgeons still used the abdominal approach as the operation of choice, particularly when dealing with pelvic pathology or carrying out oophorectomy.

Since it was first reported by Reich *et al* in 1989[5] laparoscopically assisted vaginal hysterectomy (LAVH) has gained widespread acceptance. Laparoscopic dissection of the para-uterine tissues to the level of the uterine arteries (LAVH) or to include the uterine arteries (laparoscopic hysterectomy), also permits oophorectomy or dissection of adhesions under direct vision more easily than this can be achieved at vaginal hysterectomy (VH). Farquhar and Steiner[6] found that between 1990 and 1997, in the USA, there was a growth in the number of hysterectomies performed with laparoscopic assistance (0.3-9.9%) with an associated decline in the proportion of hysterectomies performed abdominally.

Recently the eVALuate Study concluded that LAVH was associated with a significantly higher rate of major complications than abdominal total hysterectomy (TAH). LAVH took longer to perform but was associated with less pain, quicker recovery and better short term quality of life measures. The arm of the trial involving VH was underpowered and inconclusive although VH did take less time than LAVH.[6] In contrast to this the study by Lumsden et al[7] did not show any difference in post-surgery recovery, satisfaction with the outcome of the operation or quality of life four weeks post-operatively between TAH and LAVH.

The aims of our study were to compare LAVH with TAH and VH in a retrospective non-randomised analysis and to evaluate intra and post-operative complication rates and patient recovery times.

SUBJECTS AND METHODS

A retrospective observational study in the Belfast City Hospital was carried out comparing LAVH, TAH and VH. The study period was from January 2002 to January 2004 inclusive, a 25 month period. Patients undergoing LAVH for non-malignant conditions were identified from theatre diaries and the hospital based computerised coding system. A similar number of patients, matched for

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pathological diagnosis, were selected from theatre diaries for both TAH and VH.

Medical records of the patients identified were reviewed; factors examined included demographic details, indication for operation, intra-operative details, histopathology summary, post-operative recovery and subsequent post-operative review findings. One hundred and thirty five hospital charts were reviewed, 47 for patients undergoing LAVH, 45 TAH and 43 VH.

The primary operator was a consultant in 60% of patients undergoing LAVH, 31% of those having TAH and 26% of VH procedures.

Demographic characteristics demonstrated a trend of increasing age from LAVH to TAH to VH. Similarly 100% of VH's were parous in comparison with both of the other groups in which approximately 80% of patients were parous (*Table I*).

Indications for surgery are listed in Table I.

RESULTS

LAVH took significantly longer than both TAH and VH but there was no significant differences in operating times between TAH and VH (*Table 2*). The average weight of specimen increased from 100g (range 29-415g) in the VH group to 127g (range 38-515g) in the LAVH group through to 265g (range 70-1066g) for the TAH group.

Intra-operatively, adhesions were diagnosed in 30 of 135 cases (22.2%), 13/47 in the LAVH group, 15/45 in the TAH group and 2/43 in the VH group. Fibroids were diagnosed in 22 cases (16.3%) of which 14 were in the TAH group (VH 3, LAVH 5 cases).

In the LAVH group 36/47 cases (81%) included salpingo-oophorectomy or bilateral salpingo-oophorectomy, in the TAH group 37/45 cases (82%) included bilateral salpingo-oophorectomy whereas only 12/43 cases undergoing VH (28%) included uni- or bilateral salpingo-oophorectomy.

Histopathologically, fibroids were diagnosed in 54 cases (40%) with the greatest proportion in the TAH group (51%, 23 cases) compared with 19% for the LAVH group (9 cases) and 37% of patients undergoing VH (16 cases). Fibroids in women undergoing VH were typically small and this is reflected in the average specimen weight noted above.

Three patients in each of the three groups required blood transfusion. A single patient from each group sustained either a bowel or urinary tract injury (bladder injury in both LAVH and TAH, bowel injury in VH): all were noted at the time of operation, repaired and had no resultant problems at post-operative follow-up.

In the LAVH group there were five unplanned conversions to laparotomy: two cases were for dense adhesions, one for inability to maintain haemostasis, one because of a fibroid uterus and one due to minimal descent of the cervix and uterus. In four of these five cases, it was anticipated that surgery may be complicated because of historical factors. In the VH group a laparotomy was performed to rule out an intra-peritoneal bleed and a laparoscopy was performed to retrieve a swab which had migrated intra-abdominally during the procedure.

Minor post operative complications were also noted, including pyrexia, wound and urinary infection, vault and wound haematoma, and dehiscence (*Table III*). There were four readmissions following discharge, three required further treatment, two (TAH 1, VH 1) returned to theatre for drainage of vault haematoma and one (LAVH) had re-suturing of an umbilical incision. A further two patients returned to theatre during their initial admission, one (LAVH) for drainage of vault haematoma and one (TAH) for drainage of abdominal wound haematoma (*Table II*).

The median total length of stay for TAH was 8.3 days (range 5-20) but was significantly less for both LAVH (6.1 days, range 3-18) and VH (5.9 days, range 3-13). Post-operatively, patients undergoing TAH required more analgesia with only 16% requesting no analgesia during their immediate post-operative recovery period compared with 40% and 37% in the LAVH and VH groups respectively.

At six week review, patients undergoing TAH reported more post-operative problems (9/45 cases, 20%) compared with LAVH (4/47 cases, 8.5%) and VH (5/43 cases, 11.6%).

DISCUSSION

Since Reich described LAVH in 1989, the uptake of the procedure has been slow and subject to considerable geographical variation, with some units performing most of their hysterectomies by this route and others performing none. The number

TABLE I

Demographic characteristics including previous surgery, the indication for surgery, surgical intra-abdominal pathology, and histopathology summary. Values are given as percentage means with number in brackets.

	LAVH (n=47)	*TAH (n=45)*	*VH (n=43)*
Age (years)	43	46.4	48.3
Parous	82.2 (39)	80 (36)	100 (43)
Previous pelvic surgery	9 (4)	2 (1)	9 (4)
Indication for surgery			
DUB	64 (30)	60 (27)	58 (25)
Fibroids	2 (1)	9 (40)	0
Pelvic pain	4 (2)	13 (6)	0
Endometriosis	4 (2)	2 (1)	0
Prolapse	6 (3)	0	33 (14)
PMB	2 (1)	9 (4)	0
Other	17 (8)	7 (3)	9 (4)
Intra-abdominal pathology			
Adhesions	28 (13)	33 (15)	5 (2)
Fibroids	11 (5)	31 (14)	7 (3)
Endometriosis	4 (8)	2 (1)	0
Other	4 (8)	4 (2)	19 (8)
Histopathology			
No significant pathology	19 (9)	10 (4)	21 (9)
Fibroids	19 (9)	51 (23)	37 (16)
Endometriosis	2 (1)	0	0
Other	60 (28)	39 (18)	42 (18)
Weight of specimen (grams)	127	265	100

TABLE II

Major items of resource use. Values are given as percentage means with number in brackets.

	LAVH (n=47)	*TAH (n=45)*	*VH (n=43)*
Total length of anaesthetic time (mins)	95	73.9	74.4
Total length of stay (days)	6.1	8.3	5.9
Women requiring additional surgery	6.4 (2)	4.4 (2)	2.3 (1)
Readmissions	4.3 (2)	2.2 (1)	2.3 (1)
Blood transfusions	6.4 (3)	6.7 (3)	7 (3)
Primary operator consultant	60	31	26

TABLE III

Complications. Values are given as percentage means with number in brackets.

	LAVH (n=47)	*TAH (n=45)*	*VH (n=43)*
Major complications			
Haemorrhage (requiring transfusion)	6.4 (3)	6.7 (3)	7 (3)
Urinary tract damage	2.1 (1)	2.2 (1)	0
Bowel damage	0	0	2.3 (1)
Laparotomy/Laparoscopy	10.6 (5)	0	4.7 (2)
Total	**19.1 (9)**	**8.9 (4)**	**14 (6)**
Minor Complications			
Pyrexia >38°C	2.1 (1)	0	2.3 (1)
Urinary tract infection	4.3 (2)	2.2 (1)	2.3 (1)
Wound infection	4.3 (2)	4.4 (2)	0
Erythema wound	2.1 (1)	0	0
Wound dehiscence	4.3 (2)	0	0
Vault haematoma	0	8.8 (4)	4.7 (2)
Wound haematoma	1 (2.1)	4.4 (2)	0
Total	**19.2 (9)**	**19.8 (9)**	**9.3 (4)**

of hysterectomies performed in this unit for benign disease has increased as a proportion of the overall number of hysterectomies performed, with 36 hysterectomies performed laparoscopically in a previous study [8] over a time frame of 37 months compared with 47 during the time-frame of this audit (25 months). The still relatively low rate of LAVH reflects the caseload in this unit, where many of those undergoing VH have significant prolapse and those undergoing TAH have enlarged uteri or fibroids although genetic screening for hereditary non-polyposis colon cancer and breast/ovarian cancer has increased the rates of preventative hysterectomy, and may increase the number of asymptomatic cases.[9]

A greater proportion of LAVH's than both VH and TAH were performed with the Consultant as the primary operator. We feel that the reasons for this are two-fold. Firstly, the number of LAVH's performed for benign disease remains low and therefore the experience gained, even by Consultant staff, often takes a considerable time. This is reflected in the high number of conversions to laparotomy in the LAVH group, where, some of the conversions to laparotomy may have been avoided if greater experience had been accrued. The eVALuate study [10] concluded that although it could be considered that such conversions represented prudent surgery it was felt that on the balance they represented a failure of planned procedure and should be considered as major complications. The second issue is the time LAVH takes in comparison to VH and TAH. It is recognised that surgeons in training will take longer to perform surgical procedures than those who have been trained. One perception of LAVH is that the procedure takes longer and this has been shown in a number of studies, including this one, to be the case. In this circumstance, there is often reluctance, given the pressure on operating time, to spend longer performing a procedure than is necessary.

Although limited data was gathered on the post-operative recovery phase, the results of this study are similar to those of others, i.e. that patients undergoing LAVH and VH benefit from a quicker and less complicated recovery than TAH,[7,8,11] with discharge from hospital more than 2 days earlier and significantly less requirement for analgesia. These factors reduce the indirect costs of the surgery, but this must be offset against the longer operating times needed for LAVH.

CONCLUSION

The proportion of hysterectomies performed with laparoscopic assistance has increased in this unit, but the overall number remains low. Factors affecting the uptake of LAVH include surgeon's experience and training in these techniques. In operations completed laparoscopically, the complication rates were comparable to those for TAH and VH. Therefore, when possible, VH should be the procedure of choice. However, for patients with more complex pathology, the choice between LAVH and TAH will depend on the surgeon's experience. LAVH has been shown in other studies to be more expensive in direct costs, but the overall cost benefit analysis favours a laparoscopic approach over the abdominal approach.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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Paper

Fine needle aspiration cytology (FNAC) in the diagnosis of granulomatous lymphadenitis

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ABSTRACT

Objective: **To determine the final histological and clinical diagnosis of patients with granulomatous lymphadenitis on fine needle aspiration cytology (FNAC).**

Method: **A retrospective cohort study was carried out over a five year period in a tertiary referral hospital. FNAC of 22 patients with granulomatous lymphadenitis was reviewed and correlated with the final histological diagnosis and clinical outcome.**

Results: **Fourteen cases (64%) underwent surgical biopsy for histological assessment. A definitive diagnosis on FNAC with ancillary investigations was achieved in 82% (18 out of 22) of the cases: four Hodgkin's lymphoma, two non-Hodgkin's lymphoma (NHL), five tuberculosis (TB), two toxoplasmosis, one sarcoidosis and four benign reactive changes.**

Conclusion: **A significant number of cases of FNAC diagnosed granulomatous lymphadenitis have an identifiable underlying cause. Patients with reactive cytological changes, who clinically appear benign, can avoid unnecessary surgery.**

INTRODUCTION

The use of fine needle aspiration cytology (FNAC) in the investigation of lymphadenopathy has become an acceptable and widely practised minimally invasive technique, which is safe, simple, rapid and relatively pain-free. FNAC is highly cost effective and accurate as a first line investigative technique with differential diagnoses including reactive hyperplasia/ inflammatory conditions, granulomatous disorders and malignancy, stratifying cases requiring further investigations, surgical intervention or clinical follow-up. We report our experience of 22 cases of granulomatous inflammation diagnosed by FNAC.

MATERIAL AND METHODS

Patients with superficial nodes were referred to a Head and Neck clinic for physical examination and further assessment. Routine FNAC was performed by the attending pathologist. Aspiration of superficial enlarged lymph nodes was performed free hand using a 23 G needle mounted on a Cameco handle. Both air-dried and wet-fixed slides were prepared. The air-dried smears were immediately stained with Speedy-Diff (Clin-tech) and the adequacy of diagnostic material assessed. Results of FNAC were available on the day of examination.

Granulomata are recognised cytologically by observing aggregates of histiocytes with, and

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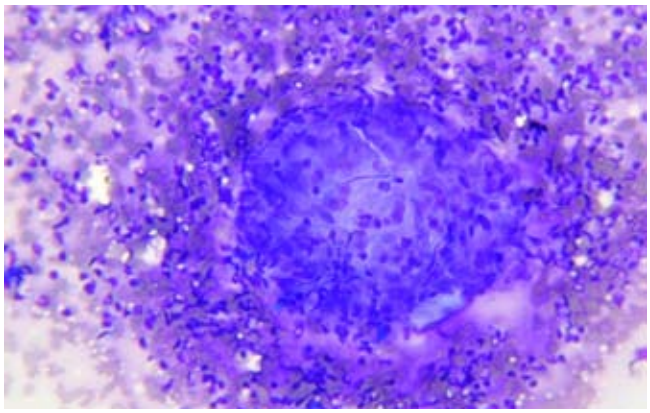


Fig 1. Granuloma formation as seen on fine needle aspirate

without, associated multinucleated giant cells. (*figures 1 & 2*) A dirty necrotic background would suggest caseation and possibly tuberculosis. In cases where an infective aetiology was thought likely, needle washings were sent for bacteriological culture and sensitivity. If TB was suspected, an additional sample was sent for culture and slides were also stained with auramine-rhodamine or Ziehl-Neelsen methods to detect acid fast bacilli (AFB) directly.

The eventual diagnosis of granulomatous inflammation by FNAC was confirmed either by surgery and/or by clinical investigations. In addition to cytological or histological features, patients suspected of TB had positive culture of Mycobacterium tuberculosis. The diagnosis of sarcoidosis was based on the generally accepted diagnostic criteria: clinical picture and chest x-ray findings compatible with sarcoidosis, elevated serum angiotensin converting enzyme (ACE) and lysozyme, skin test (Kveim and Mantoux test) and response to treatment with steroids. Patients suspected of toxoplasmosis had IgG and IgM toxoplasma antibodies assayed by micro-enzyme-linked immunosorbent assay (ELISA) method.

RESULTS

Between September 1995 and June 2001, 22 patients had the diagnosis of granulomatous inflammation made by FNAC at the Belfast City Hospital. Seven patients were male and 15 female; and the mean age of diagnosis was 54 years. All patients presented with a palpable lesion, which was usually enlarged cervical lymph nodes (n=19) or nodes elsewhere [in breast and axilla] (n=3). Fourteen out of 22 (64%) had their diagnosis confirmed through histological assessment. The eventual diagnoses based on surgical biopsy and clinical investigations were as follows: four cases of Hodgkin's disease, two cases NHL, five cases of TB, two cases of toxoplasmosis, one of sarcoidosis, four of benign/reactive and four unknown.

MALIGNANT LYMPHOMA

Six cases (20%) were reported as malignant lymphoma: four Hodgkin's disease and two NHL (one B-cell, one T-cell lymphoma). All six cases had the diagnosis confirmed by excisional biopsy. One patient was previously diagnosed with Lennert's T-cell lymphoma and had a recurrence of disease one year later, proven on FNA cytology of cervical lymphadenopathy. This patient subsequently moved to Scotland to have further treatment and follow up. The other five patients were diagnosed primarily on FNA. FNA suggested features of lymphoma, and in four patients surgical excision biopsy was undertaken which confirmed the diagnosis of malignant lymphoma. These four patients underwent chemotherapy and have remained well. One of them returned to his home in Scotland to have further follow-up and treatment.

INFECTIVE AGENTS

Four of the five patients diagnosed with tuberculous lymphadenitis on FNA presented with enlarged lymph nodes as the only clinical finding. All cases responded well to anti-tuberculous therapy. One of them was a student from the Indian subcontinent and aspirate culture for Mycobacterium tuberculosis was positive. Another patient was a 33 year old lady from China with recurrent neck lymphadenopathy which started discharging milky fluid that grew TB on aspirate culture. Another patient had no previous BCG vaccination and had been consuming un-pasteurised milk shortly before symptomatic presentation. In all cases, FNA aspirates cultured positive for TB.

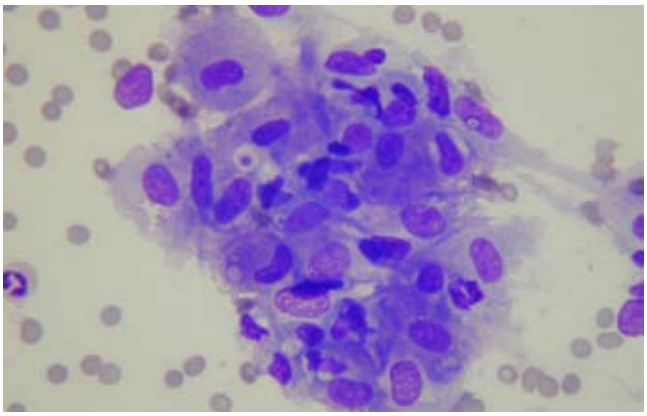


Fig 2. Granuloma-loose aggregates of epithelioid histiocytes

The two cases of toxoplasmosis, had the typical FNAC features including presence of follicular hyperplasia with secondary germinal centres rich in macrophages, presence of groups of epithelioid cells and presence of monocytoid histiocytes,[21,22] the diagnosis was confirmed with positive IgG and IgM antibody titres. The lymphadenopathy in both patients disappeared during their follow-up, and both have remained asymptomatic.

SARCOIDOSIS

One patient was diagnosed with sarcoidosis in our series. The patient was previously diagnosed with sarcoidosis following positive ACE level, Kveim-Stilzbachs test and Mantoux test one year previously. The FNA of lymph node findings were characteristic, with epitheliod non-caseating granuloma and occasional multi-nucleated giant cells. The patient was started on a course of steroid to which she had a good response. (after five days, her lymphadenopathy disappeared).

UNKNOWN CAUSE

In four patients, the precise cause for the granulomatous inflammation was not established. Of these, three patients were clinically unfit for surgical excisional biopsy due to severe co-morbid factors and the ancillary tests did not reveal any obvious cause. All three patients subsequently died of causes unrelated to granulomatous lymphadenitis. One patient refused further follow-up and investigation and decided to discharge herself against medical advice.

BENIGN/REACTIVE CAUSE

In four patients, the ancillary clinical investigations and excisional biopsies were reactive. On clinical follow-up in these patients, the lymphadenopathy had disappeared and the patients have remained well and have subsequently been discharged.

DISCUSSION

The well-defined role of FNAC in the investigation of lymphadenopathy has previously been studied.[1,2] In the context of granulomatous disorders, the possible aetiology is wide and the use of FNAC with other ancillary tests (microbiological, immunohistochemical, radiological, biochemical and special staining techniques) is useful for obtaining a definitive diagnosis. The algorithm shows a useful classification of the aetiology of granulomatous lymphadenopathy.

FNAC as a first line screening method has been recommended in suspected malignancy.[2,3] The presence of granulomata in an aspirate may indicate the presence of a neoplastic process. The background cell population needs to be scrutinised if a malignant lymphoma is suspected. Granulomata may be encountered in both Hodgkin's disease and non-Hodgkin's lymphoma, particularly T-cell lymphoma.[4] Hodgkin's lymphoma is characterised by the classic Reed-Sternberg cells in a background of sarcoid-like granulomata, reactive lymphoid cells and occasional eosinophils.[5,6,7] Occasionally, lymph nodes containing metastatic carcinoma may also show features of granulomata. Previous reports have been described in metastatic nasopharyngeal carcinoma, seminoma and malignant melanoma.[8,9] Histologically, non-caseating granulomata composed of epithelioid histiocytes with multinucleated giant cells are seen, but these can be indistinguishable from granulomatous inflammation from other causes. A series by Khurana *et al*[10] highlighted the difficulties encountered in making a definitive diagnosis of malignant neoplasm that mimics, or occurs, in association with granulomata.

Granulomatous inflammation found in lymph nodes draining carcinomas is a recognised phenomenon.[10,11,12] Such phenomenon are reported in pulmonary small cell carcinoma,[13] malignant melanoma,[9] papillary thyroid carcinoma,[14] gastric carcinoma,[15] and rhabdomyosarcoma.[16] This has been suggested to be either a response to necrotic material[12] or an immunological T-cell mediated hypersensitivity reaction to cell surface antigens.[17,18,19] However, the precise mechanism is largely speculative as the exact tumour or host factors that enable such a response remain unknown. We agree with Lui *et al*[20] in their pragmatic approach of diligent examination of FNAC slides combined with ancillary clinical, serological and imaging investigations in the drainage areas to identify any occult malignancy.

A suspicious clinical history of TB (pyrexia, night sweats, recent travel to endemic areas, no previous BCG vaccination) coupled with positive aspirate, blood, sputum or urine tests for AFB and good response to anti-tuberculous therapy supports the diagnosis of TB. One disadvantage is the inherent delay in culture result, but it is anticipated that as polymerase chain reaction and other amplification techniques become more common, detection time for the organism will shorten, improving the value of FNA in clinical practice.[21] The typical FNAC features

of toxoplasmosis include the presence of follicular hyperplasia with secondary germinal centres rich in macrophages, presence of groups of epithelioid cells and presence of monocytoid histiocytes have been previously described.[22,23] A combination of FNA features with positive serological testing and history of animal contact, as in the two patients here, gives the diagnosis of toxoplasmosis and thus avoids unnecessary surgical excision.

Sarcoidosis is a disease of unknown aetiology that can be characterised by the histological hallmark of epitheliod non-caseating granulomas, usually accompanied by multinucleated giant cells. The World Association and Other Granulomatous Diseases (WASOG) diagnostic criteria for sarcoidosis include that granulomata present in two or more organs with no agent known to cause a granulomatous response identified.[24] Although there is no single gold standard test, the important role of FNAC in histological diagnosis and its underutilisation was highlighted by Tambouret *et al*.[25] We agree with the authors that FNAC used in conjunction with clinical findings, radiological and laboratory investigations can be a cost effective method.

CONCLUSION

A significant number of cases of FNAC diagnosed granulomatous lymphadenitis have an identifiable underlying causal pathology. Our experience suggests that FNAC combined with clinical correlation is useful as a first line investigation. The high specificity of the technique helps to single out those that need further investigation or biopsy. It is also highly cost effective in the diagnosis of relapse in patients with malignancies.

