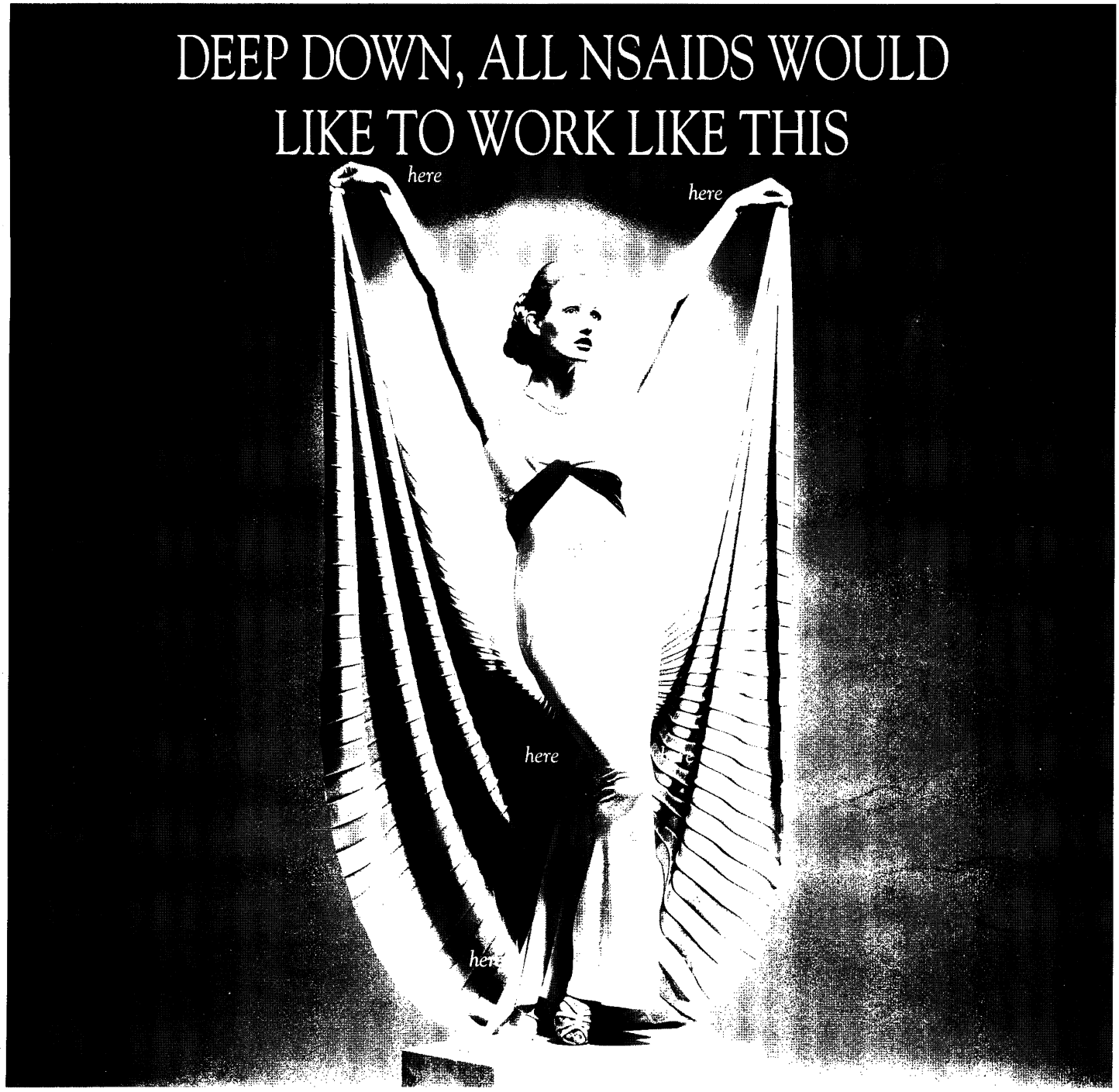
Volume 67 (S1) JUNE 1998
ISSN 0041-6193

THE ULSTER MEDICAL JOURNAL

Published by
THE
ULSTER MEDICAL SOCIETY

DEEP DOWN, ALL NSAIDS WOULD LIKE TO WORK LIKE THIS



Mobic represents a real development in the everyday treatment of patients with osteoarthritis.

The efficacy your patients need, where they need it. With a reduction in unwanted effects that nobody needs. Clinical trials in patients with osteoarthritis have shown Mobic to exert efficacy comparable with other NSAIDs,* yet with fewer GI symptomatic adverse effects.[1]

These findings have recently been supported by the first results from MELISSA, a large scale study involving more than 9,000 patients suffering from acute and painful exacerbations of osteoarthritis.[2]

That is why we believe you should let your patients experience the therapeutic performance of Mobic.