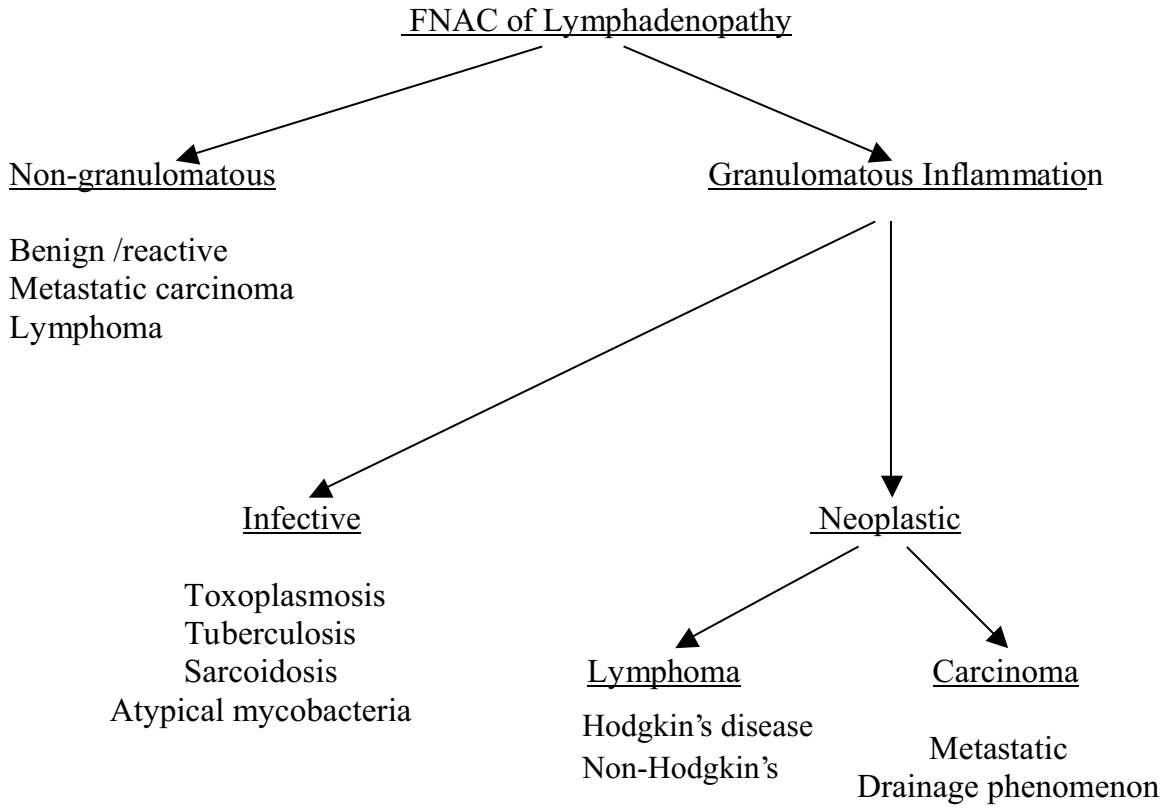
TABLE

Biopsy site, histological and clinical diagnosis of 22 patients with FNA cytologically diagnosed granulomatous lymphadenitis.

No	*Sex*	*Age*	*FNA Site*	*Histology*	*Clinical diagnosis*
1	F	91	Neck	Not done	Unknown
2	F	67	Neck	Granulomatous lymphadenitis	Unknown
3	F	40	Breast	Not done	Unknown
4	F	84	Neck	Not done	Unknown
5	F	52	Neck	Not done	Benign reactive
6	F	86	Neck	Granulomatous lymphadenitis	Benign reactive
7	F	36	Neck	Granulomatous lymphadenitis	Benign reactive
8	F	22	Breast	Granulomatous lymphadenitis	Benign reactive
9	M	60	Axilla	Hodgkin's	Hodgkin's
10	M	43	Neck	Not done	Hodgkin's
11	M	77	Neck	Hodgkin's	Hodgkin's
12	M	17	Neck	Hodgkin's	Hodgkin's
13	M	85	Neck	NHL	NHL
14	F	61	Neck	NHL	NHL
15	F	39	Neck	Granulomatous lymphadenitis	Sarcoidosis
16	F	65	Neck	Granulomatous lymphadenitis	TB
17	F	69	Neck	Granulomatous lymphadenitis	TB
18	F	48	Neck	Granulomatous lymphadenitis	TB
19	F	33	Neck	Not done	TB
20	M	33	Neck	Not done	TB
21	F	60	Neck	Granulomatous lymphadenitis	Toxoplasmosis
22	M	27	Neck	Not done	Toxoplasmosis

ALGORITHM

Aetiologies of lymphadenopathy



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Paper

Sudden Unexpected Death in Infancy: place and time of death

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SUMMARY

In recent years, many babies who die of Sudden Unexpected Death in Infancy (SUDI) in Northern Ireland are found dead in bed – i.e. co-sleeping – with an adult. In order to assess its frequency autopsy reports between April 1996 and August 2001 were reviewed and linked to temporal factors. The day and month of death, and the place where the baby was found were compared to a reference population of infant deaths between one week of age and the second birthday.

Although the rate of SUDI was lower than the UK average, 43 cases of SUDI were identified, and two additional deaths with virtually identical autopsy findings that were attributed to asphyxia caused by suffocation due to overlaying. Thirty-two of the 45 (71%) were less than four months of age. In 30 of the 45 cases (67%) the history stated that the baby was bed sharing with others; 19 died sleeping in an adult bed, and 11 on a sofa or armchair. In 16 of the 30 (53%) there were at least two other people sharing the sleeping surface, and in one case, three. SUDI was twice as frequent at weekends (found dead Saturday – Monday mornings) compared to weekdays ($p<0.02$), and significantly more common compared to reference deaths ($p<0.002$). Co-sleeping deaths were also more frequent at weekends. Almost half of all SUDI (49%) occurred in the summer months – more than twice the frequency of reference deaths.

While sharing a place of sleep per se may not increase the risk of death, our findings may be linked to factors such as habitual smoking, consumption of alcohol or illicit drugs as reported in case-control studies. In advising parents on safer childcare practices, health professionals must be knowledgeable of current research and when, for example, giving advice on co-sleeping this needs to be person-specific cognisant of the risks within a household. New and better means of targeting such information needs to be researched if those with higher risk life-styles are to be positively influenced.

INTRODUCTION

Epidemiological studies have identified several risk factors associated with Sudden Unexpected Deaths in Infancy (SUDI), also known as the Sudden Infant Death Syndrome (SIDS),* which is said to be the cause of death once other identifiable disorders have been excluded. Modification of these factors

* An unexpected death in infancy (after one week of age) where a thorough paediatric autopsy fails to find an adequate explanation for death.

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– including the prone sleeping position, smoking before, during and after (passive) pregnancy, or allowing babies to become over heated - has been associated with a marked reduction in this form of mortality world wide.[1]

In recent years, several large studies have examined the more emotive issue of co-sleeping and concluded that under certain circumstances it is inadvisable to share a bed or sofa (place of sleep or sleeping surface) with babies – generally up to three – four months of age.[2-4] Concomitantly in Northern Ireland, most SUDI occurred in infants co-sleeping with adults or older children, many during the warmer months of the year. Accordingly we undertook a retrospective review of all SUDI over a five-year period to assess both place and time of such deaths.

METHODS

The Department of Forensic Medicine, Queen's University of Belfast holds computerised records on autopsy examinations carried out at the request of a coroner. From these we identified all reports on children less than the second birthday, where the cause of death between April 1996 and August 2001 was recorded as SUDI, or as Undetermined. The history provided for the pathologist, usually obtained by a police officer included data on age and sex, where the baby was found, sleeping position, and whether at the time of death the infant was co-sleeping and, if so, with how many others.

In order to ensure that all relevant deaths were included, we also recovered data on all deaths in infants of the same age where the cause had been recorded as "interstitial pneumonitis". Within the time frame of study, this outmoded term was still in use where there was microscopic evidence within lung parenchyma of a scanty, but, in the view of some pathologists, a significant inflammatory cell response that was thought sufficient to cause death. Although such findings are no longer considered a separate cause of death or a distinct clinical entity,[5] in 14 cases this diagnosis had been used. In order to distinguish those with a genuine cause of death, a forensic pathologist (PI) who was "blind" to all historical or other information reviewed histological material. In nine, lung histo-pathology showed sufficient inflammatory change that the possibility of an infective process to account for death could not be discounted with reasonable certainty. These nine, five of whom were co-sleeping, were excluded from the SUDI group, nor were they included in the reference or comparison population that will be referred to (*Table I*). In the remaining five, no such histo-pathological ambiguity was present and they were reassigned as SUDI.

Table I

Generation of the reference population of infants deaths January 1997 – August 2001

Infant deaths in N Ireland < 2 years of age	657
Deaths excluded from Reference Group:	**475**
– consisting of those that occurred < 7 days of age	368
– those attributed to – prematurity	72
– SUDI	25
– "interstitial pneumonitis"	9
– Overlaying	1
Remaining deaths included in Reference Group	**182**

As can be seen from Table II the trend by pathologists to record an undetermined cause of death rather than SUDI has increased over the years of the study. This decision can be rather subjective, however, bearing in mind that both autopsy and histo-pathological findings in the two are indistinguishable and that abnormality likely to have caused death are absent. Moreover, pathologists are reluctant to use the term SUDI where, for example, the history tends to implicate circumstantial factors, as when a baby is found face down on soft furnishings. Hence we contend that in the context of a review that focuses on the place where a baby was found dead, it is reasonable also to include these among the index group. Death due to suffocation or overlaying also has identical post-mortem findings to those in the other two groups.[6] Therefore when analysing the data, undetermined deaths and two babies thought to have died of overlaying, were amalgamated with those referred to as SUDI, and the group as a whole was referred to by this term. Indeed the detailed work of Kemp and colleagues in the US in the mid-1990s would also encourage this approach as a public health measure.[7]

We were aware that this was a retrospective, uncontrolled analysis. A comparison or reference group of deaths was generated by the Registrar General's office in the first two years of life during a similar period of time (January 1997 - August

TABLE II

Trend in attribution of cause of death during the study period

Year	*SUDI*	*Undetermined*
1996	8	–
1997	8	1
1998	4	5
1999	1	6
2000	–	5
2001	–	5

[In addition 2 cases of overlaying/ suffocation]
Chi-square for trend = 24, p<0.001

2001). There were 657 deaths in toto, but we excluded deaths that occurred in the first seven days of life (368 in all) as this is outwith the time frame for a diagnosis of SUDI. We also removed 72 that were directly attributable to prematurity, and 35 SUDI and other deaths (*Table I*). The remaining 182 reference, or comparison, deaths were therefore entirely distinct from those due to SUDI. Causes of death in the reference group were multiple congenital anomalies including chromosomal abnormalities in 37, deaths due to major cardiovascular anomalies 37, respiratory disorders 32, sepsis 25, major CNS or muscle disorders 24, injuries 11, GI or urinary conditions 9, and deaths from neoplasm 7.

Statistical analysis was by χ^2 or Fisher's exact tests and non-parametric tests.

RESULTS

During the study period there were 45 infant deaths, 18 of which were in males. This figure includes two attributed to suffocation due to overlaying, each of whom was found dead on a sofa or armchair and at autopsy facial pressure marks were obvious. Throughout the study period, the overall rate of SUDI in Northern Ireland was 0.32/1000 live births. This compares to an overall rate of 1.71 in 1990, 0.74 in 1992, 0.37 in 1994, 0.21 in 1995 and 0.45/1000 live births in 1996.

Thirty-two of the 45 (71%) infants who died were less than four months of age, the mean age being 90 days; the range was large (13 – 390 days). The reference group was collected between the ages of 7 days and 2 years of age – mean 137 days – and was therefore higher than that of the SUDI (p=0.043).

The history given clearly indicated the last place of sleep in all 45. In 30 (67%), the baby was found dead having been sleeping with a carer; 15 were found in their cots. Of the 30, 19 (63%) died in an adult bed, and 11 (37%) on a sofa or armchair. Three infants who were not co-sleeping were not recorded as having died in their cots: one was "in bed", one "on a cushion" and one "in mother's arms". In 16 of the 30 (53%) co-sleepers there were at least two other people sharing the sleeping surface – and in one case three. Although those who died while co-sleeping were younger than those who were not, this difference was not significant (median age: 91 vs 113 days, p = 0.9 by Mann-Whitney test). Hence twelve (27%) died in their cots.

During the study period, 30 infants (67%) were found dead between Saturday morning and Monday morning (i.e. following a weekend night) and 15 infants (33%) between Tuesday morning and Friday morning (after a weekday night) [χ^2 =9.6, p<0.02]. Half the weekend deaths (one-third of all deaths) took place over Saturday night to Sunday morning (*Table III*). In regard to co-sleeping deaths of which there were 30, 11 (37%) occurred during the week compared to 19 (63%) at the weekend. Focusing on weekend deaths (30), there was no significant difference between the proportion found co-sleeping (19) and those who were not (11). We also compared the number of daily deaths from SUDI with those in the reference group. Numbers in the latter were fairly consistent throughout the week, however, SUDI was significantly more common at weekends (p < 0.02) (*Table III*).

Similarly, seasonal variation was examined (*Table IV*). Twenty-two SUDI (47%) occurred in summer compared to winter when there were eight (18%); similar numbers were recorded in spring and autumn. The proportions in the reference group were higher in winter and spring and were lower in summer and autumn as might be expected, whereas the SUDI distribution was strikingly different. There were similar proportions in all seasons except in summer when almost half the total SUDI (49%) occurred, and this was significantly more than the proportion of reference deaths (22 or 49% vs 43 or 24%, respectively; χ^2 = 8.8, p=0.02). Eleven (24%) SUDI occurred in July and August compared to 12.6%.

TABLE III

Comparison of SUDI and reference deaths by day of the week

	Weekend				Weekdays		
SUDI	30 (67%)				15 (33%)		
Reference deaths*	72 (40%)				110 (60%)		
	Saturday	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday
SUDI	8	**15**	7	3	5	4	3
Reference deaths	25	26	21	24	27	33	26

*difference between SUDI and other deaths by Chi-square test, p<0.002

TABLE IV

Comparison of SUDI and reference deaths by month of the year

	Winter			Spring			Summer			Autumn		
SUDI	8 (18%)			8 (18%)			22 (49%)			7 (16%)		
Reference deaths*	55 (30%)			59 (32%)			43 (24%)			25 (14%)		
	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov
SUDI	3	2	3	4	3	1	**11**	5	6	2	3	2
Reference deaths	13	23	19	18	19	22	20	11	12	15	4	6

*difference between SUDI and other deaths by Chi-square test, p<0.02

Although specific information was not prospectively sought, in three cases the police history given to the pathologist stated that one or both parents had taken alcohol on the night of the child's death, each of whom was co-sleeping with the baby.

DISCUSSION

Our data reflect the low incidence of SUDI in recent years in Northern Ireland. The death rate (0.32/1000 live births) is lower than that reported nationally in a similar time period – in 1995 to 2000 this was 0.54 – 0.7/1000. It is also considerably lower than that recently reported from the Wirral (population 350,000; 1.2/1000 live births).[8] In common with that in other UK regions, the rate here has declined considerably from that in the early 1990s (see above).

On the other hand, there seems little doubt both in local experience and in the literature that co-sleeping has increased in the past two decades. For example, a Norwegian study found among control (normal) families (1993-98) that 15% of parents routinely bed-shared with their baby compared to half this proportion in 1990-92, but only 4% in 1984-89.[9] Such practice has been shown to have some benefits and, for example, is known to promote breastfeeding.[10] However, the trend has been accompanied by a 17-fold increase in the proportion of babies found dead while bed sharing.[9]

In our five-year study of 45 SUDI, more than two-thirds died while co-sleeping which is in contrast to data reported by the CESDI Research Group for five English Regions [respectively, 30/ 45 (67%)

vs. 126/ 321 (39%); p=0.001].[2] That in the Wirral study was 36%.8 The rate we report is also high when compared to other western countries, such as Norway (1993 –1998, 34 %) and the USA (47% sleeping on a shared surface).[7,9] Moreover, more than 70% of SUDI occurred at less than four months of age, which is broadly similar to that in larger studies,[1,2,7,9] and confirms that the greatest risks is to younger babies. The European Concerted Action on SIDS (ECAS) which was a large case control study from 20 European regions found that the risk to babies who bed-shared all night with an adult was inversely related to a baby's age – declining by 5% each week.[11] Although our work sheds no light on this trend, we believe that the age-related risk has not been stressed sufficiently.

It was a particular worry that 11 of the 30 co-sleepers in our study were found dead on a sofa or armchair. In a large case control study, Blair and colleagues[2] have highlighted the very high risk (50-fold) that this practice carries; and two babies at death had a clear imprint on the face caused by soft furnishings. These, together with the 19 whose last sleep was in bed with an adult(s), are lying on surfaces that are inherently softer, possibly warmer, and distinctly more unsafe, which, given the age group, exposes them to various risks, such as overlaying and airway obstruction causing accidental asphyxiation, head covering (with overheating), or entrapment either in tight bedding or between the bed and a wall.[7,12]

However, the position in which a baby is found may not explain fully why death occurred. Carefully matched controlled studies (summarised in CESDI SUDI Studies, 2000[1]) have clearly demonstrated that the risks assume statistical validity when the carers are either habitual smokers, or have consumed significant quantities of alcohol (> 2 units) or of illicit or sedative drugs.[2] The risks appear therefore to relate to life-style issues. For it to be effectual, advice given by doctors, midwives and health visitors needs to be expressed with simplicity and clarity, emphasising both the benefits and risks. We question whether this is currently the case.

It is clear that in Northern Ireland there is an increased risk of SUDI both at weekends and during the warmer months of the year, patterns that differed significantly from those in the reference group.

Although the CESDI Research Group reported that there was no particular day when the number of deaths was significantly different than expected (peak days Thursday and Fridays),[1] Williams and colleagues in New Zealand reported a similar finding in respect of weekends (and public holidays). One-third of all SIDS died then, the peak day being Sunday.[13] This work followed an earlier study by the same group, and several other earlier papers both from European countries and Australia.[13] Although we lack precise data to account for our findings, given what sparse anecdotal information we have (see above) and others' published work [1,2,11] it is impossible not to speculate that bed sharing combined with a weekend lifestyle that may in some cases have included parental alcohol consumption and/or recreational drug, in habitual smokers, might alter "good enough" child care practices. The New Zealand work also found that the likelihood of SIDS after a party was higher at weekends (odds ratio 2.47) suggesting that alcohol consumption may have a role.[13] A study from Seattle found an eight-fold increased risk of weekend deaths linked to mothers' educational disadvantage.[14]

Why our findings show a very significant increase in SUDI during summer months is also open to conjecture. Is it possible that some of these life-style factors, perhaps allied to civil tension in the Province, which tends to increase at this time of year ("the marching season"), could be an added stress or distraction in some communities. These are tentative rather than judgmental comments and represent an attempt to understand findings that differ markedly from seasonal data in the Republic of Ireland (1993-97), for example, where no seasonal peak has been observed.[15] What seems clear from our work and that of others [1,2,7,9,13] is that current evidence regarding the increased risks of SUDI that arise with use of shared sleeping surfaces and adverse lifestyles needs to be further emphasised to each emerging group of parents. Much of the increased risk of SUDI relates to smoking in pregnancy;[2] and the CESDI SUDI Study found that the risk was 1 in 737 where anybody smokes in a household compared to just 1 in 5,041 where nobody smokes.[1] It is known that 28% of women in Northern Ireland are smokers – a slightly greater proportion than men. In the Republic 60% of babies are exposed to one or more adults smoking in the home despite parental awareness of its association with SUDI.[16] However, it is disappointing that a recent study aimed at helping mothers stop smoking in pregnancy was largely ineffective and the rates of validated cessation were substantially lower than self reported rates. The authors conclude that more intensive and complex interventions, appropriately targeted and

tailored, need to be developed and evaluated, which gives some indication of the formidable challenges posed by this factor alone.[17]

We recognise that our study has a number of limitations. The histories recorded were unstandardised, largely anecdotal, and were not recorded by health professionals. Factors related to perinatal health, family size or socio-economic circumstances were mentioned infrequently.[1] The information also often lacked details thought to be linked to SUDI, such as birth weight and gestation, recent symptomatology, parental or passive smoking, infant's body temperature, the nature of bed coverings, tiredness of carers, recent alcohol or recreational drug consumption. James and colleagues have also commented on the difficulties of obtaining accurate information on life-style habits on the night of death and concluded that such data tends to be under-reported.[8] Moreover, police involvement in some communities can make collection of such information problematic, albeit for public health purposes. Since this study was completed, an inter-collegiate working party of the Royal Colleges of Pathologists and of Paediatrics and Child Health chaired by Baroness Helena Kennedy QC has reported. The resulting Report sets out the necessary collaboration and communications between the police, HM coroner, pathologists, paediatricians, and others and of the need for close dialogue with the parents themselves. Clearly this protocol should result in a more structured and sensitive approach to the various strands of practice necessary in these circumstances.[18]

Our study was designed primarily to focus on the place (e.g. co-sleeping) and time of death and SUDI and was therefore largely descriptive and retrospective. Instead of contemporaneous, matched controls we sought the next best alternative – a comparison group of infant deaths that have been described – drawn from the same overall population within a virtually identical time frame (*Table I*). Although the median age of the SUDI was somewhat younger they constitute a mutually exclusive group from the reference population which we feel broadly reflects the spectrum of infant deaths province-wide.

In the early 1990's, a relatively simple change in parenting practice reduced this form of infant mortality in various countries by almost three-quarters.[19] It now seems that large numbers of parents routinely bed share with a baby. In a recent US study it was the more vulnerable infants so exposed – 50% at one month of age – reducing to 18% by six months.[20] However, to issue blanket advice directed against this practice *per se* seems unwise. The ECAS Study found, for example, that the odds ratio for a non-smoking mother who shared a bed with her baby (modal age of 10 weeks) carries only minimal risk (odds ratio 1.56).[11] Hence the approach to a well-educated, non-smoker of moderate habits, who, to facilitate breast feeding,[10] takes a baby into her bed must differ from that of a young, poorly educated woman with an adverse lifestyle living in poverty. Bed-sharing affords a range of positive benefits both to mother and baby, and a recent review concludes that the complexities of this interaction are only just beginning to be unravelled and that health care professionals must avoid over-simplistic advice that bed-sharing behaviour is inherently harmful.[21]

However, a growing body of evidence worldwide suggests that in certain circumstances (i.e. excessive parental tiredness, habitual smoking, or alcohol or drug ingestion), co-sleeping places young infants at significantly increased risk of undetermined death, overlaying or SUDI.[7] Advice on the risks of co-sleeping in a household with such adverse co-factors has not received the promotion accorded to better publicised risks such as prone sleeping and those just alluded to.[1-2,8,11]

It is crucial that health promotion agencies and the relevant practising professionals find improved ways of co-ordinating advice to parents so that a more balanced approach is presented. Advice also needs to be well targeted, especially, but not exclusively, at those with adverse or potentially dangerous lifestyles. However, it is salutary to note that the Cardiff audit study of how parents were adhering to the Back to Sleep Guidelines,[22] found significant proportions, within quite differing socio-economic communities, who regularly disregarded warnings on risk reduction.[23] A recent Irish study has reported similar findings,[16] as has one from Kentucky.[20] This causes one to wonder whether, given the increasingly robust evidence of the risks, novel ways of promoting such public health measures need to be researched jointly by health care policy-makers and the professionals with major responsibility for mother and infant care.

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CONFLICT OF INTEREST

The authors have no conflict of interest

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Medical History

The Transactions of the Belfast Medical Society, Belfast Clinical and Pathological Society and the Ulster Medical Society, with Background Notes

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INTRODUCTION

The Ulster Medical Society celebrates two important anniversaries in 2006. The first is the 200th anniversary of the beginning of the Belfast Medical Society; the second is the 150th anniversary of the death of Doctor Andrew George Malcolm (*Fig. 1*).

Malcolm started the Belfast Clinical and Pathological Society in 1853 and it was the amalgamation of that society with the Belfast Medical Society in 1862 which gave rise to the Ulster Medical Society. This paper will look in turn at each of the three societies and their transactions, the latter term taken here to mean any published account of the proceedings. All unreferenced society quotations are from the original minute books.