Mobic▼
MELOXICAM
Powerful in the right places

* diclofenac 100mg retard and piroxicam 20mg

Prescribing Information – MOBIC
Tablets containing meloxicam 7.5 mg or 15 mg; suppositories containing meloxicam 15mg. **Action:** Meloxicam is a non-steroidal anti-inflammatory drug (NSAID). It exerts its therapeutic effects by inhibition of biosynthesis of inflammatory prostaglandins. **Indications and dose:** Adults only (from 15 years). Maximum daily dose 15 mg, or 7.5 mg in dialysis patients. The tablets should be taken with food. Short-term symptomatic treatment of acute exacerbations of osteoarthrosis (tablets only): 7.5 mg daily increased to 15mg/day if necessary. Long-term symptomatic treatment of rheumatoid arthritis (chronic polyarthritis): 15 mg/day; 7.5 mg/day in the elderly; starting dose 7.5 mg/day in those at increased risk of adverse events. **Contra-indications:** Hypersensitivity to meloxicam, the excipients, aspirin or other NSAIDs; active peptic ulcer in the last six months or recurrent peptic ulcer disease; severe hepatic failure; non-dialyzed severe renal failure; pregnancy; lactation; gastrointestinal or cerebrovascular bleeding or other bleeding disorders; proctitis/rectal bleeding (suppositories). **Warnings and precautions:** Eliminate, or confirm total cure of, oesophagitis, gastritis or peptic ulcer before starting treatment. Long term treatment with NSAIDs increases the risk of gastrointestinal side effects. Stop treatment in the event of peptic ulcer or gastrointestinal bleeding, or severe cutaneo-mucosal adverse events, or significant/persistent changes in liver or renal function tests. Use with caution in the elderly and those with congestive cardiac failure, liver cirrhosis, nephrotic syndrome, renal failure, those taking diuretics or who have recently undergone major surgery leading to hypovolaemia: monitor urine output and renal function in such patients. Concomitant administration with: other NSAIDs; anticoagulants or ticlopidine; lithium; methotrexate; IUDs; diuretics; cyclosporin; antihypertensives; thrombolytics; oral anti-diabetics. **Side-effects:** digestive system disturbances (e.g. dyspepsia, nausea) may occur; more rarely ulcers or gastrointestinal bleeding. Cutaneo-mucosal reactions (e.g. stomatitis, oesophagitis, skin rash), and disorders of the CNS (e.g. lightheadedness, headache, vertigo) and cardiovascular system (e.g. oedema, palpitations) have been reported. Haematological events have been described. Bronchospasm has been precipitated in individuals allergic to aspirin or NSAIDs. Disturbances of renal or liver function tests have occurred. **Pack size and NHS price:** Tablets: packs of 30 7.5 mg £10.00 PL 14598/0002 15 mg £13.90 PL14598/0003 Suppositories 12 x 15 mg £6.00 PL14598/0001. POM. **Product licence holder:** Boehringer Ingelheim International GmbH, D-55216 Ingelheim am Rhein, Germany. For full prescribing information please see Summary of Product Characteristics. Prepared in January 1998.

References:
1. Distel M *et al*, *Br J Rheumatol* 1996; **35** (suppl.1): 68-77.
2. Data on file, Boehringer Ingelheim.

Further information is available from:
Boehringer Ingelheim Ltd, Ellesfield Avenue
Bracknell, Berkshire RG12 8YS.

Boehringer Ingelheim

MOB 0021b4

NEW FROM MSD

THE FIRST ONCE-DAILY LEUKOTRIENE RECEPTOR ANTAGONIST FOR CHRONIC ASTHMA

In mild to moderate asthma, SINGULAIR:

- *improves control when used with an inhaled steroid*[1]
- *provides prophylaxis in exercise-induced asthma*[1]
- *has excellent tolerability*[1]
- *offers the convenience of one tablet at bedtime*[1]

- *SINGULAIR 10 mg for adults*
- *SINGULAIR PAEDIATRIC 5 mg for children aged 6-14 years*

1 TABLET DAILY

SINGULAIR

montelukast sodium

A single tablet-a-day helps control chronic asthma

SINGULAIR® (montelukast sodium) ABRIDGED PRODUCT INFORMATION

Refer to Summary of Product Characteristics before prescribing

PRESENTATION

SINGULAIR PAEDIATRIC 5 mg chewable tablet: pink, round chewable tablet with 'SINGULAIR' engraved on one side and 'MSD 275' on the other, containing 5.2 mg montelukast sodium equivalent to 5 mg montelukast acid. SINGULAIR 10 mg tablet: beige, rounded square, film-coated tablet with 'SINGULAIR' engraved on one side and 'MSD 117' on the other, containing 10.4 mg montelukast sodium, equivalent to 10 mg montelukast acid.

USES

Treatment of asthma as add-on therapy in those patients with mild to moderate persistent asthma inadequately controlled on inhaled corticosteroids and in whom 'as needed' short-acting β_2-agonists provide inadequate clinical control. Also indicated for the prophylaxis of asthma where the predominant component is exercise-induced bronchoconstriction.

DOSAGE AND ADMINISTRATION

Adults 15 years of age and older: one SINGULAIR 10 mg tablet daily at bedtime with or without food. *Paediatric patients 6-14 years of age:* one SINGULAIR PAEDIATRIC 5 mg chewable tablet daily at bedtime. If taken with food, SINGULAIR PAEDIATRIC 5 mg should be taken either one hour before, or two hours after food. There are no data on safety and efficacy in children less than six years of age. Patients should continue taking 'Singulair' even when asthma is under control as well as during periods of worsening asthma. *Therapy with 'Singulair' in relation to other treatments for asthma:* 'Singulair' can be added to a patient's existing treatment regimen. *β_2-agonist therapy:* 'Singulair' can be added to the treatment regimen of patients who are not adequately controlled on 'as needed' short-acting β_2-agonist. When a clinical response is evident (usually after the first dose), the patient may be able to decrease the use of this short-acting β_2-agonist. *Inhaled corticosteroids:* 'Singulair' can be used as add-on therapy when inhaled corticosteroids provide inadequate clinical control. 'Singulair' should not be substituted for inhaled corticosteroids.

CONTRA-INDICATIONS

Hypersensitivity.