THE BELFAST MEDICAL SOCIETY

The first minutes of the Belfast Medical Society are now missing but they were available to Malcolm when he published his medical history of Belfast in 1851.[1] He did not give the date in 1806 on which the Society was founded but he did record that the nineteen physicians and surgeons involved had a desire for "mutual improvement in their common profession," and that "the selection and purchase of books &c., were entrusted to an elected Committee." Serious differences of opinion among the Hospital attendants led to the Society faltering in 1814 and ceasing to exist in 1818. It was restarted at a meeting in the Fever Hospital on 8 June 1822 "held to consider the propriety of adopting measures for the revival of the medical library…".[2] The original Society had four Presidents from 1806 to 1814 (each presumably serving two years) but until 1850 the revived Society had none, the chair at each meeting being taken by the fifth member to enter the room. This curious shunning of the office of President suggests that the difference of opinion among the more senior members of the original Society may have related to the Presidential succession.

Fig 1. Dr Andrew George Malcolm 1818–1856.

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It seems clear that both in 1806 and 1822 the main purpose of the Society was to provide a library for the members. This was not a common reason for starting a medical society, only 5 out of 135 senior Scottish medical societies having similar objects.[3] By 1859 the library held a total of 1249 titles (including journals and manuscripts). Of these, a substantial number, 538, were from the 18th century or earlier but the Society had been buying new titles and 211 of the collection had publication dates after 1838.[4]

Six clinical presentations were made to the revived Society from 4 November 1822 to 2 June 1823, the first being two cases of cynanche laryngea, read by Dr J McDonnell and presented by Mr R Coffey. The presentations seem to have been well enough received but for some reason they were not continued – whether this was by agreement or by default is unknown. Dr Malcolm joined the Belfast Medical Society in 1842 and it may be no coincidence that within three years the Society had agreed to receive clinical presentations at its meetings, to publish its proceedings, and to form a pathological museum. On 2 December 1844 it was decided that in addition to the routine business, "communications from members upon Medical and Surgical topics and reports of cases should be received and discussed" and on 3 February 1845 a subcommittee was set up to consider regulations for the conduct of future meetings. The members of the subcommittee included Malcolm and Dr JM Sanders, the proposer of the resolution. It was agreed that library business would come first; that written communications and communications of which notice had been given would take precedence over others; that the members would be permitted to speak once in turn after each presentation; and that the presenter would have the right of reply at the end. The first case under the new rules, one of haematocele, was presented by Dr Sanders on 3 March 1845. The combination of the clinical presentations and discussions at the meetings and the ready access to medical literature provided by the library, meant that the Society offered unprecedented local opportunities for professional education and advancement.

The first issue of the *Dublin Hospital Gazette* appeared on 15 March 1845, just 12 days after Sanders presented his case of haematocele. The Proprietors wished "to afford an accessible channel for the publication of every new fact in Pathology, Diagnosis, and Therapeutics", and they offered "facilities to the attendants on Provincial Institutions, for publishing those important cases and observations that are continually presenting themselves to their notice."[5] The coincidence of its appearance and the appropriateness of its objects did not pass the Belfast Medical Society by, and on 5 May 1845 it was agreed that "an abstract of the proceedings of the society be sent regularly to the Editor of the *Dublin Hospital Gazette* as the proprietors have kindly offered to insert the same." The first report, the case of haematocele by Sanders, appeared on 1 June 1845 (*Fig. 2*).[6] It was not a strong case and attracted some criticism in the discussion. Reports appeared regularly until 1 April 1846, the last being a description of one of the preparations in the pathological museum. The *Dublin Hospital Gazette* ceased publication on 1 May 1846, the proprietors explaining that "the time and labour requisite for the continuance of this Journal, is incompatible with their other avocations."

BELFAST MEDICAL SOCIETY.

Monday Evening, 3rd March, 1845.

MR. OFFICER IN THE CHAIR.

Dr. SAUNDERS opened the proceedings of the evening by drawing the attention of the meeting briefly to a case of hæmatocele, the cure of which was completely effected after simply removing the fluid. This case from the patient's own account, was one of ordinary hydrocele of six or seven years standing, and was tapped on three or four occasions. Some weeks prior to admission into hospital, an attempt at the *radical* cure by injection had been made, but the fluid seemed to have returned. He was now again tapped, and a quantity of bloody fluid with some purulent matter withdrawn. No inflammatory action ensued, and no fluid of any description was afterwards formed.*

In the remarks which followed the detail of this case, some of the members observed that the time was rather short for forming a true opinion with regard to the stability of the cure. The *rationale* of success in this case was generally admitted to depend mainly on the intensity

* This last tapping was performed about four months ago, and the patient is now quite well.

Fig 2. The first text. Dr JM Sander's case of haematocele published in the *Dublin Hospital Gazette* on 1 June 1845.

Between June 1848 and May 1849 the Dublin Medical Press published some proceedings. The first report was of a case of diseased spleen by Dr JH Halliday and a number of papers also appeared, most of them dealing with the management of cholera, an epidemic of which had started in Belfast in December 1848.

A new series of the *Dublin Hospital Gazette* began in 1854 and ran to 1862. The ninth volume (1862) has not been available for examination. The earlier volumes only contained brief accounts of the annual meetings for 1856 and 1857 and a rather longer account of the annual dinner for 1858, although some papers which had previously been read before the Society were printed in their own right.

The *Dublin Journal of Medical & Chemical Science* first appeared in 1832. It was then sequentially titled the *Dublin Journal of Medical Science,* the *Dublin Quarterly Journal of Medical Science,* the *Dublin Journal of Medical Science* and currently the *Irish Journal of Medical Science.* It was sometimes referred to as the Dublin Medical Journal. The *Dublin Quarterly Journal of Medical Science* ran from 1846 to 1871, and accounts of the proceedings of the Society appeared for the sessions 1857/58, 1858/59 and 1859/60. These proceedings were reprinted as the *Transactions of the Belfast Medical Society* by the University Press, Dublin. There were two volumes, the first contained the proceedings for 1857/58 and the second contained those for 1858/59 and 1859/60.

THE BELFAST CLINICAL AND PATHOLOGICAL SOCIETY

It was through Malcolm's efforts that the Belfast Clinical and Pathological Society was formed in 1853. The objects of the Society were "the Cultivation of Practical Pathology, Diagnosis and Therapeutics, by means of the accumulation, and Analysis of appropriate Cases and Pathological Reports, and Public Discussion thereon; the establishment of a Pathological Museum; and the keeping of Records, to indicate the progress of discovery in Medical Science."[7] Analytical and microscopical committees were set up to report on specimens sent in by members, records of each meeting were to be sent to a Dublin journal (or journals) and an annual volume of the transactions was to be printed. During the second session it was decided that lithographed abstracts of each meeting should be offered to non-resident (country) members, the only charge being postage of 1d per week (later standardised at 2/6 per session). The intention was to support the non-resident members who found it more difficult to get to the weekly meetings in Belfast and it seems to have been successful. At the Society's second conversazione held at the close of the third session on the 30th April 1856, Malcolm said "our Society has extended its operations into all parts of the province of Ulster; and its most distant members feel its improving influences almost as vividly as if they were resident, and enabled to join directly in its proceedings. This pleasing result of our weekly lithographed 'abstract' is but a slight indication of what I trust may yet be accomplished, in the way of placing the resident and non-resident members more on an equality."[8] Unfortunately, even today, that equality has still not been reached. A fortnight after the abstracts were offered to the non-resident members, the same privilege was extended to students and the resident (town) members. Malcolm seems to have been prepared to subsidise the production of the abstracts in that he guaranteed that the Society would not suffer financially for that session because of it. In this context it should be noted that he was a very generous donor to the pathological museum and that after his death, his widow had so little money that she had to ask the Society for a contribution in acknowledgement of the money he had expended.

The proceedings of the first session are not to be found in the Dublin journals. Those of the second to the eighth sessions appeared in volumes two to eight respectively (1855 to 1861) of the *Dublin Hospital Gazette* (new series).[8] Unusually, during the eighth session the Society was asked where the proceedings should be published. It was agreed on 24 November 1860 to continue to send them to the *Dublin Hospital Gazette* but the minutes do not record why the question needed to be asked. The *Dublin Hospital Gazette* was to cease publication in 1862 and perhaps there was some uncertainty about its future even then. During the ninth session the proceedings of the meetings from 26 October 1861 to 18 January 1862 appeared in volumes 33 and 34 of the *Dublin Quarterly Journal of Medical Science*. On that same 18 January 1862 the Society agreed that "Dr Jacob be informed that arrangements have been made for the publication of the transactions of the present session, but that he be thanked for his attention". Dr Arthur Jacob was the editor of the *Dublin Medical Press*[9] and the Society must have

been enquiring if the transactions could appear there. They seemed to be certain that they had made arrangements for publishing the session's proceedings in a journal other than the *Dublin Medical Press* but for meetings after 18 January 1862 that journal was certainly not the *Dublin Quarterly Journal of Medical Science*. Whether it was the *Dublin Hospital Gazette* can only be determined when volume nine is examined.

The original weekly abstracts of the meetings were handwritten and lithographically printed on a sheet of flimsy paper 10 inches wide and 15½ inches high. The script was dense and difficult to read (*fig. 3*), and the paper was not suitable for a permanent record. The annual *Transactions* were better in both respects but their appearance was delayed as they could not be printed until after the close of the session. The accounts of the proceedings published in the Dublin journals were also readable and permanent but would have suffered some delay and would not have been available to most members except through the library of the Belfast Medical Society. The possibility that the lithographed abstracts might replace the *Transactions* had been considered. Professor JC Ferguson, the president for the second session, said in his closing address at the first conversazione on 5 May 1855, "The 'Abstract,' I should hope, however, will not interfere with our volume of Transactions. In fact, I feel that in this matter we have committed ourselves; that the profession expect it from us; and I confidently trust they shall not be in any way disappointed."[8] His hope and trust might have been realised if the abstracts had remained difficult to read and preserve. Council could see, however, that typeset weekly abstracts would provide members with a readable, permanent and timely record of each meeting – and that they would replace the annual *Transactions*. It is not possible to say whether the new scheme would have saved money or not. Typesetting would presumably be more expensive than lithography but annual printing costs might be lower and binding costs would disappear. Perhaps Council was most influenced by the immediacy of publication. In any event, at a Special General Meeting held on 24 September 1859, it was agreed "that *all* Members shall contribute, with their Annual Subscription, the sum hitherto paid for the ordinary Weekly Abstract (2s. 6d), by which the Council will be enabled to issue, during the Session, improved Reports of the Society's proceedings, in a permanent form, which will be forwarded to *every* Member." This brought the cost of the annual subscription up to 12/6 for resident members and 7/6 for non-resident members. Those who took the old abstracts would have noticed no change in their annual contribution. The scheme seems to have gone ahead as in November 1859 there was a proposal to enlarge the size of the type and paper (not accepted), and on 21 November 1860 it was agreed that "the first 12 pages of the Transactions be sent out." Both a will and a way are required if records are to be kept. Council provided the way but the will must have been lacking at the time or since, as no copies of the typeset records exist in the Society's archives. Paradoxically, 23 issues of the flimsier, lithographed abstracts (all for the session 1856/57) have survived although we have lost much else over the years.

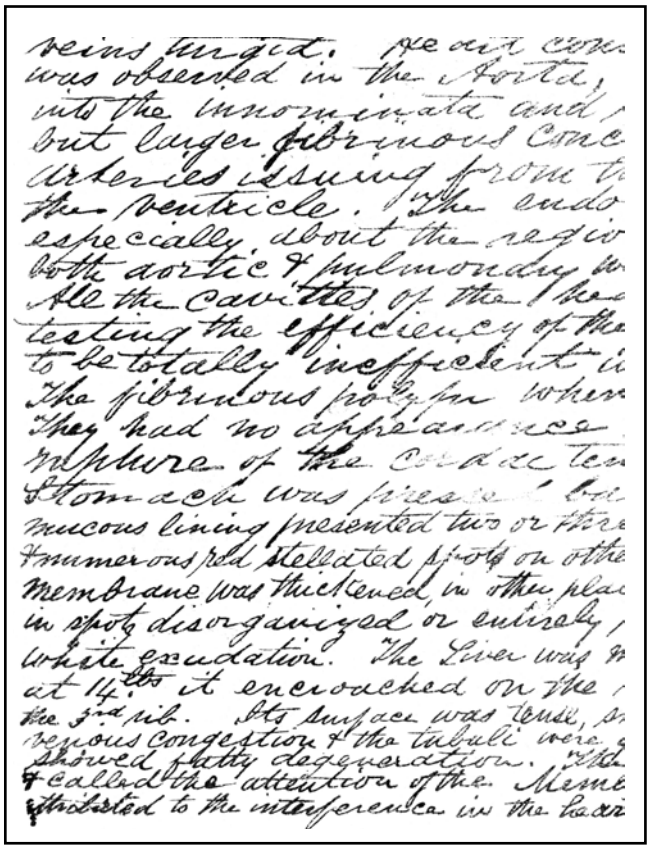

Fig 3. Reproduction of part of the lithographed abstract of the post-mortem report on the case of *Cardiac and Hepatic Disease* read by Dr McGee at the meeting of the Belfast Clinical and Pathological Society on February 21 1857.

Copies of the annual *Transactions of the Belfast Clinical and Pathological Society* for five of the Society's nine years of existence are held in various libraries. It is not known for certain what happened to the *Transactions* for the other four

years but it is likely that for 1856/57 and 1857/58 they were printed but are missing. On 26 May 1859, immediately after Council had agreed to improve the weekly abstracts, Dr H Murney proposed "that in future there be no reprint of the Transactions at the end of the Session." The minutes do not record if this motion was accepted but if it was it was ignored at least once, as a volume of the *Transactions* was published at the end of the next session (1859/60). It is unlikely that annual *Transactions* were published for 1860/61 and 1861/62 but especially so for the latter as that was the last session.

When the *Transactions* of the first session appeared, an anonymous reviewer in the *Dublin Medical Press* asked how the Belfast society, with only 96 members and half the subscription of the Dublin Pathological Society, could publish its proceedings when the Dublin society, the senior pathological society in the British Isles, could not.[10] The answer undoubtedly lay in the character and activity of Dr Malcolm and of those with him in the venture. Council spent some time deciding on the format of the *Transactions*. Initially they planned spending £5 on so many copies of a small octavo volume and asked for estimates of the number of pages they would get. Alexander Mayne offered the best value (200 copies each of 48 pages) and his estimate was accepted. However, all this careful planning came to naught when it was calculated that after "inserting laws, list of members, specimens, cases etc.", only 20 pages would remain and that these would not accommodate the debates. Council then resolved that "the Transactions be printed *in full*, including the Debates; and that the added expense be met by such means as the Council may thereafter consider expedient." This was magnificent of Council but there is perhaps a suspicion that Malcolm offered to subsidise the costs in the way that he had done for the lithographed abstracts and for the museum. The first *Transactions* contained 132 numbered pages and 11 pages of illustrations. Mr Mayne's final account was considered "very moderate and reasonable" and was paid but the actual sum was not revealed in the minutes. In the first year the cost of printing "Laws, Circulars, Case-papers, Tickets, &c." was £14 17s 2d, while in the second the cost of printing "Transactions, Reports, Circulars, &c, Binding, and Advertising" was £26 16s 8d. Binding was priced separately from the printing and cost £2 2s so perhaps the first *Transactions* cost £10 – double that which Council had originally planned. The binding included a stamped cover and the cheap appearance of this drew some mild criticism from the reviewer. However, the cheapness of the cover goes some way to answering his question as to how the Society managed it. Every member received a copy free. The original intention was to charge new members 2/6 per copy but the price was raised to 3/- to meet the increased costs. Spare copies were later offered to medically qualified non-members at the same price. The sale of the first *Transactions* brought in £1 16s.

THE ULSTER MEDICAL SOCIETY

Malcolm died on 19 September 1856 of congestive heart failure secondary to rheumatic mitral and aortic valve disease. He had been under the care of Dr JM Neligan of Dublin for about two months before his death and he must have known of the seriousness of his condition when he rose to reply to the toast, "The Belfast Clinical and Pathological Society, and its founder, Dr Malcolm", proposed by Dr McGee at the 33rd Annual Dinner of the Belfast Medical Society on 10 June 1856. Consequently it is likely that his words were chosen to reassure those who might in the future have to decide the fate of the Clinical and Pathological Society. His speech was not recorded in full but he was said to have "expressed a hope that the time was not very distant when the parent 'Medical Society' and the 'Clinical' would be united into one great Society for the medical men of Belfast and the entire province."[11] That union came about six years later, and we continue to benefit today from his foresight and genius.

By the early 1860s both societies were showing signs of faltering. The Belfast Medical Society Council Report for the 1860/61 session, read at the annual meeting on 6 June 1861, "expressed the regret of the Council that the affairs of the Society are not in a more flourishing condition, inasmuch as but one new member had joined during the past year, whilst one had died, another retired, and three others would become free members during the ensuing year." The Belfast Clinical and Pathological Society Council minutes had become neglected with no dated records for the session 1861/62 being entered in the minute book at all. Meantime, the proceedings of the Medical Society were approximating those of the Clinical and Pathological Society. It is true that the former still had the medical library and that the latter still had the pathological museum and the analytical and microscopical committees, but both were now

presenting cases at their meetings and both were publishing their proceedings (the Medical Society intermittently). With similar problems, largely similar activities, and a limited pool of potential members, it made sense to consider amalgamation. Dr Murney seems to have been responsible for most of the planning, and all came to fruition on 30 April 1862 with the formation of the Ulster Medical Society.

In 1859 there were 55 names on the list of members of the Medical Society and 99 on the list of the Clinical and Pathological Society. Thirty-one names appeared on both. Assuming that the numbers in 1862 were similar, the newly formed Ulster Medical Society might have started with about 120 members. It might be expected that the new Society would attract more members and 11 applications for membership were indeed put forward to the first meeting. The initial level of the annual subscription is unknown but a few years later, in an effort to encourage new members, it was suggested that the subscription for town members be reduced to one guinea. While this was significantly more than the subscription for the Clinical and Pathological Society, it was actually less than the subscription to the Medical Society in 1822. The combination of the greater number of members and the higher subscription meant that the Ulster Medical Society was in a stronger financial position than either of its predecessors.

On 8 November 1862, Council was asked to consider the question of the publication of the transactions and on 15 November the Society resolved "that the transactions of the Society be offered in future to the *Dublin Medical Press* for fortnightly publication." Dr Browne was asked to communicate with the Editor and a week later read a reply from Dr Jacob who must have agreed to accept the Society's offer as Dr JC Ferguson's presidential address appeared in that journal on 26 November 1862. Case reports appeared the following week (3 December) and again on 17 December and 31 December. There were a total of nine published presentations in that first month but only once were the discussions included. The significance of this is only apparent when it is known that there was disagreement within the Society on the subject. At a special meeting called for 27 December 1862, the members divided equally between those who thought that the discussion following each presentation should be published and those who thought that it should not. The President was forced to use his casting vote on two occasions and eventually it was agreed "That a Committee of Publication be appointed consisting either of the Council or a portion of the Council for the purpose of [reviewing] discussions held on papers or communications made to the Society, before issuing them to the profession in any form." Nothing further appears in the minutes on this topic but discussions, perhaps edited, were published from then on although those for the first case published in January 1863 only appeared the week after. Never again would the Society have so many presentations published in the *Dublin Medical Press* in so short a time. Indeed only six appeared during the whole of 1863 although the annual meeting, the presidential address and a dinner given for the medical officers of the Channel Fleet were all reported. The next year, 1864, was worse with only one appearing but Dr Whitaker's comments to the Society on the new edition of the British Pharmacopoeia extended over 11 pages and there was a paper from Dr Keown on Ship-Malaria.

Publication in the *Dublin Medical Press* then ceased but in 1868 the proceedings started to appear in the *Dublin Quarterly Journal of Medical Science* and selected reports continued to be printed there until 1894. The last clinical presentation appeared in volume 90 (1890) and was a report by Mr H O'Neill of two successful cases of nerve suture and tendon suture following lacerations of the forearm, while the last paper was Brigade-Surgeon FE M'Farland's presidential address which appeared in volume 98 (1894).

The *Lancet* published some proceedings of the Society but very intermittently as the Ulster Medical Society was competing with many other societies for space in the journal. Professor J Cuming's presidential address for the 1868/69 session appeared on 7 November 1868 and the first case reports, albeit very brief being part of the annual report of Council, appeared on 16 November 1872. The last paper was a summary of a lecture to the Society by Drs SB Boyd Campbell and TH Crozier on 1153 cases of cardiovascular disease, and this appeared on 2 December 1933.

On 7 February 1863 the minutes record that "A letter from the Editor of the 'Dublin Medical Press' was read relative to the reprinting of the Transactions of the Society and offering to throw off a hundred copies . . . at the rate of a guinea per sheet. The Secretary was instructed to write

the Editor and inform him that the Society would accept his terms." Despite this early decision, the first *Transactions of the Ulster Medical Society* did not appear until 1865 although they did include selected proceedings from the three sessions 1862/63, 1863/64 and 1864/65. They were printed by Thomas Deey in Dublin at the office of The Medical Press. Our knowledge of the *Transactions* for the next 20 years is incomplete. Copies exist for three sessions (1872/73, 1877/78 and 1880/81) and the Society minutes record the printing of two sessions (1873/74 and 1876/87). The Council minutes, which should contain fuller details, are missing. The volume for 1872/73 is smaller than the others and was printed by Alexander Mayne in Belfast. Up until 1889/90 all other extant volumes were printed in Dublin while after that they were printed in Belfast. The *Transactions* appeared continuously from 1884/85 to 1898/99, the last four of these volumes (from 1895/96 to 1898/99) being shared with the North of Ireland Branch of the British Medical Association. Their proceedings appeared after those of the Society and took up, on average, a third of the total pages. At a Council meeting on 29 June 1900 a letter from the Branch was read stating "that the Branch would not any longer pay their half of the cost of printing the transactions but would pay *pro rata*." After some discussion, Council decided that "the transactions of the Ulster Medical Society be not printed this year [1899/1900]." When the *Transactions* for 1900/01 appeared they contained only the Society's proceedings. Publication then continued up to 1928/29 although sometimes two or three sessions were printed in the one volume. The last paper was by Dr Foster Coates on the pituitary gland (*fig 4*).

On 22 January 1931, Professor AM Drennan raised in Council the question of the formation of a local medical journal. This suggestion was sent to a subcommittee who approved of the idea and reported back to Council on 30 April 1931 with a list of recommendations. One of these was that "the transactions of the Ulster Medical Society comprising papers read during the last two years be not published." The report was accepted by Council and by the Annual General Meeting on 20 May 1931 and so the *Transactions* came to an end, supplanted by the *Ulster Medical Journal*. One curious exchange occurred after the first issues of the Journal had been sent to the Keeper of Printed Books at the Copyright Receipt Office in the British Museum. Apparently realising for the first time that the Ulster Medical Society had been publishing the *Transactions* for many years, the Keeper wrote to the Editor of the *Journal*, Dr R Hunter, demanding a copy of every issue. Dr Hunter replied pointing out that he was not responsible for the *Transactions* and that furthermore in his view they were exempt, as they had been printed for private circulation and not offered for sale.

In conclusion, I should like to utter a protest against the indiscriminate use of gland and tissue extracts. A large number of these are now on the market, and are being boomed by the manufacturers ; the vast majority of them are inert and useless. Even the more ardent endocrine therapists only recommend the use of relatively few preparations.

Professor Swale Vincent states—" The results of endocrine therapy are chiefly due to the influence of a credulous physician upon a still more credulous patient."

Fig 4. The last text. From Dr F Coates's paper on the pituitary in the *Transactions of the Ulster Medical Society* 1928/1929.