PRECAUTIONS

'Singulair' should never be used to treat acute asthma attacks. Patients should be advised to have appropriate rescue medication available. If an attack occurs, a short-acting inhaled β_2-agonist should be used. 'Singulair' should not be substituted for inhaled or oral corticosteroids. The possibility that leukotriene receptor antagonists may be associated with the emergence of Churg-Strauss syndrome cannot be excluded. However, there is no evidence that this syndrome is associated with 'Singulair'. Patients with aspirin-sensitive asthma must continue to avoid taking aspirin and other non-steroidal anti-inflammatory drugs. Experience in the paediatric population is limited. SINGULAIR PAEDIATRIC 5 mg chewable tablets contain aspartame which is a source of phenylalanine (0.842 mg phenylalanine per 5 mg chewable tablet). *Use in pregnancy and lactation:* Do not use during pregnancy or in nursing mothers unless it is considered to be essential.

SIDE EFFECTS

'Singulair' has been generally well tolerated. Side effects, which usually were mild, generally did not require discontinuation of therapy. *SINGULAIR 10 mg tablets:* In two similarly designed trials, only abdominal pain and headache were reported as drug-related in ≥1% of patients treated with SINGULAIR 10 mg and at a greater incidence than in patients treated with placebo. The incidences of these events were not significantly different in the two treatment groups. Although a causal relationship with montelukast was not established, the following adverse events were reported in ≥1% of patients and at an incidence greater than in placebo in clinical trials: asthenia/fatigue, fever, abdominal pain, trauma, diarrhoea, dyspepsia, infectious gastroenteritis, dental pain, dizziness, headache, insomnia, nasal congestion, cough, influenza, rash. *SINGULAIR PAEDIATRIC 5 mg chewable tablets:* SINGULAIR PAEDIATRIC 5 mg chewable tablets have also been evaluated in approximately 320 paediatric patients 6 to 14 years of age. Long-term experience (more than one year) was limited to 121 patients. In an eight-week, placebo-controlled clinical trial, only headache was reported as drug related in ≥1% of patients treated with SINGULAIR PAEDIATRIC 5 mg and at a greater incidence than in patients treated with placebo. The incidence was not significantly different in the two treatment groups. Although a causal relationship with montelukast was not established, the following adverse events were reported in ≥3% of paediatric patients and at an incidence greater than in placebo in clinical trials: fever, diarrhoea, nausea, influenza pharyngitis, sinusitis. With prolonged treatment in clinical trials with limited number of patients for up to six months, the adverse experienc. profile did not change.

PACKAGE QUANTITIES AND BASIC NHS COST

SINGULAIR PAEDIATRIC 5 mg: £25.69 for 28 tablets.
SINGULAIR 10 mg: £25.69 for 28 tablets.

Product Licence Numbers:

SINGULAIR PAEDIATRIC 5 mg chewable tablet: PL 0025/0357
SINGULAIR 10 mg film-coated tablet: PL 0025/0358

Product Licence Holder:

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU

POM Date of review: April 1998

Reference:

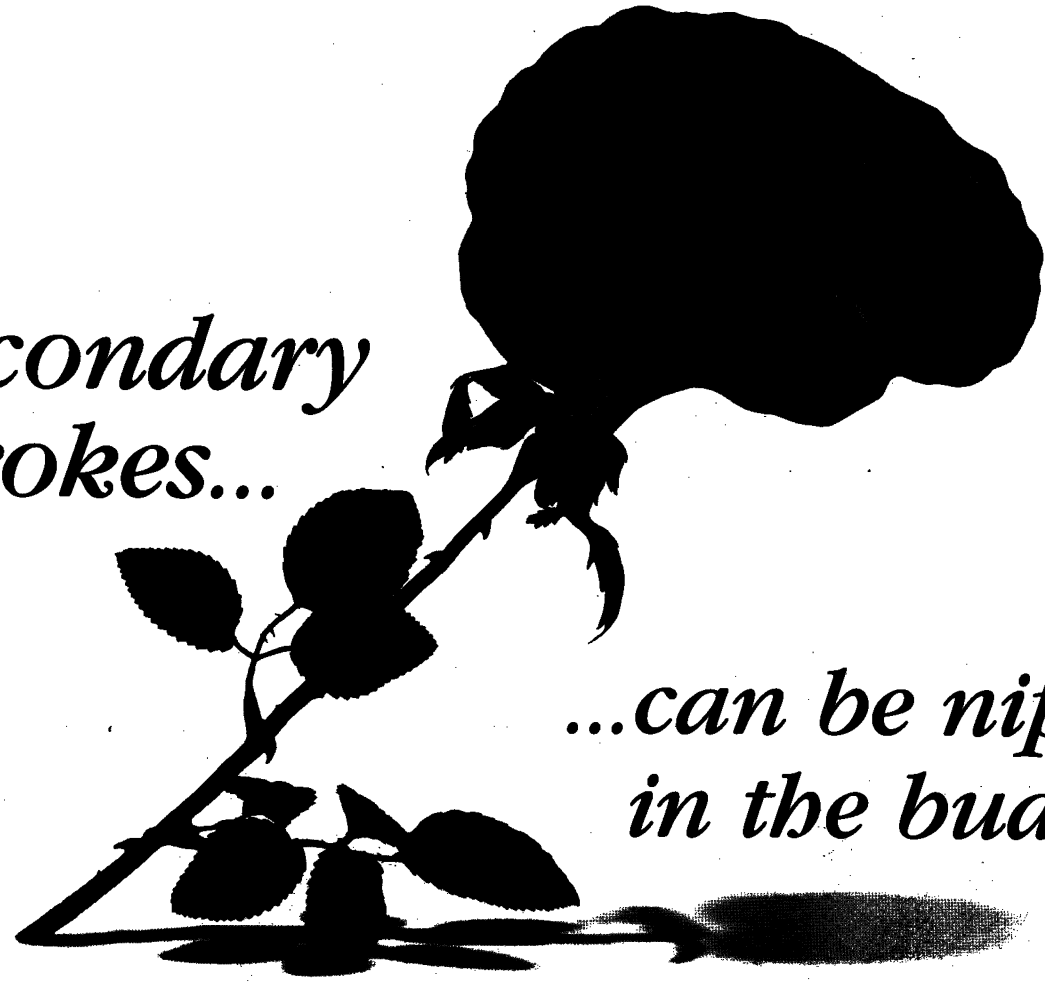
1. Data on file, Merck Sharp & Dohme Limited.

MSD

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU

04-99 SGA.97.GB.13017.J.

Secondary Strokes...



...can be nipped in the bud

Having suffered a first stroke, patients are 15 times more likely to suffer a second within 12 months than someone of similar age and gender who has not had a previous stroke.[1]

You can improve the outlook. When combined with aspirin Persantin Retard doubles the benefit of aspirin alone, giving an impressive 37% reduction in risk compared to placebo.[2]

Stroke is the most common cause of long term disability in society.

Persantin Retard offers an additional chance of reducing the burden of stroke.

PERSANTIN RETARD 200

dipyridamole modified release 200mg

alone or in combination with aspirin in the secondary prevention of stroke

References

1. Burn J, Dennis M, Bamford J, Sandercock P, Wade D, Warlow C. Long-Term Risk of Recurrent Stroke After a First-Ever Stroke. Stroke 1994; **25**: 333-337. 2. Diener H, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study 2. Dipyridamole and acetyl salicylic acid in the secondary prevention of stroke. J Neurol Sci 1996; **143**: 1-13.

Prescribing Information:

Persantin Retard (dipyridamole) 200mg

Modified release capsules each containing dipyridamole 200mg. **Indication:** secondary prevention of ischaemic stroke and transient ischaemic attacks either alone or in conjunction with aspirin; an adjunct to oral anticoagulation for prophylaxis of thromboembolism associated with prosthetic heart valves. **Dose:** Adults only: 1 capsule twice daily with meals. **Contraindications:** hypersensitivity to any component. **Precautions:** Severe coronary artery disease, subvalvular aortic stenosis, haemodynamic instability; coagulation disorders. **Interactions:** adenosine, hypotensive agents, cholinesterase inhibitors. There is evidence that the effects of aspirin and dipyridamole on platelet behaviour are additive. **Pregnancy and lactation:** caution. **Side effects:** Vomiting, diarrhoea, dizziness, nausea, dyspepsia, headache, myalgia, hypotension, hot flushes, tachycardia &, rarely, worsening of the symptoms of coronary heart disease; hypersensitivity (rash, urticaria); rarely, increased bleeding during or after surgery. **Pack size and NHS price:** 60 capsules £9.75. PL 0015/0206 POM. **Product licence holder:** Boehringer Ingelheim Ltd, Ellesfield Avenue, Bracknell RG12 8YS. For full prescribing information please see Summary of Product Characteristics.

Date of Preparation: February 1997.

Boehringer Ingelheim

CIPROXIN® I.V. FLEXIBAG - ABRIDGED PRESCRIBING INFORMATION (Refer to Summary of Product Charac-teristics before prescribing). **Qualitative and Quantitative Composition:** One flexible infusion bag containing the equivalent of 200mg ciprofloxacin USP in 100ml, or 400mg ciprofloxacin USP in 200ml. **Pharmaceutical Form:** Solution for intravenous infusion. **Therapeutic Indications:** Ciprofloxacin is indicated for the treatment of infections caused by susceptible organisms. Refer to summary of product characteristics for microbiological activity. **Posology and Method of Administration:** ***Adults*** 100-400mg administered intravenously over 30 to 60 minutes. The 400mg dose should be administered over a period of 60 minutes. Initial intravenous administration may be followed by oral treatment. *Impaired renal function* Dosage adjustment not usually required except in severe renal impairment. Reduce total daily dose by half, or adjust dose on basis of drug serum levels. *Elderly and hepatic impairment* No dose adjustment. *Adolescents and children* Not recommended. However, where potential benefit outweighs the risk, a dose of 5-10mg/kg/day in two divided doses should be used. **Duration of Treatment:** For acute infections, the usual treatment period is 5 to 7 days. Generally, in acute and chronic infections where sensitivity is proven, treatment should be continued for at least 3 days after the signs and symptoms of infection have disappeared. **Contra-Indications:** Hypersensitivity to ciprofloxacin or other quinolones; also in children and growing adolescents except where the benefits of treatment outweigh the risks. **Special Warnings and Precautions for Use:** Use with caution in epileptics and patients with a history of CNS disorders. Crystalluria has been reported so patients should be well hydrated and excessive urine alkalinity avoided. As haemolytic reactions with ciprofloxacin are possible in patients with a family history of, and actual defects in, glucose-6-phosphate dehydrogenase activity, use with caution. Tendon inflammation and rupture may occur particularly in older patients and in those treated concurrently with corticosteroids. If seen, advise patient to discontinue Ciproxin and rest limb(s). **Interactions with other Medicaments and other Forms of Interaction:** Increased plasma levels of theophylline have been observed following concurrent administration with ciprofloxacin. The dose of theophylline should be reduced and plasma levels of theophylline monitored. Where monitoring of plasma levels is not possible, avoid the use of ciprofloxacin in patients receiving theophylline. Particular caution is advised in those patients with convulsive disorders. Interactions have also been noted with anticoagulants and cyclosporin. High doses of quinolones have shown an interaction with NSAIDs in animals leading to convulsions. Administration of quinolones and glibenclamide simultaneously can potentiate the effect of glibenclamide, resulting in hypoglycaemia. Concomitant use with probenecid reduces the renal clearance of ciprofloxacin, so increasing serum levels. **Pregnancy and Lactation:** Not recommended. **Effects on Ability to Drive and use Machines:** Ciprofloxacin could result in impairment of the patient's ability to drive or operate machinery, particularly in conjunction with alcohol. **Undesirable Effects:** Local irritation at site of injection. Gastro-intestinal, CNS, hypersensitivity/skin reactions, musculoskeletal and special sense disturbances. Renal and hepatic disturbances. Effects on haematological parameters. Also reported: tachycardia. **Overdose:** Reversible renal toxicity has occurred. Monitor renal function and acidify if required to prevent crystalluria. Keep patients well hydrated. Reduce serum levels by dialysis. **Legal Category:** POM. **Package Quantities and Basic NHS Costs:** Flexible PVC bags, containing 100ml or 200ml of solution in packs of 10. 100ml £208.50, 200ml £304.50. Marketing Authorisation Number: PL 0010/0220. **Date of Preparation:** March 1997. Further information available from: Bayer plc, Pharmaceutical Division, Bayer House, Strawberry Hill, Newbury, Berkshire RG14 1JA. Telephone: (01635) 563000.