DISCUSSION

There was never an editor of the transactions as such and the honorary secretaries seem to have been responsible for arranging the material for publication. It was customary to record each case in the ordinary minutes of the meetings although sometimes the notes were very brief. In the early years the proceedings and discussions would have been transcribed from the honorary secretary's notes but the more formal papers later on must have been prepared by the authors. Dr R Esler published two papers on the early history of medicine in Belfast in the *Transactions of the Ulster Medical Society* for 1885 and 1886 [12,13] (and other histories of the three societies and their members have appeared in the *Ulster Medical Journal* [14-16] since then). The number and the quality of illustrations rose with time. The Clinical and Pathological Society had used sketches and Daguerreotypes to illustrate cases at meetings, and a number of lithographs appeared in the first and second annual *Transactions* of that society. The first photographs, a pair, were published in 1892 in the *Transactions of the Ulster Medical Society.* These were of a child, Annie B, before and after an operation for a facial naevus. The first X-ray, that of a hand in a case of acromegaly, appeared in 1909 and the first ECG in 1914.

Great advances in medicine were made over the 84 years of the transactions and, of course, even more advances have been made in the 77 years since they stopped. In the early days cupping and bleeding

were still being recommended, some patients being bled until they fainted, and drugs were prescribed with faith if not science. For instance, on January 26, 1856, during a debate on the best local treatment for severe scarlatinal sore-throat, it was reported that "Professor Ferguson varied his local treatment in each case, and thought that we should rely chiefly on the constitutional treatment of the disease. Professor Stewart, Dr Patterson, and Mr Browne confirmed the value of the strong solution of nitrate of silver, as recommended by the President. Dr Moore preferred a dilute solution of nitric acid; Dr Lynch used a syrup made with lemon juice and sugar; Dr Young preferred a linctus of muriatic acid and honey; Dr Pirrie had successfully used the tincture of iodine, but he had not much faith in local applications." [8]

On reading these early proceedings, it is difficult at first to understand how the clinicians could have believed that what they were doing was right but in some respects we may be no better. Those celebrating the 300th anniversary in 2106 may have equal difficulty in understanding how we could have applied the results of clinical trials on populations to individuals who would not be likely to benefit from the recommended treatment. Our predecessors were as clever, educated, energetic and resourceful as ourselves (perhaps more so) but they were constrained by their environment just as we are by ours. What we can do is to share with our colleagues in the past and in the future the same desire for excellence in the art of medicine and the same desire to seek the truth – *quaerere verum*.

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CONFLICT OF INTEREST

The author has no conflict of interest.

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Medical History

Ulster connections with Nelson and Trafalgar

RSJ Clarke

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Last year brought the two hundredth anniversary of the battle of Trafalgar and it is a good time to remember Ulster's strong connection with the Royal Navy over the centuries. We can identify some 200 Ulster doctors who qualified before 1900 and served in the Navy,[1] though this may well be an underestimate, for it is hard to produce a complete list to compare with the approximately 260 who served in the Army Medical Service[2] and about 100 who served in the Indian Medical Service[3] over the same period. There are excellent annotated rolls for these two services, while no biographical list exists for the surgeons of the Royal Navy and names have been obtained from Medical Directories and scattered earlier sources.

Until about 1850 most of those joining the Naval Medical Service did not have a medical qualification, but took a course of training and an examination set by the Surgeons' Company of London.[4] They would then join a ship as surgeon's mate or assistant surgeon, moving from ship to ship over their career, with often a posting on shore as physician to a hospital when they were more senior. On the other hand many served for only a few years, to retire early and move into general or hospital practice (for example Dr Samuel Browne (1809-90), attending surgeon to the Belfast General Hospital and the father of ophthalmic surgery in Belfast[5]). Often they only took a medical qualification in mid-career or on retirement from the Service and at this stage no further formal period of study might be necessary. Later in the nineteenth century recruitment was as it is now, from fully qualified doctors and the progression included the rank of staff surgeon, known from 1875 as fleet surgeon.

Two surgeons from this group are of special interest now because they served with Nelson on the *Victory* and wrote detailed letters and diaries of their experiences there. Both have been the subject of biographical articles, published some fifty and ninety years ago and Dr R.S. Allison, neurologist and medical historian,[6] collected material on both, although he never published anything on them.

LEONARD GILLESPIE

Leonard Gillespie (*fig 1*) was born at Armagh on 20 May 1758, son of Leonard Gillespie and Elizabeth Blakely.[7] His parents died when he was a child and he was brought up by his two elder sisters until he was apprenticed at the age of fourteen to a doctor

Fig 1. Leonard Gillespie, MD, RN. (from the portrait by Charles Louis Bazin)

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in Armagh. Five years later he went to Dublin where he studied for a year under various surgeons. (The Royal College of Surgeons did not receive its charter until 1784[8]). In June 1777 he attended a court of examiners of the Company of Surgeons in London and having satisfied them, was passed into the Royal Navy, to become second assistant surgeon on HMS *Royal Oak*. In this period he saw a lot of the slave coast of West Africa and made journeys to and around the West Indies, guarding merchant ships and in March 1779 heard the guns in General Washington's camp firing to celebrate the third anniversary of the Declaration of Independence. He was promoted to surgeon in 1781. The duties of the surgeon, of course, rarely involved operative surgery and both at sea and in the hospital of St Lucia, he took a particular interest in leg ulcers. These were caused by abrasions, dirt and damp, and healing was impeded by scurvy.

The peace of Versailles in 1783 saw Gillespie discharged from the Navy, with a considerable sum of prize money, and he took the opportunity to study medicine further in Edinburgh, St Andrews and Paris for two years before returning home to see his sisters. Those in Armagh advised him to practise at home, as was common with naval surgeons after a war was over, but he found the country life too narrow compared with that of London and Paris, and boredom soon set in. Within a year he was in London enjoying both the intellectual and medical stimulation, and by 1787 he was back at sea. As a humane and cultured man he deplored the press-gang methods, the drunkenness, hangings and floggings, and the constant recourse to prostitutes who made treatment of venereal disease one of his main concerns. Over the next few years society at sea must have been even narrower than in Armagh, but he took every opportunity, when his ship berthed in Edinburgh or London, to attend lectures and cultural gatherings. His ship put in at Le Havre in January 1791 and he took prolonged leave to visit Paris again and to attend the wards of the hospitals until the situation worsened with the execution of Louis XVI.

War was declared between England and France on 1 February 1793 and he rejoined the Navy on board HMS *Majestic*, taking part in Lord Howe's victory on the Glorious First of June 1794. As we have seen, surgeons' problems were often matters of health and nutrition, and he records that after the victory they took on board two hundred French prisoners, suffering from typhus fever and scurvy. The fever soon spread to his own ship's company and eventually sixty-eight men had to be sent to hospital. For the next eight years the *Majestic* was stationed in and around Martinique in the West Indies, where he gained even more experience of disease, particularly yellow fever. In this period he also wrote two books on tropical diseases and was granted the degree of MD by St Andrews University, on the recommendation of a London friend, Dr James Sims (formerly from county Tyrone). He also formed a lasting relationship with a local woman, Caroline Heiliger, by whom he had two children, as well as writing frequently to his sisters in Armagh and investing his large sums of prize money. Gillespie left detailed journals of his stay in Martinique which are full of concern for the welfare of the negro slaves, the treatment of prisoners and the spiritual and moral welfare of the British soldiers and sailors.

The peace of Amiens in 1802 allowed him to return home again, but he realised that war was likely to be resumed soon. In 1804 he rejoined the Navy, being promoted to the advisory role of physician and Inspector of the Naval Hospitals in the Mediterranean. This brought him into close contact with Nelson for the first time. Both were of the same age and both held similar humanitarian views on the health and welfare of the sailors and the evils brought on by rum in particular. He joined the *Victory* in January 1805 and grew to share the general admiration felt by all for their leader.

One typical day in the Mediterranean he recalled in a letter to his sister Jane, written between January and March 1805. His servant woke him at 6.00 am with a light and a weather report, after which he dressed and went on deck to watch the dawn, then joining Lord Nelson, Rear Admiral Murray, Captain Hardy and others at breakfast. This was followed by a day of study, writing and exercise, visiting the sick berth only when asked by the surgeon. There was a band performance at two o'clock, followed by an excellent dinner with the best wines, for the officers at least. This was followed by more band music and after tea, Gillespie wrote, "Nelson generally unbends himself, though he is at all times as free from stiffness and pomp as a regard to proper dignity will admit, and is very communicative. At eight o'clock a rummer of punch with cake or biscuit is served up, soon after which we wish the Admiral a good night (who is generally in bed before nine o'clock)". This was too early for

Gillespie, who would then read for an hour or join old friends in the ward room.

Much of 1805 was spent in fruitless chase of the French fleet which, perhaps wisely, kept retiring to the safety of port. On August 18, when the *Victory* was anchored off Spithead, Gillespie resigned and was granted prolonged leave to go to London. It is surprising that he should have done so at this time, but it seems that he felt that his own health was not good and, fearing a major battle, he did not relish the brutal surgery which would inevitably accompany this. He also thought that he had persuaded the Admiral to rest more now and look after himself, though Nelson notoriously paid little heed to medical opinions and was in vigorous mental and physical health for the battle of Trafalgar in October. In the autumn Gillespie went to the spa at Cheltenham but was well enough to attend Nelson's funeral at St Paul's Cathedral on the ninth January 1806. He held no more naval appointments and retired on half-pay in 1809. After the peace of 1815 he returned to Paris which, in spite of twenty years of war, he had come to regard as his home. His portrait was painted in Paris by Charles Louis Bazin in 1837 and through the window in the background HMS *Victory* is proudly shown. He died in London on 13 January 1842 at the age of 84 but was buried in the Pere Lachaise Cemetery in Paris.

SIR WILLIAM BEATTY

The other distinguished naval surgeon was Sir William Beatty (*fig 2*), remembered now for having attended Lord Nelson during the battle of Trafalgar. Beatty was born c. 1773, the oldest of six children of James Beatty of HM Customs in Londonderry, and Ann Smyth.[9] Two brothers and a brother-in-law had naval connections, which is not surprising considering the importance of Londonderry as a port and the progress of the Napoleonic Wars as they were growing up. William seems to have been educated locally and was trained by apprenticeship as a surgeon's mate. It is evident from his Journal that he also must have had some practical instruction in anatomy. He is first recorded as surgeon to HMS *Flying Fish* in 1793, with subsequent appointments to HMS *Alligator*, HMS *Amethyst*, HMS *Alcmena*, HMS *Resistance*, and HMS *Spenser*. He was appointed surgeon to HMS *Victory* on 14 December 1804, replacing George Magrath, another Ulster surgeon, and had two surgeons under him, as well as a third transferred to the ship on the evening of the battle of Trafalgar, 21 October 1805, to deal with the heavy casualties.

Fig 2. Sir William Beatty, MD, RN. (from the original portrait)

Beatty has left records of his patients in his Journal, preserved in the Public Record Office, Kew. There was, of course, no physician on board the *Victory*, and Beatty records five deaths in the ten months before the battle, of which three were due to consumption, one to fever and one to injury. As a result of the battle there were about 55 killed immediately, together with 102 wounded, of whom 7 died. Beatty and his team seem to have treated all the wounded, although five of the worst were left behind at Gibraltar and five others were later transferred to the hospital ship Sussex, lying off Sheerness.

As well as the manuscript Journal, Beatty published an "*Authentic Narrative on the death of Lord Nelson: with the circumstances preceding, attending and subsequent to that event; the Professional Report of His Lordship's wound and several interesting anecdotes .....*". This gives a graphic picture of the day of the battle and we feel we can re-create the whole scene of Nelson's wounding and death. The Admiral was in good

spirits on the morning of the 21st October and confident of victory. Contrary to advice, he insisted on dressing up in his uniform coat, which had all his orders and decorations conspicuously displayed. The French ship *Redoutable* was very close, with a sniper posted high up on the mizen-top only 15 yards from the quarter-deck of the *Victory*. Nelson was an easy and identifiable target, so a sniper was able to take steady and fatal aim. Two snipers were immediately shot from Nelson's ship but Nelson was already mortally wounded. As Beatty wrote later "The ball struck the forepart of his Lordship's epaulette, and entered the left shoulder immediately below the processus acromion scapulae, which is slightly fractured. It then descended obliquely into the thorax, fracturing the second and third ribs; and, after penetrating the left lobe of the lungs, and dividing in its passage a large branch of the pulmonary artery, it entered the left side of the spine between the sixth and seventh dorsal vertebrae, fractured the left transverse process of the sixth dorsal vertebra, wounded the medulla spinalis, and fracturing the right transverse process of the seventh vertebra, made its way from the right side of the spine, directing its course through the muscles of the back and lodged therein about two inches below the inferior angle of the right scapula. On removing the ball a portion of the gold lace and pad of the epaulette, together with a small piece of his Lordship's coat, was found firmly attached to it".

All this information was, of course, not available at the time of injury. When Nelson had been carried below and was being examined, he said "Ah, Mr Beatty, you can do nothing for me, I have been shot through the spine." He knew the symptoms of paraplegia since Beatty had explained them in the case of a boy in the crew who had been similarly injured a few days earlier. Nelson had severe bleeding and suffered greatly from thirst, but no treatment was possible and he died two and three-quarter hours later.

Nelson specifically asked for his body not to be thrown overboard but buried in St Paul's Cathedral, if the people wished it. Beatty, therefore had the task of preserving the body. This was undertaken by immersing it in the largest cask that could be found, surrounded by brandy – a procedure which was successful for all but the intestines, which did decompose and had to be removed when he carried out a full post mortem examination in Spithead. The body was eventually taken by sea to Greenwich, where it lay in state for three days before the state funeral to St Paul's. The bullet was retained by Beatty, mounted in crystal and subsequently passed from his family to Queen Victoria who had it placed in the Armoury, Windsor Castle. The bullet and Nelson's naval coat have been reunited in an exhibition during 2005 in the National Maritime Museum to commemorate the battle.

After the war Beatty took the MD of St Andrews in 1817, followed by the LRCP London in the same year. He was elected a Fellow of the Royal Society in 1818. He was appointed resident physician to Greenwich Hospital in 1822, and remained on its staff until his retirement in 1839. William IV, who always took a great interest in naval matters, conferred a knighthood on him in 1831. He never married and spent his last years in London, dying at 43 York Street, Portman Square on 25 March 1842, to be buried in Kensal Green Cemetery (where there is sadly no memorial).

Many other Ulstermen served as naval surgeons during the 18th and early 19th centuries. These included David McBride (1726-1778) who obstinately recommended malt for the prevention of scurvy, even after it had been superseded by James Lind's lemon juice. He was subsequently one of the founding surgeons of the Meath Hospital, Dublin.[10,11] There were also Richard McClelland (c. 1761-1807), one of the founding surgeons of the Belfast Dispensary in 1792, Andrew Marshall (1779-1868) who was attending surgeon to the Belfast Fever Hospital 1807-28, and David Moore (1780-1849) who had been appointed surgeon in the navy by Lord Nelson in 1803 and was attending surgeon to the Fever Hospital 1821-45.[12] Sir George Magrath (1775-1857) was a flag medical officer to Lord Nelson before Sir William Beatty, as we have seen, and was awarded the KCB by his former shipmate, King William IV in 1831.[13] James Johnson (1777-1845) was a more eccentric shipmate of the King, who also served in the Napoleonic wars, but is more famous as a medical writer and for a prolonged lawsuit with Thomas Wakley of *The Lancet*, resulting in his having to pay damages of £100 to Wakley.[14] Finally, we may mention Sir James Prior (c. 1790-1869) who was present at the surrender of Heligoland in 1814 and of Napoleon himself in 1815.[15]

This list only covers some of the more celebrated surgeons, but in many of the small dispensaries

throughout the British Isles there would have been surgeons who had trained in the Royal Navy during these wars. Fortunately for the patient, a surgeon could acquire more surgical experience during one naval battle than he would require during the remainder of his life.

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If at first you don't succeed … sue

In times past if you failed an exam at medical school you had a "long dark tea time of the soul." You asked yourself why you spent all that time in the college bar, the snooker hall, or in classical civilisation lectures. You vowed not to leave it all to the last minute for the repeats. But these days—in the United States at least—if you don't succeed you can always sue.

Firstly, you and your lawyers can look at the validity of the exam. If you pass the exam does that mean that that you're ready to work as a doctor? If you fail does that mean that you're not ready? If the answer to either of these questions is no then you may have a case. For example, if many of the questions in the final medical exam test knowledge of basic sciences then the exam may not be a valid test. A doctor may not know the ins and outs of the Krebs cycle, but he or she may still be able to give sensible and evidence based dietary advice to patients. And what about reliability? Test-retest reliability is a good place to start. How many students who passed their final exams in May would still pass them if they were taken again in September? If large numbers of your students would fail in September, then your exam is not reliable and your students are probably crammers.

So if you are setting an exam, how do you avoid these pitfalls? Firstly, make sure that the exam tests what it's supposed to test. If it is a test of whether candidates would make good general physicians then ensure that the questions deal with common medical problems that would be seen on an average take. So most of the questions should be on chronic bronchitis rather than porphyria, and they should test candidates' knowledge of the diagnosis and treatment of chronic bronchitis rather than its pathophysiology or epidemiology. And if you want to stop the crammers concentrate on continual assessment rather than a single high-stakes exam at the end. It is strange that some people are calling for doctors to do an exam to stay on the medical register when universities are increasingly realising that the best way of deciding who should get on the register is by regular assessment.

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1 Harris JM Jr, Salasche SJ, Harris RB. Can internet-based continuing medical education improve physicians' skin cancer knowledge and skills? *J Gen Intern Med* 2001;16:50-6.

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Case Report

Biliscrotum and Retroperitoneal Biloma:

Spontaneous Rupture of the Biliary System presenting as an Incarcerated Inguinal Hernia

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ABSTRACT

Spontaneous rupture of the biliary system is a well documented condition in infants[1] but is rare in adults.[2] We report the case of a 73-year-old gentleman who presented with clinical signs and symptoms mimicking that of a strangulated right inguinal hernia. At emergency operation the scrotum was found to contain bile. Following radiological imaging and exploratory surgery, a large retroperitoneal biloma was found. We discuss the clinical signs associated with biliscrotum and retroperitoneal biloma and describe our operative management of this patient. We review the previously reported cases of these rare clinical entities. We found that our case exhibited similarities in terms of the age of presentation and presence of distal common bile duct stones. This is, to our knowledge, the only reported case of a patient presenting with biliscrotum secondary to the assumed spontaneous rupture of the common bile duct and development of a retroperitoneal biloma.

CASE REPORT A 73 year old male presented as an emergency with sudden onset of severe pain distributed in the right inguinal region, anorexia and vomiting. The patient had no pyrexia and was haemodynamically stable.

Examination revealed a mass within the right inguinal region, a fullness in the right iliac fossa and tender enlargement of the right side of the scrotum. These signs were associated with a brown discoloration of the skin overlying the right inguinal mass and the right side of the scrotum. His history included a right inguinal hernia repair in 1973.

Blood results on admission revealed obstructive liver function tests. The patient proceeded to emergency contrast-enhanced CT-scan of abdomen. A right inguinal hernia containing mesenteric fat and vessels was reported, with a fluid collection extending along the iliopsoas muscle and around Gerota's fascia of the right kidney. Calculi were noted within the gallbladder.

The patient proceeded to emergency right inguinal hernia exploration. A process of mesenteric fat was found within the inguinal canal. In addition, there was a copious amount of green fluid that tracked along the mesenteric fat process and pooled in the right hemiscrotum (*Fig 1*). An oedematous and inflamed spermatic cord was found. The patient underwent repair of the inguinal defect.

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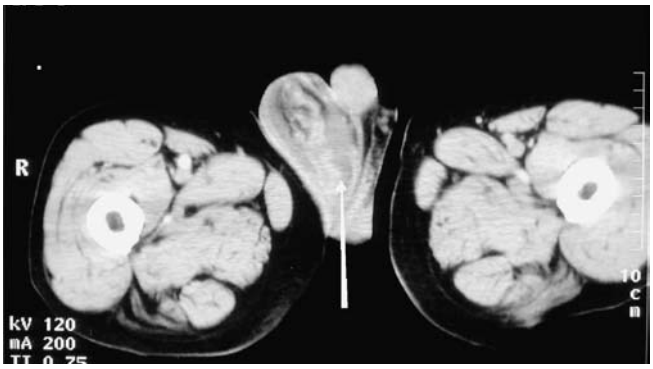

Fig 1. Biliscrotum. Axial CT scan at the level of the scrotum/inguinal canal showing bile extending around the pampiniform plexus.

The patient's clinical status improved post-operatively. His obstructive liver function tests and bilirubin levels normalised. A CT scan was repeated on post-operative day 3 in order to assess the size of the retroperitoneal collection and to guide towards aetiology. This described an increase in the size of the retroperitoneal fluid collection since the previous scan. Calculi were still noted within the common bile duct (CBD) which was 1.2 cm in diameter. (*Fig 2*).

The patient proceeded to exploratory laparotomy. Following extensive examination of the gallbladder, bile ducts, duodenum, liver and colon, there was no obvious perforation, leak of bile or connection with the retroperitoneum. There was no bile collection found intra-peritoneally. Examination of the gallbladder revealed multiple gallstones and exploration of the CBD was performed. A biliary fogarty catheter trawl of the CBD resulted in the retrieval of 2 large stones. An intra-operative cholangiogram revealed no perforation or abnormalities of the CBD apart from distension. A t-tube drain was placed within the CBD and a cholecystectomy was performed. The right retroperitoneum was entered lateral to the ascending colon. A large collection of bile stained liquid was encountered and evacuated. Drains were placed in the right retroperitoneum and around the gallbladder bed.

The patient's post-operative course was uncomplicated. The drainage from the retroperitoneal drain progressively decreased and there was consistent bile drainage from the t-tube. A t-tube cholangiogram on day 10 demonstrated no residual stones stricture or perforation. Pathological examination of the gallbladder post-operatively revealed no perforation or tissue necrosis and confirmed the finding of large gallstones intra-luminally.

Following transfer for further rehabilitation, the patient was discharged from hospital without complication and at 1 year post-operatively is continuing to progress well.

DISCUSSION

The presence of a bile collection within the retroperitoneum is extremely rare.[3] Since 1975 only 5 other cases have been reported.[3-7] Two describe complications arising from invasive surgical procedures[4,5] and 3 were attributable to the spontaneous rupture of either the gallbladder[6] or CBD.[3,7]

The authors have assumed the site of perforation was within the CBD given the dilatation of the duct at the time of the surgery and the obstructive liver function tests. In addition, the presence of CBD intra-ductal stones, an intra-operatively normal duodenum and the post-operative gallbladder pathology findings which demonstrated no fistulae or perforation support our assumption. We postulate that the release of pressure on the biliary system following perforation had allowed the resolution of the liver function tests and that the subsequent absence of extra-ductal contrast on cholangiogram could have resulted from a resealed perforation following decompression of the obstructed system. This precedent has been noted to occur in previous cases.[7]

Previous authors have either surgically or pathologically been able to identify the cause of

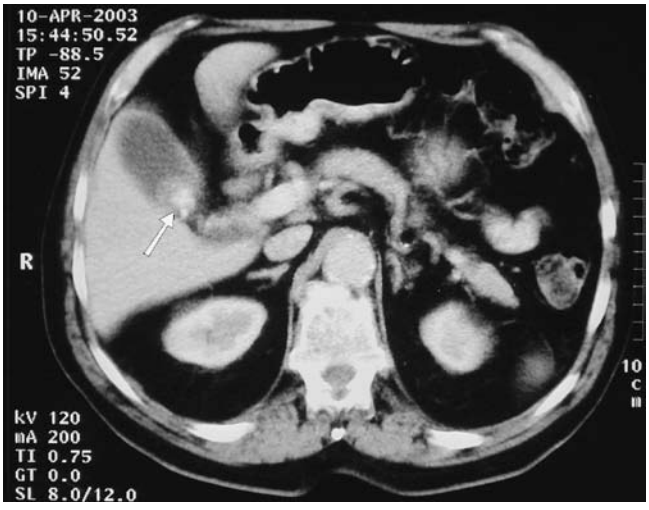

Fig 2a Axial CT-scan at the level of the gallbladder, showing a large calculus within the gallbladder and a further small calculus in adjacent dilated CBD.

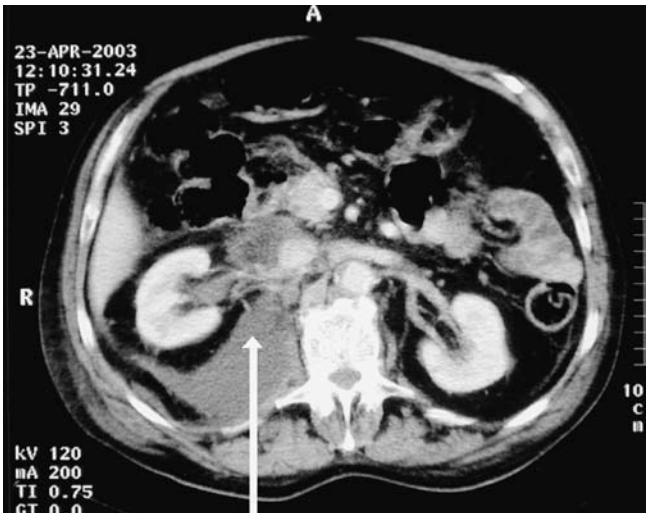

Fig 2b. Bile is extravasating from the biliary tree, around the inferior vena cava and right kidney.

the retroperitoneal connection. Such authors have described internal biliary fistula (secondary to postoperative CBD stricture), or gallbladder fistula to the retroperitoneum.[6] Satake[3] described the first retroperitoneal biloma secondary to spontaneous perforation of the CBD due to an erosive obstructing CBD stone. Hsieh,[7] in comparison with our case, described a 74-year-old male with a spontaneous retroperitoneal biloma. Following percutaneous drainage of the biloma and the gallbladder, cholangiography demonstrated a calculus within the distal CBD, but as no other abnormality was found, the site of perforation, was assumed to have sealed spontaneously.

Whipple[8] first described the term biloma in relation to a cystic swelling containing bile stained fluid. Gould and Patel[9] further refined this definition as an encapsulated bile collection outside the biliary tree, which was again expanded to include intra-hepatic collections.[10] Colovic[4] was the first author to use the term retroperitoneal biloma to describe a retroperitoneal collection of bile. Hsieh[7] continued this precedent even in the absence of a demonstrable capsule on CT scan. Vasquez[11] *et al* in their review of 21 bilomas found that "on CT scans, bilomas do not often show an identifiable capsule".

Previous authors have reported the clinical signs in association with these conditions. Neoptolomos[5] described an area of "discolouration in the right flank" and right sided scrotal swelling which "contained fluid which proved to be bile on aspiration (Biliscrotum)". The formation of Biliscrotum relies on bile tracking from the retroperitoneum along fascial planes formed by embryological fascial planes. Horowitz[6] details a palpable mass within the right inguinal region, this patient also undewent an operation for incarcerated inguinal hernia. Satake[3] and Colovic[4] both described a large mass felt in the right lower abdomen in their reports.

This report emphasises the importance of being aware of the clinical signs associated with retroperitoneal biloma and involvement of distal CBD stones or operative trauma in the aetiology of this condition.

CONFLICT OF INTEREST

None Declared

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Case Report

Bilateral Renal Artery Thrombosis due to Heparin-Induced Thrombocytopenia-Thrombosis Syndrome. Successful treatment with longterm application of lepirudin

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INTRODUCTION

Heparin-induced thrombocytopenia with thrombosis (HITT) is a rare but potentially fatal autoimmune syndrome, which is caused by antibody formation against complexes of heparin and platelet factor 4 (PF4). It typically develops five to fourteen days after the initiation of unfractionated or much less frequently low molecular weight heparin. The mortality rate can reach 20-30% and is associated mainly with thrombosis. Thrombotic events are most frequently venous but arterial thrombosis leading to myocardial infarction and ischemic limb damage requiring amputation also occur.[1] No consensus currently exists on the best alternative anticoagulant treatment, especially in cases with renal compromise or other major organ involvement.

We report a case of a patient with HITT syndrome, renal failure and diffuse thrombosis who was successfully treated with intermittent intravenous bolus administration of recombinant hirudin (lepirudin) for a long time (forty days).

CASE REPORT In May 2003, a 55-year-old woman was admitted to our hospital for evaluation of hypertension. Her past history was unremarkable. The physical examination and laboratory findings were both normal. CT-scan of the abdomen revealed a mass (diameters 3.2x4.2x2.1cm) on the upper pole of the left kidney. Renal angiography showed normal patency of both renal arteries. Surgical resection of the renal mass was performed. Histopathological examination was consistent with an angiomyolipoma. The immediate post-surgical course was uneventful and the patient was discharged on the seventh post-operative day. Ten days after the surgical procedure and twelve days after the angiography, the patient was readmitted to our hospital because of an acute substernal pain with electrocardiogram findings suggestive of acute myocardial infarction. On clinical examination an intense oedema with pain and redness on her right forearm was noticed. A duplex ultrasound study revealed thrombosis in the right subclavian vein. The laboratory tests were as follows: haemoglobin 7.1g/dl, white cell count 22.5x10^9/l (neutrophils 88%, lymphocytes 8%, monocytes 4%), platelets 45x10^9/l, coagulation tests were normal except for the presence of elevated D-Dimers, urea 38.5mmol/l (normal range 3.5-14), creatinine 371.3μmol/l (normal range 44.3-105), lactate dehydrogenase (LDH) 750 iu/l (normal range < 190), creatine phosphokinase (CPK) 810 iu/l (normal range < 100).

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The rest of the biochemical work-up was normal. Doppler examination of renal arteries revealed total absence of blood flow bilaterally. Because of the recent exposure to unfractionated heparin during angiography, there was a strong suspicion of HITT syndrome, which was confirmed, with the identification of antibodies against complexes of heparin and PF4 by gel microtube system[2] (Diamed,[R] Cressier sur Morat, Switzerland). The patient was admitted to the intensive care unit and because she was completely anuric, renal dialysis was started on the same day. Lepirudin, the only available thrombin inhibitor in Greece, is excreted exclusively by the kidneys and is contraindicated in severe renal failure. The therapeutic target was an APTT value at 1.5 to 2.5 times the baseline value. She received a loading dose of lepirudin (Refludan) 0.08mg/kg bolus iv, thereafter a dose of 0.04 mg/kg iv was repeated every 24 hours. A lepirudin dose was omitted if the APTT was >2.5 times the baseline value. Haemodialysis was performed using a polysulfone low-flux hemodialyser membrane. A locking dose of 0.02 mg of lepirudin was inserted into each lumen of the hemodialysis catheter at the end of dialysis and aspirated before initiation of the next dialysis. Each hemodialysis session was completed successfully, clot formation in the extracorporeal circuit was prevented and no bleeding complications occurred. Her clinical condition gradually improved and the platelet count restored to normal after thirteen days. Sixteen days after the thrombosis, renal function started to recover. There was a gradual increase in daily urine volume while urea and creatinine concentrations gradually decreased to 15mmol/l and 270μmol/l respectively. Magnetic resonance angiography (MRA) revealed a minimal flux on the right renal artery, while the left renal artery was totally occluded. Forty days after the initial thrombotic episode, renal dialysis was stopped. At that time we stopped lepirudin and the patient was commenced on oral anticoagulation with Warfarin (target INR 2.5 to 3.5). Two years later, the patient is in excellent clinical condition with stable renal function.

DISCUSSION

Heparin-induced thrombocytopenia (HIT) is an immune-mediated clinicopathological syndrome where the diagnosis should be based on the concurrence of an appropriate clinical picture together with detection of platelet activating and/or platelet factor 4 (PF4) dependent antibodies. These antibodies (most frequently IgG) activate platelets causing release of prothrombotic platelet-derived microparticles which in turn promote thrombin generation. Thrombosis appears to be due to heparin-like molecules (glycosaminoglycans) on the endothelial cell surface that, like heparin, can bind PF4. Immediate cessation of heparin is mandatory when HIT develops, but this will not stop continuing thrombin generation, nor will it help to avoid subsequent thrombotic events, which occur in as many as 40-50% of patients in subsequent days or weeks. Thus, an alternative anticoagulant should be substituted for heparin when HIT is strongly suspected.[1]

Direct thrombin inhibition may be beneficial in managing HIT. Several acting anticoagulants able to inhibit thrombin are available. Among them, only lepirudin is currently available in Greece. Lepirudin is the recombinant form of hirudin which is a thrombin inhibitor originally isolated from the salivary gland of the medicinal leech. It is a polypeptide of 65 amino acids which is renally metabolized and excreted with a half-life of 80 min. It does not show any reactivity *in vitro* for heparin and heparin induced antibodies. Lepirudin inactivates not only free thrombin but also fibrin clot bound thrombin.[3] Its anticoagulation effect can be monitored by APTT and/or ecarin clotting time (ECT). Potzsch *et al.* have further shown that the ECT test is the most appropriate for laboratory monitoring, especially when lepirudin is used in high concentrations or in particular patients.[4] Unfortunately, ECT is not commercially available. Bleeding complications are the most important adverse effects of the drug. No antidote currently exists for lepirudin. According to previous studies, the therapeutic target is an APTT value at 1.5 to 2.5 times the baseline value. Despite all limitations, we used lepirudin because it was the only available agent in Greece at that time. No significant experience exists concerning the use of lepirudin in renal failure.[5-8] To our knowledge, the longest application of lepirudin in a haemodialysis patient covered more than 50 haemodialysis sessions in one single patient.[9] There is currently no ideal haemodialysis anticoagulation agent for a patient with HIT, although Argatroban could have some theoretical advantages. Other procedures and agents which

are probably efficient in HIT (plasmapheresis, high dose intravenous gammaglobulin, antiaggregants, prostacyclin analogues, thrombolytic therapy as well as thromboembolectomy) could not be used in our patient because of her unstable clinical condition. In a dose-escalation study, a bolus dose of 0.08 mg/kg lepirudin before haemodialysis was found to be effective. In patients with HIT and acute renal failure, a reduced dosage according to the degree of renal dysfunction is proposed but the optimal dosage schedule to induce therapeutic effect without bleeding is still unknown. Bolus doses as low as 0.005mg/kg have been advocated in anuric patients. Recovering renal function however, can lead to the need for drastically increased doses.[10] In our patient, intermittent intravenous administration of lepirudin once daily according to APTT values for forty days was effective. After commencing lepirudin the patient didn't experience any other thrombotic episode, haemodialysis sessions were uneventful and bleeding did not occur. It was surprising that partial recanalization of the right renal artery was gradually restored with the right kidney regaining partial function allowing the patient to become dialysis independent.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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Letters

Epidemic Jaundice: Harvard's 5th General Hospital at Musgrave Park in World War II.

Editor,

Ireland could not be described as an area of high risk for yellow fever, and the curious might wonder why US troops stationed in Ulster had received the yellow fever vaccine responsible for the serum hepatitis epidemic described by Dr Hedley-Whyte.[1]

There had been an epidemic of fever in Dublin in the winter of 1826/27 in the course of which nearly twenty patients died after developing jaundice. Professor Robert J Graves described the outbreak in his book Clinical Lectures on the Practice of Medicine in a chapter entitled "Yellow Fever of the British Islands." [2] He felt that several of his cases presented "all the characters of yellow fever" and he noted that "This is a very remarkable fact, for this form of fever has been very rarely witnessed in this country". He was aware that true yellow fever usually occurred in warmer climates and had a higher mortality than he had observed in Dublin but he argued that because "even in the warmest latitudes epidemics of yellow fever are always mixed with fevers of a bilious character, but of a milder type", so, if the infection should spread to temperate latitudes, "the reverse would happen, and this influence would then produce an epidemic of bilious or gastric character, with comparatively few cases approaching in violence to yellow fever." When Nogueira gave a talk in 1955 on the history of yellow fever before 1905,[3] the above report lead him to place Ireland on a list of countries which had experienced epidemic viral yellow fever, but it is extremely unlikely that the Dublin epidemic in the middle of winter was due to that.[4] Lieutenant-General Sir William MacArthur, in a discussion of the famine fevers in Ireland, suggested that the sixth century yellow pestilence or Buidhe Chonaill was due to "a severe form of relapsing fever [caused by louse-borne Borrelia recurrentis], with jaundice common enough to dominate the general picture of the disease",[5] and perhaps Graves' epidemic was due to the same.

The explanation for the vaccination of the US troops is more prosaic and does not involve reference to the epidemic in Dublin. Up until January 1942 only those stationed in or passing through tropical areas required vaccination but in that month it was decided that all US military personnel were to be vaccinated as soon as practicable. An epidemic of jaundice followed, peaking in June or July 1942 and affecting in all some 50,000 troops.[6] Similar epidemics were seen in civilian practice.[7] Human serum was used in the preparation of the vaccine and evidently, despite treatment by heat and Seitz filtration, the final product was sometimes contaminated by the hepatitis B virus. A serum-free vaccine was introduced after April 1942 and proved safe.[6]

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Response to JS Logan and JI Logan's Letter to the Editor re: "Epidemic Jaundice: Harvard's 5th General Hospital at Musgrave Park in World War II"

Editor,

The Logans' comments are most timely. The decision in January 1942 that United States military personnel should be vaccinated as soon as practical against yellow fever[1] was predicated by the active battlefields of World War II at that time. The US Army's 34th Infantry Division, National Guard from the Dakotas, Iowa and Minnesota, landed in Algiers on 8th November 1942. In Tunisia they were in 2nd Corps under the command of Patton and Tyrone-born Alexander. In Italy they landed at both Salerno and Anzio and attacked Monte Cassino. They captured Bologna on 21st April 1945.[2]

David E Bloom, Clarence James Gamble Professor of Economics and Demography, Harvard University, and colleagues have recently written a survey of the benefits and costs of vaccination, including against yellow fever. The benefits and challenges world-wide are enormous. This paper sheds interesting light on mischief-makers from George Bernard Shaw to Prime Minister Blair.[3]

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Air Raids

Editor,

Since publication of my paper on the air raids and the Ulster Hospital,[1] some additional interesting material has come to light. There is extensive correspondence on the amount of compensation to be paid by the Government for the damage suffered, not only for the building but also for each and every item lost.

Many letters of sympathy were received by the Board of Management from various organisations, individuals, etc. Amongst these is a letter from Sir Dawson Bates (Minister of Public Security) dated 23 July 1941 in which he praises the efforts of Mr RJ McConnell (Surgeon), Mr HI McClure (Gynaecologist), Miss EE Aicken (Matron) and Miss Dickson (Radiographer). This may have been in response to a letter dated one week earlier from Major J Maynard Sinclair MP (President of the Board) bringing to the Minister's attention the efforts of Mr McConnell and Miss Aicken but not mentioning Mr McClure or Miss Dickson. There are also letters dated six months later from Mr McConnell and Miss Aicken thanking the Board for their congratulations. In the Annual Report of the Board Management it is recorded "For their resolution and valiant services Mr RJ McConnell, MB, MCh, the Matron Miss Aicken and Miss Dickson, have been publicly commended …..". There is no record of any honours or decorations being presented to them so how they were commended cannot be accurately recorded.

Letters of sympathy were received from the other Belfast Hospitals, together with practical offers of assistance. The Royal Victoria Hospital offered two beds in each female surgical ward plus ten beds in the gynaecological ward – a total of twenty beds. There was also an offer of nurse training. A similar offer also accompanied the Royal Belfast Hospital for Sick Children's "very cordial invitation to the members of your Medical Staff to make all possible use of our Wards and Theatres for patients they wish to admit, under their own supervision, for treatment or operation".

The Samaritan Hospital suggested handing over a twenty-one bedded ward which was accompanied by a detailed contract of the costs to be paid by the Ulster Hospital (£2.10 per patient per week). In reply the generous offer was turned down " . . . in view of the fact that we have received other offers of assistance from hospitals in Belfast, we do not feel justified in entering into an arrangement from you on the terms proposed". In the event facilities became available at a disused school at Haypark off the Ormeau Road and while the generosity of the other hospitals was appreciated it was not necessary for the staff to use any of the facilities which were offered. Nevertheless the correspondence shows that there was a close and generous relationship between the hospitals in Belfast at that time.

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A Rash Imposition from a Lifestyle Omission: A Case Report of Pellagra

Editor,

Pellagra, described by Casal in 1735, is endemic in Africa and Asia where staple food is nicotinic acid deficient corn-based diet and related to poverty among refugees or displaced people.[1] It is infrequently seen in developed countries in chronic alcoholics or rarely in anorexia nervosa.

Case History: A 57 year-old chronic smoker and alcoholic, suffering from pulmonary Koch's and peeling dermatitis, had presented with confusion, involuntary flinging of legs and irresistible grasping of hands. Bladder-bowel functions were normal. Besides pallor, beefy tongue and polymorphic ronchi, physical examination was unremarkable. Neurological examination revealed rigidity and weakness in all four limbs, brisk reflexes, bilateral up-going planters, positive sucking and grasp reflex. Dermatological examination showed peeling dermatitis with erythema and pigmentation (*Fig 1*). Medication consisted of asthalin, rifampicin, isoniazide, pyrazinamide, ethambutol and multivitamin. Except 9.8gm% haemoglobin, routine plasma glucose, electrolytes, renal and liver function tests were normal. Chest x-ray and abdominal ultrasound showed emphysematous lungs and hyperechoic 16cm fatty liver. Computerized tomography of brain was normal.

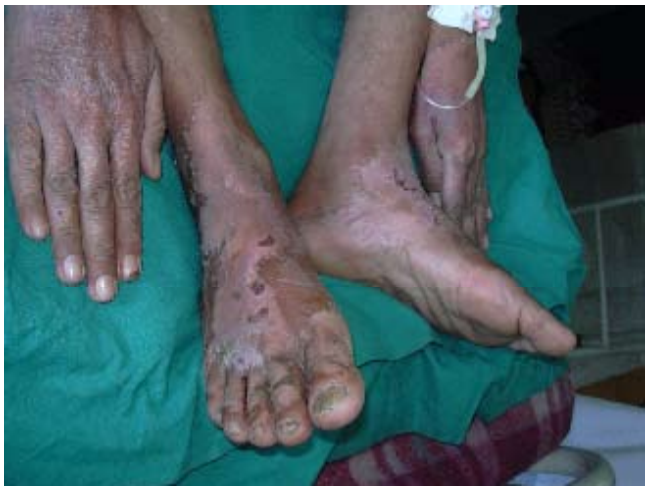

Figure 1. Peeling dermatitis of pellagra

Discussion: Antitubercular drug induced pellagra encephalopathy has never been described in the literature as opposed to that caused by chronic alcoholism and diarrhoea. We presenting an interesting case of full blown pellagra with cutaneous and neuro-psychiatric manifestations possibly caused by isoniazid-pyrazinamide and alcohol, treated with intravenous niacin leading to a dramatic recovery. Nicotinic acid dinucleotide and nicotinic acid dinucleotide phosphate, derived from dietary tryptophan, are essential co-enzymes in metabolism of intestinal, epidermal and more electron-sensitive neuronal cells. Pellagra is common in raw-spirit drinkers of rural populations in the Third World whose staple diet is niacin deficient jawar or maize with inadequate animal protein, fruits and vegetables. Secondary deficiency of niacin occurs in malabsorption and carcinoid syndrome, cirrhosis of liver and Hartnup disease. Prolonged therapy with

pyrazinamide, isoniazide, 6-mercaptopurine and 5-flurouracil may also result in pellagra like syndromes. Pyrazinamide and isonicotinic acid hydrazide (INH) are structural analogues of niacin and can depress endogenous niacin production by feedback inhibition or substrate competition. INH impairs the functioning of pyridoxine, a cofactor in tryptophan-niacin pathway and inhibits the niacin synthesis leading to pellagra.[2] Dermal pathogenesis reveals lowered collagen and urocanic acid content, serving as a filter for ultraviolet radiation, may cause photosensitive pellagra dermatitis. Chromatolytic changes are found in Betz cells of motor cortex. Similar cerebellar changes, optic neuropathy and cerebral deficit seen in pellagra encephalopathy may not resolve completely even with high doses of niacin. The diagnosis of pellagra is clinical. Laboratory diagnosis by fluorometric assay of urinary metabolites (2-pyridone/ N-methylniacinamide ratio less than 2.0) is not unequivocal evidence of pellagra. The recommended daily allowance is 10-20mg/day. Since niacin causes flushing, headache, burning and tingling sensations, niacinamide is prescribed orally (300-500 mg) and parenterally (100 mg per day) in divided doses. Neuropsychiatric manifestations are relieved dramatically overnight. Topically zinc oxide and para-aminobenzoic acid ointment may be advised.

Conclusion: Physicians should be aware of such cases and should treat any "sick" person with unexplained skin, neuro-psychiatric changes or gastrointestinal complaints with safe, inexpensive doses of niacin.

Acknowledgement: We are thankful to Prof PVS Rana, MD, DM (Neuro), Professor of Neurology, Manipal Teaching Hospital, Pokhara, Nepal, for his valuable guidance in preparing this manuscript.

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Benign signet ring cells in the subserosa of the small intestine: a pseudoneoplastic phenomenon

Editor,

Aggregates of non-neoplastic signet ring cells have been previously described in the small intestine mucosa in ischaemia[1] and in association with Peutz-Jeghers polyps,[2] and in the colonic mucosa in ulcerated adenomas[3] and pseudomembranous colitis.[4] They are an uncommon finding that may be mistaken for signet ring cell carcinoma.

A similar phenomenon has also been identified outside the gastrointestinal tract.[5,6,7] We report a case in which non-neoplastic signet ring cells in the subserosa of the small intestine could potentially have been mistaken for signet ring cell carcinoma. As far as we are aware, benign signet ring cells mimicking signet ring cell carcinoma have never before been described in the subserosa of the intestine.

CASE REPORT A 76-year-old man presented with subacute bowel obstruction. Three years previously he had an extended right hemicolectomy for colonic adenocarcinoma. His past medical history included ischaemic heart disease and an abdominal aortic aneurysm. A barium enema showed a tight stricture, proximal to the point of previous anastamosis, suggestive of an obstructing tumour. He subsequently underwent laparotomy, resection of the strictured intestine and ileocolic anastamosis.

The surgical specimen consisted of 28cm of small intestine anastamosed to 3cm of large intestine. The distal small intestine was concentrically strictured adjacent to the point of anastamosis. Fibrinous exudate was present on the serosal surface and the small intestine wall was thickened. There was shallow mucosal ulceration in the strictured area.

Multiple sections were examined histologically. These showed features of an ischaemic stricture. There was mucosal ulceration and the submucosa was lined by inflamed granulation tissue. There was also fibrosis of the submucosa and subserosa. Where the mucosa was intact there was hyalinisation of the lamina propria. However, in several sections there was an abundance of cells with signet ring morphology localised to the subserosa (*Figure 1*). We were immediately concerned that these cells represented locally recurrent or metastatic signet ring cell carcinoma.

We reviewed the histology from the initial case. This was found to be an adenocarcinoma with an intestinal pattern and there was no signet ring differentiation. In addition we performed immunohistochemistry. The signet ring cells were negative for the epithelial markers CAM5.2 and AE1/AE3. We concluded that these cells were in fact not malignant and are a non-neoplastic mimicker of signet ring cell carcinoma.