Bayer

If only everything was as reliable as Ciproxin

Flexibag IV 400mg

Ciproxin®

ciprofloxacin

10 years of rapid & reliable recovery

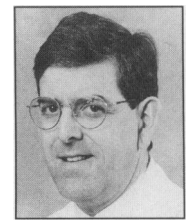
The Ulster Medical Journal, Volume 67, Supplement 1, June 1998

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)

Foreword



Julian R Johnston MD, FFARCSI

Chairman, Bicentenary Scientific Meeting Committee.
Royal Victoria Hospital

This special supplement of the Ulster Medical Journal is a record of the **Royal Victoria Hospital Bicentenary Scientific Meeting** held in the Waterfront Hall, Belfast from the 25th - 26th September 1997. More than 2 years in planning, it was one of a series of events celebrating the establishment of the first independent hospital in Belfast on the 27th April 1797.

A meeting of firsts, it was the first medical conference in the 2000 seat auditorium of the prestigious Laganside Conference and Concert Hall. It incorporated the first teleconference from the Waterfront Hall to the Royal site allowing hospital staff to watch proceedings whilst still on duty. With over nine hundred delegates attending over the two day period, it was the largest medical conference of its kind to date and was also the means for introducing the Royal to the World Wide Web and vice versa.

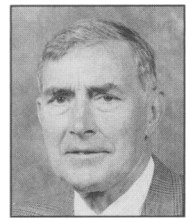
The theme for the meeting was to review historical items from the past 200 years in the Royal and then focus on medical advances by **"Looking *FORWARD* to the Year 2000"**, paying particular attention to covering topics that highlighted the multidisciplinary nature of current hospital life. Keynote speakers featured experts from current Royal Victoria Hospital medical, nursing and other healthcare staff and distinguished speakers from abroad, many who were expatriate. Session chairmen were drawn from the senior medical, nursing and management staff of the Hospital as well as from representatives of Queen's University of Belfast.

Delegates came from around the world and again reflected a wide cross section of healthcare professionals. Many resident medical houseofficers returned as did many medical year reunions. It was a tribute to both the organizers and delegates that, at a time of great political activity within the Province, there was such a good attendance.

The organization of such a unique meeting was only possible through teamwork and its success owed much to the multidisciplinary nature of the Scientific Committee. I have to thank them for their knowledge, selfless dedication and tireless effort. They put together an exciting exhibition, a full social programme and all the facets that make such events educational and enjoyable. Special mention must be made of the exhibition which was dominated by the "Royal Hospitals Timeline"- a collage of words and pictures tracing the origins of the RVH and correlating them with events in Belfast, Ireland, the United Kingdom and the Rest of the World - organized by Dr. Barry Kelly.

I also extend my thanks to Professor John Bridges, Chairman of the Bicentenary Committee for his support and guidance. Support in generous measure was also given by the two Chairmen of the Medical Staff Committee during the year - Mr. Roy Gibson and Dr. Elizabeth Mayne.

Also recorded in this archive is a lecture which marked the special relationship between the Royal and Queen's University of Belfast, given by Sir Peter Froggatt in the New Physics Lecture Theatre, Queen's University of Belfast on the 5th November 1997.