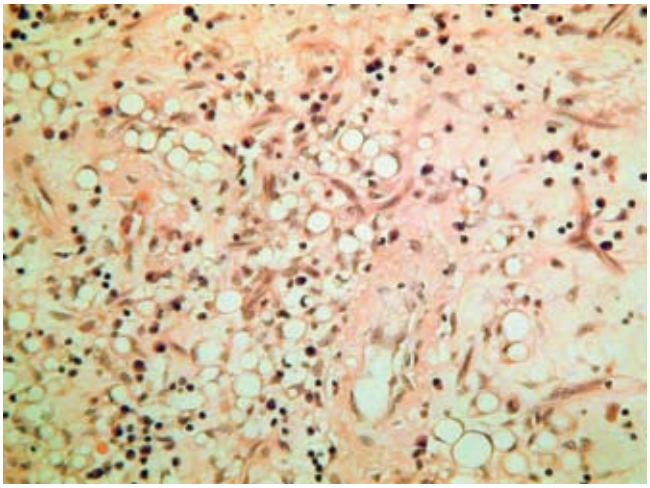

Fig 1A. Subserosal signet ring cells in groups and singly dispersed.

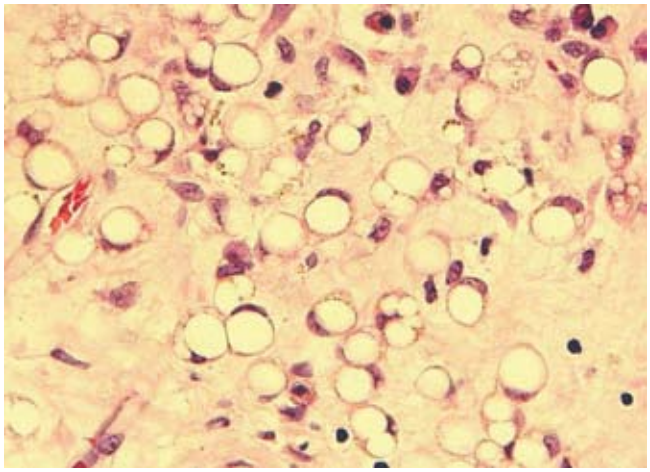

Fig 1B. High power view showing signet ring morphology.

DISCUSSION

Stricture of the small intestine can arise from a number of causes including ischaemia, carcinoma, lymphoma, Crohn's disease and tuberculosis.[8] This patient had a past history of vascular disease including myocardial infarction and an abdominal aortic aneurysm, and while histology of the small intestine showed features of an ischaemic stricture, the abundance of signet ring cells in the subserosa was alarming.

He had a previous colectomy for adenocarcinoma and we considered the possibility that these signet ring cells represented local recurrence. We reviewed the histology from this tumour and found it to have an intestinal pattern with no signet ring differentiation. In addition we thought that these cells could represent metastatic signet ring cell carcinoma from a distant primary site such as the stomach. However in view of the overall context of ischaemia the possibility of a non-neoplastic process was entertained. Negative staining with epithelial markers and awareness of previously described accounts of benign signet ring cells in the intestine and at other sites helped us make the diagnosis of a non-neoplastic mimicker of signet ring cell carcinoma.

Aggregates of benign signet ring cells in the intestinal mucosa have previously been documented and are characterised by cells that are cytologically similar to signet ring cell carcinoma.[9] Distinguishing signet ring cell carcinoma from these non-neoplastic signet ring cells is difficult using morphology alone as features of malignancy, such as cytological atypia, are often not marked in signet ring cell carcinoma.[9] The subserosal benign signet ring cells in this case are a similar diagnostic dilemma and in our opinion, could have been mistaken for signet ring cell carcinoma.

A wide panel of immunohistochemical markers was performed. We considered a mesothelial origin for these cells given the subserosal location but staining with calretinin, thrombomodulin and WT1 proved negative. The histiocytic marker CD68 was also negative. The cells were positive with S100. While S100 positivity is seen in wide variety of cell types, in view of the morphology of these cells and given their location in the subserosa, we feel that they are most likely adipocytes distorted by subserosal fibrosis that has occurred secondary to intestinal ischaemia.

In contrast, mucosal aggregates of benign signet ring cells are thought to be dispersed Goblet cells derived from multipotent stem cells in the crypt base following ischaemic injury.[1] These cells stain positive for neutral mucins[1] and they are also positive immunohistochemically with pan-cytokeratin.[1] The subserosal aggregates of signet ring cells in this case are negative for both neutral mucins and epithelial immunohistochemical markers.

In summary, the distinction of non-neoplastic signet ring cells from signet ring cell carcinoma is vital as the incorrect diagnosis of signet ring cell carcinoma has obvious prognostic and therapeutic implications. We have described a case in which aggregates of benign signet ring cells in the subserosa of the small intestine could have been mistaken for signet ring cell carcinoma. An erroneous diagnosis was avoided by consideration of this finding in the context of all the changes present, through awareness of the existence of benign mimickers of signet ring cell carcinoma, and by the use of immunohistochemistry.

CONFLICT OF INTEREST

The authors have no conflict of interest

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Abstracts

Junior Members Forum

Thursday 24 November 2005

Ulster Medical Society Rooms, Whitla Medical Building, Belfast

PROGRAMME

1. 8.00 pm Introduction - Dr Stanley Hawkins, UMS President
2. 8.10 pm Mr Christopher Hoo MRCS (Research Fellow in Surgery) "Molecular Determinants of Prognosis in Malignant Melanoma"
3. 8.25 pm Dr Lorraine Graham MRCP (SpR in Rehabilitation Medicine) "The Physical and Psychological State of Amputees from the Northern Ireland Troubles 1969 – 2003"
4. 8.40 pm Dr Damian McCall MRCP (Research Fellow in Medicine) "Studies on Familial Medullary Thyroid Cancer"
5. 8.55 pm Dr Orla Gray MRCP (SpR in Neurology) "Studies of Mortality in Multiple Sclerosis"
6. 9.15 pm Discussion
7. 9.30 pm Close

SPOKEN PAPERS

S1. Molecular determinants of the invasive potential of malignant melanoma

Chris Hoo, M El-Tanani, FC Campbell.

Department of Surgery, Queen's University Belfast.

Objective: The molecular changes associated with transition of melanoma cells to the invasive phenotype are poorly understood.

Methods: In this study, B16-F1 melanoma cells will be transfected into a gene construct that may influence cell invasion. Expression of this gene and its coregulators will be assessed by immumohistochemistry in human archival melanoma samples, against the Breslow thickness scale, differentiation and nodal metastasis.

Outcome: This study may elucidate molecular determinants of melanoma prognosis and provide novel molecular targets for therapy.

S2. A study of the physical rehabilitation and psychological state of patients who sustained limb loss as a result of terrorist activity in Northern Ireland 1969-2003

Lorraine Graham, RC Parke, M Stevenson, M Paterson.

Department of Rehabilitation Medicine, Musgrave Park Hospital, Belfast.

Objective: To benchmark the psychological state and physical rehabilitation of patients who have sustained limb loss as a result of terrorist activity in Northern Ireland and to determine their satisfaction with the period of primary prosthetic rehabilitation and the artificial limb.

Methods: All patients who sustained limb loss as a result of the Troubles and were referred to our rehabilitation centre were sent a questionnaire. The main outcome measures were the SIGAM mobility grades, the General Health Questionnaire (GHQ12) and 3 screening questions for Post Traumatic Stress Disorder (PTSD).

Results: 66% response rate. 52 (69%) patients felt that the period of primary prosthetic rehabilitation was adequate. 32 (54%) lower limb amputees graded themselves SIGAM C or D. 45 (60%) patients stated that they were still having significant stump pain. Significant stump pain and symptoms of PTSD were both associated with poorer mobility. 9 (56%) upper limb amputees used their prosthetic limb in a functional way.

33 (44%) patients showed psychiatric caseness on the GHQ 12 and 50 (67%) had symptoms of PTSD.

Conclusions: Most patients felt that the period of physical rehabilitation had been adequate those who did not were more likely to be having ongoing psychological problems. A high percentage of patients continue to have psychological problems and stump pain both of which were associated with poorer mobility.

S3. The RET mutation E768D confers a late onset FMTC-only phenotype with incomplete penetrance

Damien McCall, T Dabir,[1] CFJ Russell,[2] PJ Morrison,[1] SJ Hunter.

Regional Centre for Endocrinology and Diabetes and [2]Department of Endocrine Surgery Royal Victoria Hospital, Belfast.

[1]Department of Medical Genetics, Belfast City Hospital.

Objective: Mutations of the RET proto-oncogene are associated with MEN and FMTC and aid diagnosis and predictive testing in family members. Genotype-phenotype correlations are also used to plan therapeutic decisions.

Methods: We describe a four generation family with a rare E768D mutation in exon 13. The index case was diagnosed with MTC at age 54 and remains free of clinical disease eleven years following thyroidectomy and neck irradiation. Two further family members were identified with MTC at age 25 and 50 years.

Results: Of five gene carriers two are asymptomatic at age 70 and 61 years. The former of these asymptomatic carriers has three gene carrier sons who have undergone prophylactic surgery with one having a normal thyroid at age 46, one with C-cell hyperplasia at age 39 and one with a focus of MTC at age 45. No members had evidence of phaeochromocytoma or parathyroid disease on screening.

Conclusions: The RET E768D mutation is associated with a MTC-only syndrome with a later age at onset, incomplete penetrance and less aggressive clinical course compared with other high risk RET mutations. The appropriate screening strategy for and management of E768D carriers is difficult reflecting the phenotypic heterogeneity.

S4. Trends in survival and cause of death in patients with multiple sclerosis in Northern Ireland

Orla M Gray, SA Hawkins

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Objective: To investigate trends in survival and causes of death in patients with multiple sclerosis, and to investigate the use of death certification in epidemiological research.

Methods: The Northern Ireland Multiple Sclerosis Registry, containing all cases of multiple sclerosis attending neurology outpatients between 1947 and the 1980s, was linked to the Northern Ireland Research and Statistics Agency to identify those who had died and their death certificate documentation.

Results: Of 1919 cases on the registry (766 males, 1153 females), 1393 had died, with death certificate data available in 1354 cases, 325 were alive and resident in Northern Ireland and 201 were untraceable. Mean age at onset was 31.16 years and mean age at death 63.65 years. Median survival time was 35 years, with no significant difference between genders, with age of onset or decade of onset. Standardized Mortality Ratios were 1.89 for males (CI 1.73-2.06) and 2.75 for females (CI 2.56-2.95). Multiple sclerosis was documented as the cause of death (Part I) in 27%, as a contributing factor (Part II) in 44% and not at all in 29% of death certificates.

Conclusions: Multiple sclerosis is associated with an elevated risk of death with an overall standardized mortality ratio of 2.32. Median survival time was 35 years with no significant difference between genders or with age of onset or decade of onset. Death certificates produce unreliable estimates of mortality rates. In isolation, they underestimate the number of cases and the mean age at death in multiple sclerosis.

Abstracts

8th Meeting of the Irish Society of Human Genetics, Monday 19th September 2005

Postgraduate Centre, Belfast City Hospital

PROGRAMME:

10.00 – 11.00 Registration/coffee

11.00 – 13.00 Plenary session

13.00 – 14.00 Lunch and poster viewing

14.00 – 15.30 Symposium –
"Population Genetics of the Irish"

15.30 – 16.00 Tea & Poster viewing

16.00 – 16.15 Business meeting

16.15 – 17.15 Guest lecture –
Dr Beverly Davidson, Iowa, USA
"RNAi for neurogenetic diseases"

17.15 – 18.00 Wine reception, presentation of winner of the Young investigator & poster prizes

18.00 – meeting close

SPOKEN PAPERS

S1. Association analyses of the BLOC-1 genes suggest the involvement of BLOC-1 in schizophrenia etiology:

Morris DW,[1] Murphy K,[1] Kenny N,[1] Williams NM,[2] McGhee KA,[1] Schwaiger S,[1] Nangle J-M,[1] Donohoe G,[1] Clarke S,[1] Owen MJ,[2] O'Donovan MC,[2] Waddington JL,[3] Gill M,[1] Corvin AP.[1]

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Dysbindin is known to (a) bind ß-dystrobrevin in postsynaptic densities in a number of brain areas, and (b) be a component of the biogenesis of lysosome-related organelles complex 1 (BLOC-1). Reduced levels of dysbindin have been identified presynaptically at hippocampal formation sites lacking ß-dystrobrevin in schizophrenia cases. This suggests a role for dysbindin in schizophrenia pathobiology independent of the ß-dystrobrevin complex and therefore possibly involving the BLOC-1 complex. As dysbindin is a susceptibility gene for schizophrenia, we considered the remaining 7 BLOC-1 genes as suitable candidate genes for association analysis. BLOC-1 consists of proteins encoded by at least 8 genes - dysbindin, MUTED, PLDN, CNO, SNAPAP, BLOC1S1, BLOC1S2 and BLOC1S3. Functional regions of all genes were subjected to mutation detection analysis using DHPLC. Polymorphic markers identified were supplemented with additional SNPs from dbSNP. All markers (n=50) were typed in a sample of 92 individuals to elucidate LD structure and inform on choice of markers (n=29) for analysis in our full sample of 373 schizophrenia cases and 812 controls. Evidence of association was detected with single markers at BLOC1S2 ($p = 0.05$) and BLOC1S3 ($p = 0.003$). We are currently testing our associated SNPs in a large independent replication sample. Should our results replicate independently it would suggest a role for BLOC-1 in schizophrenia etiology.

S2. Mutation screening of a break-point candidate gene for autism, UBE2E3, on chromosome 2q31.3

Lalor S,[2] Gallagher L,[3] Kearney G,[3] Fitzgerald M,[3] Barton DE,[1,2] Green AJ,[1,2] Gill M,[3] Ennis S,[1,2].

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2. National Centre for Medical Genetics, Our Lady's Hospital for Sick Children, Crumlin, Dublin 12, Ireland.
3. Department of Psychiatry, Trinity Centre for Health Sciences/Dublin Molecular Medicine Centre, St. James's Hospital, Dublin 8.

Autism is a relatively common neurodevelopmental disorder characterized by impaired social interaction and communication, and repetitive and stereotyped behaviours and interests. It occurs in around 1 in every 1000 births, has an onset in the first three years after birth, and persists throughout life. There is a strong yet complex genetic component and since the biological basis of the disorder is unknown, much research is focused on the identification of susceptibility genes. Several groups have identified associations between autism and a wide area of chromosome 2q, suggesting a predisposing gene or genes to autism within the 2q region. We have previously reported a patient with high-functioning autism, who has a small but cytogenetically visible *de novo* translocation 46,XY, ins(9;2)(q31.1;q32.2q31.3). The chromosome 2q31.3-q32.2 region falls within the above linkage findings. This would appear to be the smallest known deletion of this part of chromosome 2, suggesting that the region includes a predisposing gene or genes for autism.

UBE2E3, a gene encoding a ubiquitin-conjugating enzyme, lies just 3kb from the proximal breakpoint of this translocated region. This gene seemed, therefore, to be a good candidate for mutational screening for variants that may increase the risk of developing autism. We performed sequencing analysis on the

5 coding exons and intronic flanking sequences of UBE2E3 in probands from 77 Irish autism families. As a result of this analysis we have identified two sequence variants comprising an apparently synonymous SNP (T/A) in exon 2 and a change of a G to a T at the +5 position in intron 6. While other studies are required, our results to date appear to reduce the likelihood that UBE2E3 has a role in the aetiology of autism.

S3. Leri-Weill dyschondrosteosis in a large Northern Irish pedigree

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3. Centre of Human Genetics, Bioscientia Institute, Ingelheim, Germany.

The aetiology of short stature is largely unknown. The Short HOmeoboX (SHOX) containing gene located on the pseudoautosomal region of the sex chromosomes has been implicated in short stature, including Turner syndrome (TS). Heterozygous and homozygous deletions of SHOX result in Leri-Weill dyschondrosteosis (LWD) and Langer dysplasia (LD) respectively. The clinical features of Madelung deformity, short fourth metacarpals and high arched palate are common to these three conditions. LWD is further characterised by disproportionate short stature and mesomelic shortening of the forearm and lower leg.

We report a large four-generation Northern Irish pedigree, with seven clinically affected individuals. The proband was referred with learning difficulties and short stature. Both parents and extended families had significant short stature. Examination of the proband and his mother suggested a clinical diagnosis of LWD, confirmed by radiological findings. In other less clinically affected relatives, radiology was needed to confirm the diagnosis. SHOX gene mutation screening in mother and son has demonstrated a heterozygous deletion.

Phenotypic heterogeneity, a recognised feature of LWD, is extensively observed in our pedigree. The use of radiological investigation in apparently clinically unaffected individuals is important. Investigation of short stature is essential, even if present in both parents.

S4. Reproducing the haplotype; the role of the 5-lipoxygenase activating protein in ischaemic heart disease in Ireland.

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3. Department of Medical Genetics, Queen's University Belfast, Royal Victoria Hospital, Grosvenor Road, Belfast BT12 6BJ, Northern Ireland, UK.
4. Department of Epidemiology and Public Health, Queen's University Belfast, Mulhouse Building, Grosvenor Road, Belfast BT12 6BJ, Northern Ireland, UK.

Introduction: Low-density lipoprotein (LDL) oxidation by leukotrienes and the 5-lipoxygenase activating protein (FLAP) plays a central role in atherosclerosis. A four single nucleotide polymorphism (SNP) haplotype (HapB) in the gene encoding FLAP has been shown to be associated with myocardial infarction (Helgadottir *et al*. Nature Genetics, 2004). Within HapB, SNP SG13S114 has been shown to be associated with stroke (Lohmussaar *et al*. Stroke, 2005). We investigated HapB in an Irish study group with premature ischaemic heart disease (IHD).

Methods: 1494 individuals (580 families) were included. 10 individuals (3 families) were excluded due to insufficient DNA, leaving 799 discordant sib-pairs and 62 parent-child trios. Linkage disequilibrium between HapB and IHD was tested using the combined transmission disequilibrium test and pedigree disequilibrium test.

Results: SNP SG13S377 was excluded as it showed no heterogeneity in our study group. The numbers of informative families for SG13S114, SG13S41 and SG13S35 were 271, 79 and 127, respectively. A significant association between the informative SNPs of HapB and IHD was detected (p=0.032) due to the preferential transmission of the T allele of SG13S114 (p=0.015).

Conclusions: Using family-based association tests we have shown association between the FLAP gene (particularly SG13S114) and IHD. Replication of previous work suggests an important role for FLAP in the pathogenesis of atherosclerosis.

S5. Incidence of BRCA1 and BRCA2 Mutations in Irish Breast Cancer Families.

McDevitt T,[1,2] O'hIci B,[1,2] Cody N,[1,2] Adams M,[1,2] Miller N,[1,2] Ormiston W,[3] BerkeleyE,[3] Nolan C, Clarke R,[3] Daly PA,[3] McDermott E,[2,4] Carney DE,[2,5] Green AJ,[1,2] Barton DE.[1,2]

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Breast cancer is the most common cause of cancer-related deaths for women in Ireland. While it is estimated that between 5 and 10% of breast cancers may be due to inherited predisposition involving mutations in BRCA1 and BRCA2, the role of these genes in Irish breast cancer families is as yet unknown. As a result of a HRB-funded research initiative from 1998-2002, a total of 362 breast/ovarian cancer patients selected on the basis of early onset disease and/or a family history of breast/ovarian cancer, have been recruited by two Centres in Dublin. These patients have received screening for mutations in BRCA1 and BRCA2. Of these patients, 280 have received a partial screen (exon 11 PTT of both genes, cDNA PTT and dHPLC); while an additional 82 patients have received comprehensive mutation screening of BRCA1 and BRCA1 by bi-directional sequencing, together with a limited deletion screen.

To date, deleterious mutations have been identified and characterised in 33 patients. The spectrum of deleterious gene alterations identified comprises nonsense (BRCA1: 2, BRCA2: 4), frameshift (BRCA1: 9, BRCA2: 11), splice-site (BRCA1: 1, BRCA2: 1) and missense (BRCA1: 0, BRCA2: 2) mutations. Two recurrent mutations have been identified, namely BRCA1 E143X [c.546G_T] and BRCA1 c.1294_1333del40, found in 13 and 4 unrelated patients respectively. Based on these findings, 161 unaffected family members have received predictive testing at the NCMG to date.

We present details of these results and assess the information generated in terms of incidence of BRCA1 and BRCA2 mutations in Irish breast cancer families and the clinical criteria used to select them. We also consider the family-wide implications of providing a BRCA1 and BRCA2 mutation screening service to these patients. Results of mutation analysis in this cohort of patients will provide useful information should a diagnostic service providing mutation screening of BRCA1 and BRCA1 be implemented in the Republic of Ireland.

S6. Gain of imprinting of SLC22A1L sense and antisense transcripts in human breast cancer.

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Natural antisense transcripts (NATs) have been implicated in many aspects of eukaryotic gene expression including genomic imprinting. The 11p15.5 region harbors 3 imprinted sense/antisense transcript pairs, IGF2/IGF2AS(PEG8), KvLQT1/KvLQT1AS(LIT1) and SLC22A1L/SLC22A1LS. SLC22A1L(Solute-carrier-family-22(organic-cation-transporter),member-1-like), displays preferential expression of the maternal allele in foetal samples; with polymorphic imprinting in adult tissue. SLC22A1LS shares 31bp with SLC22A1L, is also maternally expressed in fetal tissue, but its imprinting status in adult tissue remains elusive. This study investigated the imprinting phenotype of SLC22A1L/SLC22A1LS in a cohort of benign and malignant breast tissues. SLC22AIL DNA-PCR-RFLP analysis using *Nla*III restriction digestion and 6% PAGE evaluation, identified SLC22A1L heterozygotes within the cohort (n=89). Commercial sequencing (MWG) identified informative SLC22A1LS samples. Random-hexamer primed cDNA synthesis (Superscript TmII) followed by SLC22A1L/SLC22A1LS specific RTPCR, and imprinting evaluation by commercial sequencing (MWG) demonstrated that SLC22A1LS, displays a non imprinted profile in reduction mastectomy cases (n=6). However, for SLC22A1L 1/4 (25%) of reductions showed a gain of imprinting (GOI). In the malignant cohort, GOI was also demonstrated in 18.2% for SLC22A1L and 15% for SLC22A1LS. One case demonstrated GOI at both loci concomitantly. Novelly, this study reports the imprinting status of SLC22A1LS in adult tissue, and highlights a common epigenetic alteration affecting gene expression at these paired loci.

S7. Is there an association between GGC length shortening and development of androgen-independent prostate cancer?

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2. Trinity Centre, St. James's Hospital, Department of Urology,
3. St. James's Hospital & Department of Pathology, AMNCH, Dublin.

Progression to androgen independent (AI) prostate cancer (PC) can take approximately 18 months and is poorly understood. Although epidemiological studies show that shorter GGC repeat in exon 1 of the androgen receptor (AR) confers a higher risk of PC, there is no information of GGC repeat status in androgen dependent (AD) & AI patients with PC.

The aim was to compare GGC repeat numbers in patients where PC is initially AD and progresses to AI state.

Eleven patients with AD PC underwent a second trans-urethral resection of prostate when their PC became AI. Pure population of benign & tumor cells were isolated from paraffin tissue blocks using Laser capture micro-dissection. The GGC repeat was amplified by nested PCR and repeat number was determined using ABI 3100 genetic analyzer and genescan software.

Three out of 11 patients (27%) had shortening of the GGC repeat by 7, 9 & 15 repeats in the AI PC compared to their benign cells and AD PC.

GGC shortening in AI PC suggests an alteration occurring in the AR gene with androgen ablation, and could explain the development of AI PC in certain patients. This finding may be clinically significant in early detection of AI phenotype.

S8. The Complexity of Hereditary Non-Polyposis Colon Cancer (HNPCC) Diagnosis in the Irish Population.