Professor John Bridges
Chairman of the Bicentenary Committee

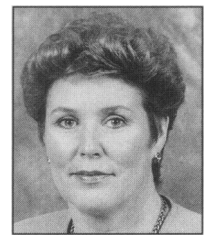
Mr Roy Gibson
Chairman of RVH Medical Staff Committee

Dr Barry Kelly
Consultant Radiologist

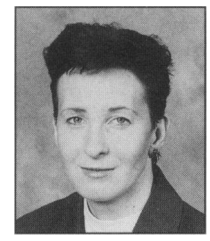
SCIENTIFIC MEETING COMMITTEE

Dr Julian R Johnston (Chair) - Consultant Anaesthetist
Mrs Mary Graham - Bicentenary Coordinator
Miss Tracey Nicholl - Bicentenary Secretary

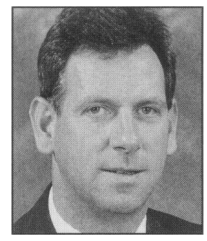
Mr John Barr - Consultant Orthopaedic Surgeon
Dr Patrick M Bell - Consultant Physician
Mr Gerry Carson - Director of Corporate Affairs
Professor Richard SJ Clarke - Emeritus Professor of Anaesthetics
Miss Rita Fox - Superintendent Physiotherapist
Miss Barbara Hunter - Professional Development Manager
Dr Barry Kelly - Consultant Radiologist
Dr Michael McBride - Consultant in Genitourinary Medicine
Mr Jim Sharkey - Consultant Ophthalmic Surgeon
Dr Ed TM Smyth - Consultant Microbiologist
Dr Carol M Wilson - Consultant Cardiologist



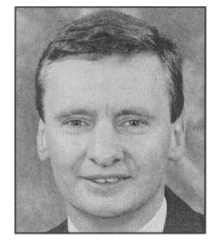
Mary Graham



Tracey Nicholl



John Barr

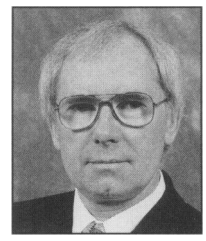


Patrick Bell

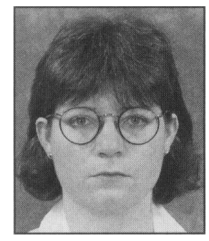
SPONSORS

Enthusiastic support was given by our main sponsors who provided much needed financial assistance.

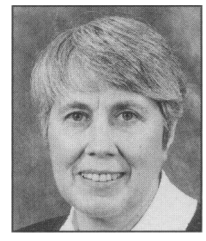
Baxter Healthcare
Boehringer Ingelheim
British Telecom
Cardiac Services
GlaxoWellcome
Hewlett Packard
Keymed
Rhone-Poulenc Rorer
Zeneca
Ethicon Endosurgery
Ethicon Sutures Ltd



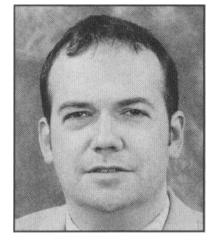
Gerry Carson



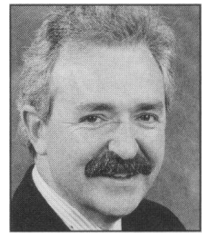
Rita Fox



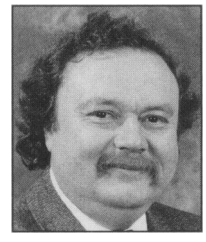
Barbara Hunter



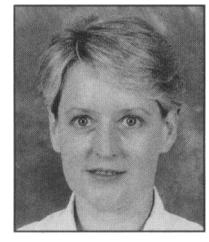
Michael McBride



Jim Sharkey



Ed Smyth



Carol Wilson

The Ulster Medical Journal

VOLUME 67

PUBLISHED BY
THE ULSTER MEDICAL SOCIETY
1998

CONTENTS

THE MULTIDISCIPLINARY HEAD

CHAIRPERSONS - INGRID V ALLEN / DERMOT P BYRNES

DRUGS, MONEY & ETHICS

CHAIRPERSONS - ROBIN G SHANKS / W NORMAN BENNETT

SURGERY IN THE NEXT MILLENNIUM

CHAIRPERSONS - BRIAN J ROWLANDS / JP HOWARD FEE

THE HOSPITAL IN THE YEAR 2000

CHAIRPERSONS - AH GARY LOVE / HUGH MCCAUGHEY

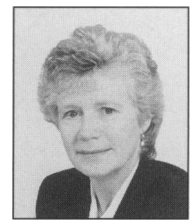
MEDICINE IN THE YEAR 2000

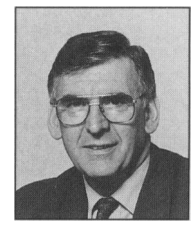
CHAIRPERSONS - IAN W CARSON / DEIRDRE O'BRIEN

SPECIAL LECTURE

THE QUEEN'S UNIVERSITY OF BELFAST

Opening Ceremony





Dr. Henrietta Campbell MB, FFPHM, FRCP
Chief Medical Officer

Tony Worthington M.P.
Minister of Health

Dr. Henrietta Campbell

Welcome to this Scientific Meeting, celebrating the Bicentenary of the Royal Victoria Hospital. The Royal Victoria Hospital may have had humble beginnings, but it now stands as one of the important landmarks of our city, held in the highest regard by the whole community as an oasis of care, compassion and feeling. All through the years of economic recession and indeed more recently, during the worst of the troubles the Royal has remained as a strong and secure presence in our physical and emotional landscape. The health service in Northern Ireland is indebted to the Royal for its leadership and skills and many of the professionals here today, including myself, owe it much.

This morning it is my responsibility to introduce the Minister for Health & Social Services, Mr. Tony Worthington.

Tony Worthington M.P.

Distinguished guests, ladies and gentlemen I am absolutely delighted to be with you to formally open this prestigious meeting which is such an integral part of the Royal's Bicentenary celebrations. The Royal Hospitals have a well earned international reputation for innovation, for research and for teaching and it owes much of its distinguished record to the work of the Royal Victoria Hospital, the senior of its four hospitals, which together form the Royal Group of Hospitals Trust. Advances in coronary care, anesthesia, intensive care and neurosurgery and for the treatment of patients suffering major trauma has kept the hospital at the forefront of treating the casualties of over 25 years of political and civil unrest.