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National Centre for Medical Genetics and Histopathology, Department of Pathology & Laboratory Medicine,* Our Lady's Hospital for Sick Children, Crumlin, Dublin 12.

HNPCC is an autosomal dominant cancer predisposition syndrome, characterised by colorectal adenocarcinoma, with or without extracolonic cancers. It is estimated that HNPCC may be responsible for ~ 1-4 % of all colorectal cancers. Diagnosis of the syndrome is complex, both from a clinical and laboratory perspective. Clinically, because sporadic colorectal cancer is common, selection of possible HNPCC families for mutation screening is performed using the 'Amsterdam Criteria' (based on specific family history and early age (<50yr) of onset). In the laboratory, a complex multidisciplinary approach is required, as there are several large genes, with a wide mutation spectrum, responsible for HNPCC, often with mutations unique to a family.

HNPCC is caused by germline mutations in DNA mismatch repair (MMR) genes, with mutations in MLH1, MSH2 and MSH6 accounting for ~ 95 % of those found. Inactivation of MMR genes leads to a failure in repairing DNA replication errors, which can be detected as microsatellite instability (MSI) in tumour DNA and is highly characteristic of HNPCC, with 90-95 % of HNPCC tumours displaying MSI. Immunohistochemistry (IHC) using monoclonal antibodies to determine the expression of MMR gene protein products in tumour tissue can indicate which specific gene to screen.

Large genomic rearrangements, such as whole exon deletions or duplications in MLH1 and MSH2 can account for 6-10 % of HNPCC mutations. These can be detected by multiplex ligation dependent probe amplification (MLPA).

Where MSI is found and/or IHC indicates loss of MMR protein(s), analysis by MLPA and/or mutation screening of the MLH1 and MSH2 genes by denaturing high performance

liquid chromatography (dHPLC) and/or direct DNA sequencing is undertaken.

We have investigated over 50 Irish families, referred to the National Centre for Medical Genetics, suspected of having HNPCC. Through applying this complex and multidisciplinary approach, complete or partial mutation screening has been carried out on 29 patients and germline mutations in MMR genes have been identified and a diagnosis of HNPCC confirmed in 11 patients to date.

S9. Frequencies of ten mutations associated with common inherited disorders in Northern Ireland.

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1. Department of Biochemistry, Royal College of Surgeons in Ireland, Dublin;
2. Department of Epidemiology and
3. Newborn Screening Programme, Royal Victoria Hospital and Queen's University, Belfast.

The genetic disorders Haemochromatosis (*HFE*), Cystic Fibrosis (*CFTR*), Phenylketonuria (*PAH*), Galactosaemia (*GALT*) and Homocystinuria (*CBS*) have a higher incidence in Ireland than elsewhere in Europe. In an investigation of the Northern Ireland population, a representative cohort of 900 anonymous DNA samples (150 x 6 counties) in the form of newborn screening 'Guthrie' cards was collected with appropriate ethical approval and genotyped for ten common mutations associated with these disorders: C282Y, H63D (*HFE*); G551D, R117H, DF508 (*CF*); R408W, F39L, I65T (*PAH*); Q188R (*GALT*); G307S (*CBS*). Some variation was observed between counties (and in some cases between genders) for individual mutations; however, these differences did not attain significance on statistical testing. The eastern counties (Antrim, Down and Armagh) exhibited lower carrier frequencies for several mutations compared with the western counties (Derry, Tyrone and Fermanagh); eg: the R408W *PAH* mutation. In direct contrast to the literature, the *CFTR* mutation R117H exhibits a higher carrier frequency to that of G551D (1 in 251 versus 1 in 884).

S10. Comparing Y chromosome haplotypes and surnames of Norse and Irish origin in men in Northern Ireland.

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Single Nucleotide Polymorphisms (SNPs) found on the paternally-inherited Y-chromosome are used by human population geneticists to trace human lineages. Unlike autosomal markers, Y chromosome haplotypes are uni-parentally inherited and therefore useful in untangling historic human migration patterns. Y chromosome markers also have the advantage of being passed from father to like surnames, allowing for the comparison of cultural and genetic inheritance. Ireland's relatively recent colonization by modern humans, coupled with its relative geographic isolation, makes it an ideal location for surname/Y-chromosome comparative study. Earlier work focused in the Republic of Ireland has shown the majority of Irish males (>98% in Connaught) belong to a single haplotype, R1b1 (within the haplogroup PR*). By contrast, a sample of the modern Norse population contains only 23% R1b1. This work suggests the possibility to distinguish genetically groups of Irish-Gaelic and putative Viking (Norse) origin. We have begun typing 197 buccal swabs from men in Northern Ireland for 10 SNP markers on the Y chromosome. Preliminary results show little difference in men with Irish-Gaelic surnames: 39 of 42 samples in haplogroup PR* and 3 of 42 in haplogroup GJ*, and those with Norse surnames (57 of 62 in PR* and 5 of 62 in GJ*).

S11. Intraallelic variability in the R408W Phenylketonuria mutant lineages in Europe.

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2. Dipartimento di Biologia, Università di Ferrara, Ferrara, Italy;
3. Department of Biochemistry, The Royal College of Surgeons in Ireland, St. Stephen's Green, Dublin, Ireland.

The common Phenylketonuria mutation in Europe, R408W, is observed on chromosomes of two distinct haplotypes as the result of recurrent mutation: the two lineages are referred to as R408W-2.3 and R408W-1.8. Spatial autocorrelation analysis of their frequency distributions suggests that R408W-2.3 was dispersed across central and eastern Europe by human migration while R408W-1.8 arose in Ireland with limited subsequent spread [O' Donnell *et al*, *Eur J Hum Genet* 2002, **10**: 530-538; Tighe *et al*, *Hum Mutat* 2003, **21**: 387-393].

Three novel dinucleotide Short Tandem Repeat (STR) markers within and flanking the human Phenylalanine Hydroxylase locus were identified and used to assess relative levels of genetic diversity within the R408W lineages. Phylogenetic analysis based upon STR haplotypes produced unrooted star-like networks demonstrating comparable levels of diversity for R408W-2.3 and R408W-1.8. Both networks were centred on a major haplotype [61% of R408W-1.8 alleles; 49% of R408W-2.3 alleles] and contained a total of 17 mutational steps. Estimates of allele age based upon intra-allelic variation generated values of 4,850 - 37,975 yBP for R408W-1.8 and 7,700 - 44,050 yBP for the R408W-2.3 mutation. Neutrality tests suggested that the two R408W lineages increased in frequency over time due to population expansion rather than heterozygote advantage.

S12. Signature of Recent Positive Selection in the Irish Population.

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A single population test (Ewens-Waterson test) applied in a genomic context was used to investigate the presence of recent positive selection in the Irish population. Several lines of evidence suggest that the Irish population has a relatively undisturbed genetic heritage which dates to the Paleolithic (pre-farming era). We first recognize outlier SNPs (23), from previously published data, with high Fst branch specification in a European-American population. We then identified those,

from the 23 SNPs, which were within or close to known genes. The presence of selection was then investigated through additional genotyping of microsatellites flanking these outlier SNPs. The results were also assessed in the context of a genome–wide distribution of the Ewens-Watterson's statistic, designed for the Irish population, to capture the effect of the population's unique demographic history. The signature of selection was detected in 5 genes out of 6 associated with outlier SNPs. The gene PKCη (protein kinase C, eta) show the most extreme signature of positive selection. The two microsatellites within this gene are in linkage disequilibrium, although they are 79 kb apart. Moreover, the cystic fibrosis gene (CFTR), a disease which has the highest worldwide frequency in Ireland, was among the genes showing evidence of selection.

S13. Heterogeneous levels of inter-population differentiation among different functional classes of immunologically important genes.

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3. Smurfit Institute of Genetics, Trinity College, Dublin 2, Ireland.

It has been postulated that biological function may influence the degree to which allele frequencies at a locus differ among geographical populations. In order to evaluate this effect, genotypic data from re-sequencing studies of cytokine, cytokine receptor, cell adhesion molecule, Toll-like receptor and coagulation genes from public databases were analysed for genetic differentiation (F_{ST}) between population samples of European and African descent. There was no difference among observed levels of differentiation when F_{ST} was calculated as a weighted average from all variants of each gene. However, when a corresponding analysis was performed using only non-synonymous (functional) variants for each gene, median F_{ST} values among gene classes were statistically different ($P = 0.0424$). Interestingly, functional classes also differed statistically in the number of SNPs which are non-synonymous ($P = 0.0278$). Particularly high levels of differentiation were shown by individual non-synonymous SNPs at some Toll-like receptors, which encode components of the innate immune response, and *ICAM1*, the rhinovirus receptor. Variation in natural selection in different geographical regions may have inflated inter-population differentiation at these loci. Consequently, studies of genetic susceptibility to disease, using protein variants which potentially interact with pathogens, are more likely to be confounded by population admixture.

Poster Presentations:

P1. Characterisation of the *MTHFD1* promoter.

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5. Department of Clinical Medicine, Trinity College Dublin, Dublin, Ireland.

The human *MTHFD1* gene encodes a trifunctional cytoplasmic enzyme involved in folate metabolism and plays an important role in the biosynthesis of DNA. A polymorphism, R653Q, in MTHFD1 has previously been identified as a risk factor for neural tube defects (NTDs) in the Irish population. Characterisation of the *MTHFD1* promoter will lead to an understanding of how this gene is regulated and will provide an insight into how this gene influences NTD risk.

Analysis of the *MTHFD1* upstream region to date shows that this promoter lacks both a TATA box and an Initiator element. Transcriptional initiation has been identified at multiple start sites over a 120bp initiation window adjacent to the translation start site, using the 5'RLM-RACE method. Many putative regulatory elements have been identified in the promoter region, including Sp1, E2F, and USF sites, which may be important in both initiation and control of transcription. An upstream region of 594bp has been shown to induce a high level of gene expression, which is significantly decreased when this region is reduced to 393bp. Putative Sp1 and E2F elements, located in the 200bp between these regions, are believed to be necessary for activated transcription of the *MTHFD1* gene.

P2. Adult presentation of Tuberous Sclerosis Complex (TSC).

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TSC is an autosomal dominant multisystem disorder characterised by hamartomas in major organs of the body. The age of onset of symptoms can range from infancy to adulthood, with a variable degree of expression.

We present a 55-year-old lady referred via dermatology, with a four-year history of multiple periungual fibromas affecting her toenails and fingernails. She had a facial rash consistent with adenoma sebaceum. She had seizures in childhood and had a brain lesion removed in 1962 at the age of 12. She has had no seizure activity since and is of normal intelligence.

Clinical examination and investigations confirmed a diagnosis of TSC. There were bilateral renal cysts on ultrasound and enhanced CT of brain revealed calcified subependymal nodules. A mutation, 1210insT, was identified in exon 10 of the TSC1 gene.

The patient has one daughter who is asymptomatic. Her granddaughter, born in October 2002, developed seizures at 9 months of age, but has no physical or radiological evidence of TSC. Further investigation is underway to establish this child's TSC status.

Molecular identification of mutations responsible for TSC is a valuable adjunct to clinical and radiological investigation of family members of affected individuals.

P3. Use of multiplex ligation dependant probe amplification (MLPA) for mutation detection in familial keratoconus with cataract.

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Previously we reported linkage of dominantly inherited keratoconus with cataract to chromosome 15q and excluded several positional candidate genes by PCR-based sequencing. Large deletions and duplications are normally missed by this method, but can be detected by quantitative methods such as MLPA. MLPA is based on hybridisation and ligation of two adjacent primers which include different universal primers on opposite ends, permitting simultaneous amplification of several ligated sequences. One fluorescently labelled universal primer allows the products of differing size to be quantified.

We performed long range PCR of multiple exons of candidate genes in family members of the keratoconus with cataract pedigree, and detected no length variation. Next we interrogated the primer binding sites using MLPA and found one biased result inferring deletion in a candidate gene. The method was controlled using an X-linked marker, which showed the expected ratios in DNA from XY, XX and XXX patients.

Deletions may be responsible for about 10% of all pathogenic mutations. They may be difficult to detect, but should be considered in high priority candidate genes before proceeding to screen low priority candidates. MLPA is a straightforward method for identifying most deletions or duplications, but not rearrangements that do not affect dosage.

P4. Lethal nonpulmonary anomalies associated with congenital diaphragmatic hernia, "a twenty year series".

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The high mortality of congenital diaphragmatic hernia (DH) is due to the presence of abnormalities of other organ systems that commonly co-exist. Antenatal identification of isolated DH allows selection of these infants for delivery in specialist centres to facilitate curative surgery. Certain patterns of associated abnormality are commonly found and can be assessed by ultrasound.

In our series of 52 cases of DH born in the National Maternity Hospital, 15 babies were stillborn, 18 died in the early neonatal period and 21 were transferred for surgery. 1 neonatal death did not have autopsy. A very high rate of associated major congenital malformation was identified in stillbirths and early neonatal deaths.

Abnormalities fell into 3 main groups: neural tube defects (NTDs), major cardiac defects(CHD) and chromosomal abnormalities(CA). Of 15 stillbirths, 8 had NTDS, 8 had CHDs, 5 were shown to have numerical chromosomal abnormalities and 2 had DH only. Of 18 neonatal deaths, 2 had NTDs, 5 had CHDs, 3 were shown to have CA (including 1 case of Pallister-Killian Syndrome), there were six with other malformation syndromes and 6 with DH only.

P5. Expanding Fragile X Phenotypes.

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As the number of Fragile X families identified continues to grow, the spectrum of phenotypes associated with particular genotypes becomes less clear. We describe a female patient (Patient A) with a family history of Fragile X, whose brother was identified as having a full Fragile X mutation. Patient A's mother and maternal grandmother were both found to have expansions in the premutation range. Patient A is a healthy 18 year old, pursuing third-level education, who presented to Gynaecology having had only 3 menstrual periods between the ages of 15 and 16. Gynaecology confirmed Premature Ovarian Failure (POF) and subsequent molecular analysis showed a full Fragile X mutation. POF has been described as being "unique to the premutation range" (~ 20% of premutation females) but has never been associated with a full Fragile X mutation. Conversely, we describe a female patient (Patient B), who presented to the genetics clinic with a family history of Fragile X, having two nephews with full Fragile X mutations. She reported that she had learning difficulties from an early age and was unable to complete secondary school. She was found to have a small premutation (78 repeats +/- 1). Case A raises the question of whether POF can also be associated with full Fragile X mutations, while case B may support recent evidence for mild clinical involvement in premutation carriers, or is it possible that mosaicism is clouding the Fragile X genotype-phenotype correlation.

P6. CHARGE syndrome: confirmed CHD7 mutation in sibs, with paternal mosaicism.

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Mutations in the CHD7 gene were associated with CHARGE syndrome in 2004. We present a sister and brother with clinical features of CHARGE syndrome who have a confirmed 2520G>A (W840X) mutation. The parents have also had analysis of CHD7 and the father is a mosaic carrier of the mutation.

This 14 year-old girl was born at 39 weeks gestation to non-consanguineous Caucasian parents. At birth she had abnormal ears, pulmonary stenosis and a VSD. Later she presented with seizures, and was noted to have congenital dislocation of the hip, developmental delay, facial and limb asymmetry, conductive deafness, choanal narrowing, and thoracic kyphosis. Her 11 year-old brother was born at 38 weeks gestation. He had very similar features with abnormal cup-shaped ears, ASD and VSD, facial asymmetry, dysplastic capital femoral epiphyses, micropenis, absent testes and developmental delay. Both children have absent punctae and bilateral choroidoretinal colobomata. Initially, autosomal recessive inheritance was considered, along with the possibility of gonadal mosaicism. The parents have two other clinically unaffected children. Confirmation of the molecular genetic basis of CHARGE syndrome in this family has added to our knowledge of the condition and allowed more accurate counselling and risk estimation for the family.

P7. Analysis of the pathogenicity of two missense HNPCC mutations c.302G>A (G101D) and c.2146G>A (V716M) within a diagnostic laboratory.

Logan WP, Devlin LA, McKee S, Sweet K, Magee A, Morrison PJ, Graham CA.

Northern Ireland Genetics Service, Belfast City Hospital.

Establishing the pathogenicity of missense mutations detected in a proband of Hereditary Non Polyposis Colorectal Cancer (HNPCC) families is a recurring problem for diagnostic laboratories. Here we consider two Northern Irish families who meet Amsterdam Criteria for HNPCC, who have been shown by the CAPP study to carry a missense mutation in the MLH1 gene.

The proband of Family 1 was shown to carry a c.302G>A transition (G101D) in MLH1 exon 3. This mutation occurs within an ultra-conserved region of MLH1, disruption of this motif is predicted to disrupt ADP/ATP binding, resulting in a functionless protein. This mutation was not detected in over 160 population-matched control chromosomes. Family studies have shown that all five HNPCC-affected individuals are heterozygous for this mutation. Two-point linkage analysis (FASTLINK) of disease phenotype and G101D gave a maximum LOD score of 1.91 at theta=0, further supporting the association of the mutation with HNPCC in this family. This is to our knowledge the first report of this mutation.

The proband of Family 2 was shown to carry a c.2146G>A transition (V716M) in MLH1 exon 19. This mutation is in a poorly conserved region of MLH1 and was not detected in over 150 population-matched control chromosomes. Two affected family members have been studied but only one carries the mutation. The mutation has been previously reported in the literature.

In conclusion, we provide evidence of a low allele frequency of the G101D and V716M mutations within our normal population. We have shown co-segregation of G101D with an HNPCC phenotype through family studies and we propose a possible mechanism of disease. In contrast, we have failed to determine a disease mechanism for the V716M mutation and family studies throw doubt on its pathogenicity.

P8. Hypoxia-inducible suicide gene therapy strategy for prostate cancer.

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We have chosen to exploit the hypoxic nature of prostate tumours to gain a therapeutic advantage. Gene therapy targeted to hypoxic tumour cells will allow selective killing of malignant cells.

The induction of gene expression under hypoxic conditions is governed by the activation of hypoxia-inducible factor 1 and its subsequent binding to hypoxia response elements (HREs). HREs are found in the promoter of various oxygen-responsive genes, including vascular endothelial growth factor (VEGF) and glyceraldehyde-3-phosphate dehydrogenase (GAPDH).

We propose to use arrangements of increasing copy number of the HRE core sequence isolated from the VEGF and GAPDH promoter to drive the expression of the cytosine deaminase (CD) gene. CD is a prodrug activation enzyme, which converts inactive 5-fluorocytosine (5-FC) to active 5-fluorouracil (5-FU), allowing selective killing of vector containing cells. Hypoxic cells transfected with these constructs would express CD and therefore would be killed when treated with 5-FC.

A series of expression vectors were constructed which contain arrangements of 2, 5, 6 or 8 copies of the GAPDH or VEGF HREs. These constructs were transfected into 3 prostate cancer cell lines (DU145, PC-3, 22Rv1) and were tested for their efficacy when exposed to oxygen concentrations of 0.1% for 24 hours.

P9. Interchromosomal insertion resulting in partial trisomy 11q.

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We present a case of partial trisomy 11 resulting from an interchromosomal insertion. A newborn male infant was initially referred with dysmorphic facies, saddle nose, low set ears, inspiratory stridor, short neck, micropenis, hypotonia and a wide interdigital cleft between the great toes. A genetic assessment further revealed redundant neck skin, a carp like mouth, epicanthic folds, strabismus, retrognathia and tapering fingers. The infant also required tube feeding. Subsequent development was severely delayed in all areas. At age 16, he was unable to walk, had no speech and had epilepsy controlled with sodium valproate. Chromosome analysis of cultured lymphocytes revealed an unbalanced 46,XY, der(2)ins(2;11)(q32.2; q23.1q25), t(10;13)(q24.3; q14.3) karyotype. The mother previously had 3 early miscarriages and one liveborn normal female. Examination of parental chromosomes revealed that the derivative chromosome 2 had been inherited from the mother who carried the balanced form of the insertion. The t(10; 13) translocation found in the infant had arisen de novo and was not felt to carry a major contribution to the overall phenotype. This infant has clinical features overlapping with partial trisomy 11q syndrome. Trisomy 11q syndrome is a rare but recognized syndrome and our case is interesting because it has arisen from an interchromosomal insertion. This appears to be the first case of trisomy 11q arising from an interchromosomal insertion.

P10. Increasing complexity of the CF mutation spectrum in the Republic of Ireland.

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The incidence of cystic fibrosis (CF) at birth in the Republic of Ireland is 1 in 1461. Since 1995, CF testing has been performed at our Centre by an ARMS method that has been designed to detect the 11 most common mutations in this population, at a sensitivity of 93%. To date, we have used this method to test 2729 patients who either have classical CF that has been diagnosed clinically, or who have symptoms suggestive of CF. Our ARMS test has provided a confirmatory genotype in 730 of these patients (approximately 27%). Following further clinical assessment, a cohort of 122 probable CF patients in whom one or no mutation had been identified by the ARMS method, were selected for further analysis. Mutation screening of the

CFTR gene was performed by DGGE, dHPLC and sequencing initially to identify small gene alterations, followed by QMPSF (quantitative multiplex PCR of short fluorescent fragments) to identify large genomic rearrangements.

This additional analysis has so far resulted in the identification of a second CFTR gene alteration in 31/122 patients, and the identification of both CFTR gene alterations in 1/122 patients. Six of the CFTR gene alterations have not been reported previously, and in four of these cases, the pathogenicity is uncertain. Six CF mutations were detected in more than one apparently unrelated individual.

We present details of these findings and assess their contribution to the CF mutation spectrum of the population of the Republic of Ireland. We also report unusual cases involving the identification of a de novo mutation in one family and the identification of a CFTR deletion spanning exons 2, 3 and 4 in three apparently unrelated families.

P11. Evaluation of a Luminex-Based Multiplex Assay for Cystic Fibrosis Mutations.

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Plans for newborn screening for cystic fibrosis (CF) and issues of sensitivity and efficiency with our current "home-brew" ARMS™ assay led us to look for a multiplexed CF assay which could be adapted to the mutation spectrum of the Irish population. We have an excellent knowledge of the Irish mutation spectrum, as all patients with mutations not detected by our ARMS assay are screened by DHPLC of the entire CFTR gene at the laboratory of Professor Claude Ferec in Brest, France. We are currently evaluating the Ambion Signature™ CF 2.0 ASR. This assay involves single-tube/well multiplex amplification followed by direct hybridisation of amplified products to allele specific capture probes without intervening purification steps or secondary amplification. Products are then measured by Luminex^{100} IS xMAP™ Technology.

To date, we have evaluated the core 29-target assay on a large cohort of DNA samples of known genotype, from different tissue sources, to examine sensitivity and specificity of the ASR. Results of these studies, as well as an analysis of cost and efficiency, will be presented.

P12. Longitudinal Autosomal Genetic Variation in Ireland.

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Substantial differences between Eastern and Western regions have been a recurring finding in investigations of Irish population variation, most notably in the paternally inherited Y-chromosome. These differences have often been attributed to the preferential migration of post-foundation settlers to eastern regions of the island due to the relative proximity of Britain and Europe. Under this scenario Britain and the West of Ireland represent migration source and destination populations respectively, with the eastern region a zone of contact and admixture between the two. The impact and signature of any such process on the autosomal (biparentally inherited) genome was examined using intra-Ireland classical gene frequencies in a European context, and secondly in 380 autosomal microsatellites, typed in 194 British and Irish individuals, and analysed using both traditional genetic distance and model-based clustering approaches. No general or extensive longitudinal pattern of variation was detected. The apparent contrast with the Y chromosome and agreement with the maternally inherited mtDNA suggests that Y-chromosome differentiation was driven and exaggerated by male specific behaviours during or before Ireland's population history. However a fuller assessment of Irish autosomal regional variation will probably require larger samples sizes and greater knowledge of wider European variation at individual loci.