It is no exaggeration to say that the story of the Royal Victoria Hospital is known world-wide. So this year marking the Bicentenary of the Royal Victoria has featured a fascinating range of celebratory events starting with a gala ball and Ophthalmology conference in January.

But since then people from all backgrounds and disciplines have come together at different events to mark the unique contribution which the Royal Victoria has made to the health service, to the people of Northern Ireland for the past 200 years and Dr. Campbell referred to the fact that I have only been in this job for a few months but it takes about one day to be told about the contribution the Royal Victoria has made and the huge affection and support which it has. The events have included functions as diverse as an interdenominational service of thanksgiving in St. Anne's Cathedral, a race meeting at Down Royal Race Course, fun day for children and international fashion show here at the Waterfront Hall.

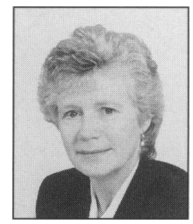
There is the new book by Professor Richard Clarke I am pleased to see tracing the history of the Royal Victoria Hospital has been published and it makes a superb memento of this year.

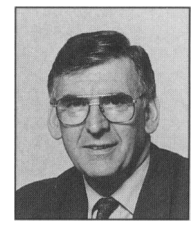
This scientific meeting however can fittingly be regarded as the climax of the year of celebration although it is of course by no means the final event. I think it is a very fitting occasion because by definition a scientific meeting is targeting the future.

The scientific programme with its theme of looking forward to the year 2000 starts by reviewing the last 200 years of and takes a considered view of the year 2000 and beyond, bringing speakers of international distinction, so my congratulations to Professor John Bridges, Chairman of the Bicentenary Celebratory Committee and to Dr. Julian Johnston, the main organizer of this meeting, for all their efforts in making the celebrations so successful. But I am pleased as well to see that there are some superb social activities running in conjunction with the business activities for the next few days.

Northern Ireland and the city of Belfast have a great deal to offer visitors and I would warmly encourage people go out and about and enjoy the hospitality and see the scenery. I am of course particularly pleased to see that scientific topics seem to cover a fascinating range of subjects and that all disciplines are reflected in one way or another, if I could attend only one of your sessions it would be the one, "Lies, damned lies and cost effectiveness."

Opening Ceremony





Dr. Henrietta Campbell MB, FFPHM, FRCP
Chief Medical Officer

Tony Worthington M.P.
Minister of Health

Dr. Henrietta Campbell

Welcome to this Scientific Meeting, celebrating the Bicentenary of the Royal Victoria Hospital. The Royal Victoria Hospital may have had humble beginnings, but it now stands as one of the important landmarks of our city, held in the highest regard by the whole community as an oasis of care, compassion and feeling. All through the years of economic recession and indeed more recently, during the worst of the troubles the Royal has remained as a strong and secure presence in our physical and emotional landscape. The health service in Northern Ireland is indebted to the Royal for its leadership and skills and many of the professionals here today, including myself, owe it much.

This morning it is my responsibility to introduce the Minister for Health & Social Services, Mr. Tony Worthington.

Tony Worthington M.P.

Distinguished guests, ladies and gentlemen I am absolutely delighted to be with you to formally open this prestigious meeting which is such an integral part of the Royal's Bicentenary celebrations. The Royal Hospitals have a well earned international reputation for innovation, for research and for teaching and it owes much of its distinguished record to the work of the Royal Victoria Hospital, the senior of its four hospitals, which together form the Royal Group of Hospitals Trust. Advances in coronary care, anesthesia, intensive care and neurosurgery and for the treatment of patients suffering major trauma has kept the hospital at the forefront of treating the casualties of over 25 years of political and civil unrest.

It is no exaggeration to say that the story of the Royal Victoria Hospital is known world-wide. So this year marking the Bicentenary of the Royal Victoria has featured a fascinating range of celebratory events starting with a gala ball and Ophthalmology conference in January.

But since then people from all backgrounds and disciplines have come together at different events to mark the unique contribution which the Royal Victoria has made to the health service, to the people of Northern Ireland for the past 200 years and Dr. Campbell referred to the fact that I have only been in this job for a few months but it takes about one day to be told about the contribution the Royal Victoria has made and the huge affection and support which it has. The events have included functions as diverse as an interdenominational service of thanksgiving in St. Anne's Cathedral, a race meeting at Down Royal Race Course, fun day for children and international fashion show here at the Waterfront Hall.

There is the new book by Professor Richard Clarke I am pleased to see tracing the history of the Royal Victoria Hospital has been published and it makes a superb memento of this year.

This scientific meeting however can fittingly be regarded as the climax of the year of celebration although it is of course by no means the final event. I think it is a very fitting occasion because by definition a scientific meeting is targeting the future.

The scientific programme with its theme of looking forward to the year 2000 starts by reviewing the last 200 years of and takes a considered view of the year 2000 and beyond, bringing speakers of international distinction, so my congratulations to Professor John Bridges, Chairman of the Bicentenary Celebratory Committee and to Dr. Julian Johnston, the main organizer of this meeting, for all their efforts in making the celebrations so successful. But I am pleased as well to see that there are some superb social activities running in conjunction with the business activities for the next few days.