P13. Alpha T-Catenin (CTNNA3) is subject to structural and epigenetic alterations in transitional cell carcinoma of the bladder (TCCB).

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Loss of the adhesion protein E-cadherin occurs frequently in TCCB and is integral to development of the epithelial-mesenchymal transition (EMT). CTNNA3 is one of a small family of catenins whose interaction allows the association of other catenins to cadherins. Importantly, CTNNA3 is downregulated in EMT, hypothetically compromising E-cadherin associated cell-cell adhesion. The objectives of this current study are:

1) To investigate the imprinting status and phenotype of alpha T-catenin in a cohort of primary bladder cancer samples and matched paired normal samples.

2) To establish if alpha T-catenin is subject to loss of heterozygosity (LOH).

Using primers to a published transcribable SNP in exon 12, (Van Dijk *et al,* 2004), CTNNA3 specific DNA and cDNA PCR products were amplified, purified and commercially sequenced to identify informative cases. (MWG). Of the cohort so far examined, 40% of samples were heterozygous, with one paired case displaying LOH. CTNNA3 was also shown to display gain of imprinting (GOI). CTNNA3 loss through LOH or epigenetic downregulation could play a key role in rendering cells less adherent to each other thereby favouring a more metastatic phenotype. Reference: Van Dijk *et al* 2004 PMID:15533819.

P14. Maple Syrup Urine Disease: The Mutational Spectrum Associated with MSUD in Ireland.

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Maple Syrup Urine Disease (MSUD) is an autosomal recessive metabolic disorder caused by a deficiency in activity of the branched-chain keto acid dehydrogenase (BCKD) complex, and occurs with an incidence of 1:125000 in Ireland; it is one of the five disorders screened for as part of the newborn screening programme in Ireland. Mutations in the human BCKD genes, E1α(BCKDHA), E1ß(BCKDHB), E2(DBT) and E3(DLD) result in MSUD and are known as Type Ia, Ib, II and III respectively.

This study seeks to establish the mutation spectrum associated with MSUD in Irish patients by means of a PCR-based exon sequencing strategy. Preliminary data, from 7 patients has demonstrated three type II mutations in the E2 sub-unit. The first, found in two siblings, is a single base pair deletion 81_83del in exon 5 resulting in a frameshift which introduces a premature stop codon predicting a loss of at least 50% of the mRNA transcript. The second, found in two independent cases, is a G>C transversion in exon 10 resulting in substitution of alanaine with proline. The third is a splice-site mutation in intron 9. Additional intronic SNPs have been detected and these are currently being investigated as to their functional relevance.

P15. The MTHFD1 R653Q polymorphism and complications of pregnancy.

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5. Molecular Pathogenesis Section, Genome Technology Branch, National Human Genome Research Institute, Building 50, Room 5306, 50 South Drive, MSC 8004, Bethesda, MD 20892-8004.

Background: The *MTHFD1* gene encodes a trifunctional enzyme that plays a central role in folate metabolism. Maternal folate status and/or homocysteine levels have been implicated in a range of pregnancy complications, most notably in pregnancies affected by a neural tube defect (NTD). We have previously identified the R653Q polymorphism in MTHFD1 as a maternal risk factor for NTDs.

Aim: The aim of this study was to initially confirm the association of the MTHFD1 R653Q polymorphism as a maternal risk factor for NTDs in the Irish population and also to consider whether the MTHFD1 R653Q polymorphism had a role to play in other pregnancy complications.

Results: We have confirmed the association between the MTHFD1 'QQ' genotype and maternal NTD risk in a second cohort of women from the Irish population (OR 1.49 (95% CI 1.07- 2.09), P= 0.02). We also found that the MTHFD1 'QQ' genotype is a significant risk factor for severe abruptio placentae (OR 2.85 (95%CI 1.47-5.53), P= 0.002) but not for pre-eclampsia (OR 1.44 (95%CI 0.78-2.67) P= 0.25).

P16. Tetrasomy 9p : a case report.

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Tetrasomy 9p is a rare chromosome syndrome with less than forty cases reported in the literature. Previously described cases have a fairly recognizable phenotype comprising multiple craniofacial, limb and cardiac abnormalities. It is suggested that presence or absence of mosaicism has an effect on phenotypic differences and mortality rates. Nonmosaic tetrasomy 9p cases have poor prognosis. We report a new case of de novo nonmosaic tetrasomy 9p with multiple dysmorphic features. Our case was a full term IUGR female infant who survived for ten days. The dysmorphic features included brachycephaly, broad nasal root, prominent forehead, wide sutures, large anterior fontanel, micrognathia, micropthalmia, grossly hyperextended lower limbs, bilateral hip dislocations, small toes, a skin tag over chest, overlapping fingers and hypoplastic nails. The infant also had cardiac anomalies, Dandy Walker malformation and a partially septate uterus. Skeletal survey revealed 11 pairs of broad ribs, platyspondyly, poor acetabular and femoral head development and absent patellae. Chromosome analysis of peripheral lymphocytes and fibroblasts revealed nonmosaic tetrasomy 9p. The clinical features of our case, compared with cases reported in the literature give an additional support to the emerging phenotype of this chromosomal syndrome.

P17. Trisomy 10p with clinical features of facio- auriculo-vertebral spectrum: a case report.

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Trisomy 10p is a rare syndrome with a variable phenotype. The most commonly described clinical features of trisomy 10p are mental retardation, proportionate growth retardation, hypotonia, microcephaly, bossing of forehead, dysplastic ears, high arched or cleft palate, nose abnormalities, and club foot. Most cases result from familial balanced translocation. Pure and de novo cases are rare. We describe a case of de novo partial trisomy 10p with clinical features suggestive of facio-auriculo-vertebral spectrum. The clinical features include hemifacial microsomia, external ear atresia, ear tags, and normal physical and mental development. These clinical findings have not been described in previously reported cases of trisomy 10p.

P18. siRNA mediated suppression of IMPDH1 transcripts: Relevance to therapy for RP10 form of Retinitis Pigmentosa.

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Retinitis pigmentosa (RP) is a group of inherited retinopathies that gradually results in blindness due to degeneration of the retina. The rod and cone photoreceptors found in the retina are responsible for the conversion of light into electrical impulses, which are then transmitted to the brain via the optic nerve. However in RP patients, these photoreceptors deteriorate over time until the ability to transmit electrical messages is lost. RP can be inherited in an autosomal dominant, autosomal recessive, x-linked recessive or digenic fashion. In addition,

mutation within mitochondrial DNA can also cause RP. RP is genetically heterogeneous with 29 genes being identified in disease pathology to date. Furthermore, RP is also characterised by intragenic heterogeneity where many different mutations within a given gene are responsible for causing the disease in different families.

The gene that is responsible for the RP10 form of autosomal dominant retinitis pigmentosa (adRP) has been mapped to human chromosome 7q31.1, and accounts for 5-10% of all RP cases in the US and Europe. In our lab, comparative analysis of the transcriptional profiles within the retina of mice carrying a targeted disruption of the rhodopsin gene identified the gene encoding inosine monophosphate dehydrogenase 1 (IMPDH1) as a candidate gene for RP10. In addition, several studies have also revealed that specific mutations within IMPDH1 segregate with RP affected families (Kennan A *et al. Hum Mol Genet* 2002: **11:** 547-558), thus providing further evidence that mutations in IMPDH1 are the cause of the RP10 form of adRP. Structural protein analysis have indicated that mutant IMPDH1 protein misfolding or aggregation is the likely cause of severe retinopathy in human (Ahern A *et al. Hum Mol Genet* 2004; **13:** 614-650). In contrast, IMPDH1 $^{-/-}$ mice at four months of age, which is equivalent to a teenage human subject, have shown no structural or functional degeneration in the retina. This observation suggests that the dominant segregation pattern associated with RP10 is not caused by haploinsufficiency of normal IMPDH1 gene, but the disease pathology is caused by a dominant negative phenotypic effect exerted by mutant protein.

The collective findings summarised above represent RP10 as a potential target for therapeutic intervention where simultaneous ablation of wild type and mutant IMPDH1 transcripts by siRNA molecules may alleviate the severe retinopathy of RP10 by prolonging the survival of photoreceptor neurons.

P19. The role of regulatory regions on chromosome 5q in genetic susceptibility to coeliac disease.

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The risk of developing Coeliac Disease is determined by interactions between environmental factors and multiple contributing loci. Microsatellite repeat markers studies in affected Italian sib-pairs have indicated linkage between the 5q31-33 region and Coeliac Disease. We sought to investigate this region for extra-genic evolutionarily conserved regions (ECRs) which may be indicative of gene regulatory sequences. ECRs were identified using ECR Browser by comparing orthologous sequences from human and mouse. SNPs within Transcription Factor Binding Sites (TFBS) may result in altered gene expression, thus we sought to identify polymorphic TFBS within ECRs and determine whether specific polymorphisms are associated with disease pathology.

The ECR browser is linked to dbSNPs, allowing identification of SNPs within selected sequences. ECRs containing SNPs were analysed via rVISTA2.0. However, TFBS identified solely on resemblance to consensus binding sequences results in the generation of large numbers of false positive results. rVISTA2.0 reduces the false positive TFBS identification rate by identifying conserved TFBS via comparison of orthologous sequences from two species (in this case mouse and human) with regard to sequence identity and relative position. 34 SNPs were identified which altered conserved putative TFBS over 1Mb, a frequency of 1/29.4Kb. These sites are being evaluated for disease association.

P20. A case series of diploid/triploid mosaicism in Northern Irish patients.

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Triploidy, the most frequent chromosomal abnormality in first trimester spontaneous miscarriages is estimated to occur in 2% of human conceptions. A true incidence of diploid/triploid mosaicism is difficult to obtain. Severe intrauterine growth retardation, facial or body asymmetry, asymmetric digit syndactyly, characteristic facial dysmorphism, abnormal male genitalia and mental retardation are characteristic features.

Three cases are presented:

Case 1: A history of intrauterine growth retardation, postnatal chest infections and feeding difficulties were noted. Profound hypotonia, facial and body asymmetry, asymmetric digit syndactyly, thoracic scoliosis, facial dysmorphism and a pigmented skin area were observed. Skin chromosomes were reported as 69, XXY[9]/46, XY[21] at 5 months.

Case 2: Truncal obesity, facial and foot asymmetry, dysmorphism with asymmetric toe syndactyly and microgenitalia were observed. Skin chromosomes were reported as 69, XXY[16]/46, XY[14] at 8 years.

Case 3: A history of poor tone, learning difficulties, truncal obesity, facial dysmorphism, kyphoscoliosis and asymmetric toe syndactyly were observed. Skin chromosomes were reported as 69, XXY[17]/46, XY[15] at 15 years.

This diagnosis should be considered in all individuals with truncal obesity, syndactyly and asymmetry. We could not demonstrate any correlation between level of triploid mosaicism and phenotype.

P21. Analysis of subtelomeric aberrations suspected in unknown causes of mental retardation via Multiplex Ligation-dependent Probe Amplification (MLPA).

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Multiplex Ligation-Dependent Probe Amplification (MLPA) is a novel method employed to detect copy number aberrations of several nucleic acid sequences in a single reaction. Deletions and amplifications of a gene, or part thereof, are not detected by sequence analysis of Polymerase Chain Reaction (PCR) amplified gene fragments as a normal copy is still present. MLPA provides a faster, more robust and efficient method than Fluorescent In Situ Hybridisation (FISH), allowing up to 45 specific sequences to be amplified simultaneously with the use of only one pair of PCR primers. In this study we have

used MLPA to screen for subtelomeric abnormalities in 105 patients with unknown causes of mental retardation (MR). Subtelomeric abnormalities are responsible for 5% to 10% of unexplained MR cases. The P070 Telomere Kit, from MRC™ Holland, was employed for this procedure. This kit includes probes for each autosomal telomere, two probes within the Pseudoautosomal Region (PAR) common to the X and Y chromosomes, and two Y probes. The results of this study will be presented. It is hoped that this method will replace the labour-intensive FISH analysis and will become routinely incorporated into our diagnostic laboratory thus reducing analysis time and increasing analysis efficiency.

P22. Haplotype analysis of ICAM-1 in premature ischaemic heart disease: a family based study.

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Introduction: The two pillars of atherosclerosis are inflammation and dyslipidaemia. Inflammatory cell recruitment and transendothelial migration are mediated by molecules such as intercellular adhesion molecule-1 (ICAM-1) and are crucial for plaque development. There is little information on the role of single nucleotide polymorphisms (SNPs) and haplotype analysis in ICAM-1 in ischaemic heart disease (IHD). We investigated this using an Irish family-based study, where affected individuals had early-onset IHD.

Methods: A total of 1494 individuals from 580 families were included (800 discordant sib-pairs and 64 parent-child trios). Seven markers (SNPs) across the ICAM-1 gene were selected. Linkage disequilibrium (LD) between both the 7 SNPs and resultant haplotypes and disease status was examined using family-based tests of association (combined transmission disequilibrium test and pedigree disequilibrium test).

Results: The number of informative families for the SNPs IC1, IC3, IC4, IC6, IC7, IC8 and IC9 were 117, 275, 278, 271, 264, 132 and 242, respectively. Strong LD between the SNPs was found. No association was detected between any of the 7 marker SNPs or the 3 common haplotypes (frequency >10%) and IHD.

Conclusions: Haplotype analysis of the ICAM-1 gene using family-based tests has not detected association with IHD within an Irish population.

P23. Why do people fail to attend genetics clinics in Ireland?

Lambert DM, Lynch SA.

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The failure-to-attend rate in our clinics was found to be 24%. A postal questionnaire was constructed to assess barriers to attendance to clinic. Anonymous surveys were divided by type of referral (counsellor; developmental delay; deafness; clefting; other consultant) to assess difficulties experienced when trying to attend clinics. Questions included difficulties with practical arrangements (time/date/transport), lack of information about the appointment, or concerns about a genetics appointment (insurance/blame). Questionnaires were sent to 83 attenders and 91 non-attenders. 38 responses (46%) were received for attenders and 30 (33%) from non-attenders (4 blank : 3 moved and 1 died). Responses from attenders included : 3/5 clefting, 21/49 other consultant, 5/12 developmental delay, 1/3 deafness, and 8/14 counselling. Responses from non-attenders included : 0/3 clefting, 16/55 other consultant, 2/9 developmental delay, 3/11 deafness and 9/13 counselling. Among attenders, 13 (34%) were afraid of what they would be told and 12 (32%) had issues involving practical arrangements. Among non-attenders, 19 (73%) had issues involving practical arrangements, 5 (19%) were afraid of what they would be told, 4 (15%) did not know why they were referred and 1 (4%) was concerned about payment. Although all participants had received a Genetics information leaflet with their appointment letter, significant numbers from both groups remain concerned about what is said in a Genetics clinic.

P24. Accuracy of a Clinical Diagnosis of Marfan Syndrome.

Murphy AM, Lynch SA, Green AJ.*

National Centre for Medical Genetics, Our Lady's Hospital, Crumlin, Dublin 12 and *Conway Institute, University College Dublin.

Marfan's syndrome is a multisystem autosomal dominant disorder characterised by skeletal, ocular and cardiac involvement. Mutations in the fibrillin 1 gene on chromosome 15 have been found in some people with Marfan syndrome. The Ghent clinical diagnostic criteria were agreed and published in 1996.

We reviewed a series of 83 patients referred to the National Centre for Medical Genetics where a clinical diagnosis of Marfan's was raised. We determined from which clinicians the referral came, whether the patient fulfilled the Ghent criteria, whether an alternative diagnosis was offered, and whether FBN1 gene analysis was carried out.

Of the 83 index cases, 196 family members were seen. 26 patients (31%) were confirmed to have a clinical diagnosis of Marfan, 3 (4%) had an alternative diagnosis, (65%) did not fulfil the Ghent criteria. FBN1 gene analysis was carried out in 18 patients with clinical Marfan, and of these 2 had a confirmed FBN1 mutation. The final diagnosis of Marfan was more likely when the patient was referred from cardiology or ophthalmology, than paediatrics or primary care.

Only 31% of patients referred had a final diagnosis of Marfan. The diagnosis is still to be made on clinical grounds. The use of the Ghent criteria needs wider dissemination in the medical community.

Book Reviews

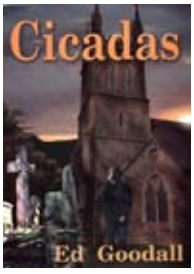
Medical Genetics: Ian D Young. Oxford Core Texts. Oxford University Press, 2005. (p. 315.) £22.00. ISBN 0-19-856494-5

Medical Genetics has long been a part of the undergraduate curriculum and is a rapidly increasing component of post-graduate training at all levels, in all specialities. Ian Young has provided a textbook which will delight both undergraduate and postgraduate readers.

There are many textbooks which claim to cover essential medical genetic teaching, but many of these are too big, too detailed and too expensive. This text is presented in a clear, logical manner with well illustrated chapters and excellent use of colour for key points and boxes. The text is interspersed with case histories, landmark publications and the novel use of a "case célèbre" to illustrate many chapters – and what an excellent memory tool that is. Do you know why Dolly the sheep was called Dolly? Or that Frédéric Chopin may have had cystic fibrosis? There are fourteen chapters from the first "Gene structure and function" travelling through the realm of clinical genetics to end with chapters on "Clinical skills" (so you think you know how to interpret a laboratory report?) and "Applied clinical genetics". The useful appendices cover medical school core curriculum and teaching medical genetics to undergraduate medical students. Each chapter ends with a few MCQs, the answers having succinct explanations.

Ian Young is respected world-wide as a clinician, author and teacher of medical genetics. From Northern Ireland originally, he has not lost the art of communication. This is a text clinicians at any level will enjoy either for serious study or occasional casual reading (it is just about the right size and has enough flexibility for reading in bed). My one criticism is that it was not available when I needed it as a student (far too many years ago).

ALEX MAGEE



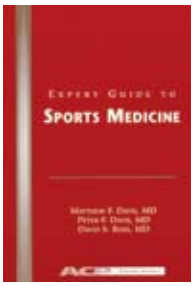
Cicadas: Ed Goodall. Bluberry Press. November 2004. ISBN 0-9548705-0-6. £7.99 (inc. postage and packing direct from www.blueberrypub.com).

An Irish-American medic called Gus McWilliams returns home to Northern Ireland, his urgent mission to find a donor kidney for his ill son – whose renal function is deteriorating – at all costs. His own kidney problems suggest hereditary renal disease and other modern (and old) ethical and genetic dilemmas feature in this novel where in the quiet village of Rostrevor, his genealogy research uncovers a mysterious crime committed in the last century against his ancestors. He uncovers evidence of a 19th century rogue scientist called Diogenes who has discovered the secrets of human cloning. Sinister elements from both sides of the local terrorist divide mix with some international terrorism from the aftermath of 9/11 to both aid and hinder his research leading to an exciting climax.

This is an altogether gripping tale of a doctor struggling to combine his research skills with a hope that he can save his son's life. Goodall has woven a masterpiece of intrigue in a book that will appeal to all. His attention to detail draws on his own research and veterinary background and is fastidious. Factual information is stretched credibly to give a book full of surprises; personal ethics is stretched to the limit.

The book contains 28 beautifully short chapters – just short enough to read individually in a few snatched spare moments of time such as between consultations or in the departure lounge. As the story gets more exciting by the chapter, these are gobbled up by compulsive reading as the patients sit in the waiting area wondering why the 'consultation' is taking so long . . .

PATRICK J MORRISON



Expert Guide to Sports Medicine: Matthew F Davis, Peter F Davis, David S Ross (Editors). ACP series-Expert Guides, American College of Physicians, October 2005. 165pp. £24.95. ISBN 1-930513-64-X

Books are a generation thing. Inevitably out of date before they are published, seldom peer reviewed, and rarely reflecting a systematic search of evidence. Medical textbooks are the ultimate in vanity publishing. We all love to see our names on the sleeves. But, with every new book, irrespective of the specialty, we need ask what it adds. Most are simply a repetition of last year's knowledge.

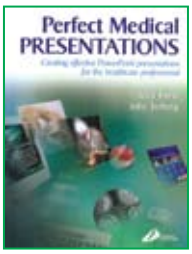
Sports medicine is no different. While it is difficult for any textbook to capture the latest research findings and keep pace with clinical innovations, this book tries hard. Published by the American College of Physicians (ACP), which has a good pedigree in evidence based medicine, I expected innovation. But, this is a traditional textbook aimed at practicing primary care doctors. And with 10% of consultations for musculoskeletal injury, there is a big market. So, if faced with a clinical question in the surgery, would you look to this book for the answer? Let's try out some topical issues – Sudden cardiac death has particular resonance locally and a very difficult problem. No clinical examination alone is likely to pick up at risk individuals in primary care, yet many guidelines still imply that clinical examination has a role. This book does not dodge the question and states that "give the large numbers of athletes to be screened, non invasive testing is thought to be cost- prohibitive and troubled by both false positive and false negative tests". It addresses the appropriate tests necessary in a pre-participation examination, states the limitations honestly, and doesn't shirk the issue of medico legal liability.

The phone rings. An invitation to provide medical cover at a major sports event. What should you do and how do you prepare? This is another interesting and useful chapter and although it is rather US focused, the principles are the same. Recent high profile tragedies in mass participation running

event make this chapter particularly relevant. As you might expect, it doesn't include the recommendations of the Taylor report which give specific guidelines on care of spectators in the UK. In contrast, the chapter on anaemia and other haematological issues includes a section addressing the widespread abuse of erythropoietin happily skips over any of the well documented US blood doping scandals. A rather naive section on coping with lightening strikes undermines the book's credibility. "Avoid sports performance in thunderstorms… educated on how to calculate the storms distance…,, do not take refuge under a lone tree… do not take a bath or shower during electrical storms".

Exercise prescription, infectious diseases, dermatology and useful case reports reflect the particular focus on primary care and the photographs, illustrations and radiographs are very helpful. But time has moved on. Most GPs now have desktop computers in the consulting room with online textbooks and web access. A traditional textbook is more likely to gather dust on the shelf than be used in the consultation. Future text books will be electronic compendiums of the latest research findings, portfolios of self direct learning, and constantly updated from the web. The hand held and pocket PC is the textbook of the future. This is a traditional textbook: yesterday's news using last years medium.

DOMHNALL MacAULEY



Perfect Medical Presentations: Terry Irwin, Julie Terberg. Churchill Livingstone 2004 (244pp). ISBN 0-44307485-2. £19.99.

A book which does just what it says. Reading this book will improve how you put together and present talks, regardless of your level of experience. The style throughout is consistent, readable and easy to understand, which is surprising given the number of contributors.

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The common sense advice on preparation, presentation technique, and how to present yourself at a meeting is invaluable to the inexperienced, and will offer areas for improvement for more experienced presenters.

Issues of ethics and consent relating to patient images and data in UK law are dealt with in a straightforward manner. There are also sections covering advanced techniques and shortcuts for those who present frequently and the more technologically aware amongst us!

Make sure you get an original copy, as the enclosed CD ROM includes exercises illustrating the techniques, describes with step by step instructions, has 20 novel slide templates and a trial version of Adobe® Photoshop Elements™.

I wish this book had been available earlier in my career. It allows a relative novice to prepare a professional presentation with the minimum of fuss. I find it an invaluable tool.

JAMES PATTERSON

THE ULSTER MEDICAL JOURNAL

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Legend for cover:

Conservation between the *HOM-C* and *HOX* gene clusters.

The four *HOX* gene clusters found in mammals are conserved from the *Drosophila HOM-C* complex in terms of nucleotide sequence and colinear expression. During embryonic development, the genes are expressed in a pattern that correlates with the chromosomal positioning, depicted here for human and mouse. The 3' genes are expressed both earlier and more anteriorly than the 5' genes. *Ulster Med J* 2006; **75(1):** 23-31.