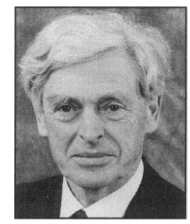
Northern Ireland and the city of Belfast have a great deal to offer visitors and I would warmly encourage people go out and about and enjoy the hospitality and see the scenery. I am of course particularly pleased to see that scientific topics seem to cover a fascinating range of subjects and that all disciplines are reflected in one way or another, if I could attend only one of your sessions it would be the one, "Lies, damned lies and cost effectiveness."

There is however, a serious angle to this. The new Labour government is firmly committed to enhancing the quality and level of care provided to the population of Northern Ireland by the health service as you know we are intent on removing the internal market and its wasteful concentration on bureaucracy. We are determined also to ensure equity of access to treatment and care and have announced some initial steps on this but before too long I would hope to set out my proposals for the future shape of the health service in Northern Ireland in parallel with ministerial colleagues in Great Britain. These will be able to establish the necessary framework to ensure that the efforts of the health service are directed and delivery of strategic objective for improving the health and social well-being of the population. To see that the needs of patients and clients are paramount. That we secure the necessary money for input but equally ensure that no more resources than are necessary are devoted to management and administration.

In all of this I will want to ensure that the interests of the tax payer are protected. This involves great care in the use of the significant resources (£4.6 billion spent on health in Northern Ireland) but it also carries the objective to explore new paths of treatment and care and perhaps leave behind some which served us in the past. To find new ways of working and crucially to ensure the collective input in terms of skills and experience of professional disciplines produces a synergy which provides added benefit to those at risk or vulnerable in our society. Perhaps above all it ties in with a meeting I have later this morning where I will be putting my energies to preserving and stimulating health rather than just curing sickness. The key to this is research and the advancement of knowledge and across the NHS there is increasing emphasis on research and development, we in Northern Ireland are following suit with a creation of local research and development office headed by Professor Ingrid Allen.

But what this meeting is testimony to is the commitment of the Royal Victoria Hospital and its clinical skills over the years to broadly acknowledge and pushing back the frontiers. It is important indeed essential that this culture surrounding the Royal Victoria Hospital continues and flourishes for unless we continue to move forward in terms of knowledge and application of new technology we will be simply unable to keep pace with the demographic and social pressures that are upon us. So the government will do its best to maximize the resources available to the health service both nationally and in Northern Ireland and we will look to you increasingly to find new and better ways of harmonizing these to the benefit of those whom we serve.

From Factory Row to the Grosvenor Road



Richard SJ Clarke MD, PhD, FRCA
Emeritus Professor of Anaesthetics, QUB
Honorary Archivist
Royal Victoria Hospital

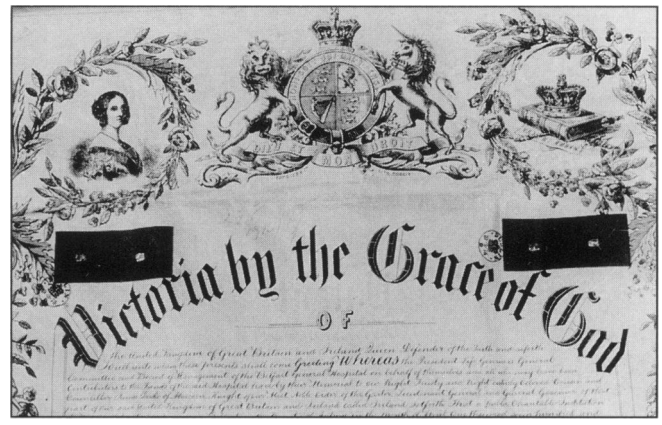
Belfast in 1780 was a town of 13,000 people but it was already expanding rapidly. There was a small middle class often inter-related and certainly knowing each other well and a large working class. Many of the latter had come in from rural areas in search of work and had very poor living conditions indeed. The better off could afford nursing at home when ill but the sick poor could hope for little care until the Poor House was opened in 1774. It could only look after the destitute who became sick but the general population still needed both outpatient attention and inpatient nursing. As a result some of Belfast's philanthropists in 1792 met and decided to open a dispensary and on 27 April 1797 a house was taken as a hospital, in Factory Row (the present Berry Street).

This early hospital had only six beds and patients were cared for by one nurse, while the leading physicians of the town, notably Dr James McDonnell, provided medical attention as required. Dr McDonnell was one of the MacDonnells of the Glens of Antrim and although practising as a private physician in the town and having political involvement in the 1798 era, he devoted his working life to the hospital.

Engraving of the Belfast Fever Hospital as it was built in 1817 (without side wings)

We can trace the hospital in direct line from this house in Factory Row, through its successor in West Street (on the other side of Smithfield Market) to the distinguished Georgian building in Frederick Street opened in 1817. It consisted of three floors of wards, plus a basement and resident doctors and nurses all slept on the premises. Temporary wards could be opened in the space behind the hospital. The same Committee of Management and the same medical-staff looked after the growing numbers of patients during the various moves. The initial need was for a fever hospital and it was typhus, trench fever and relapsing fever as well as epidemics of cholera that swamped it in waves during the first half of the eighteenth century. Between the epidemics it was possible to admit general medical and surgical patients to the wards but fever had to take precedence both for reasons of isolation of infection and the definite chance of recovery with good medical and nursing care.

One of the leaders of this era was Dr Andrew Malcolm, who was not only a truly caring physician with an interest in the living conditions of the poor, but was the hospital's first historian. His *History of the General Hospital, Belfast*, published in 1851, is a fund of information on all the medical institutions of Belfast in the first half of the nineteenth century and contains a wealth of biographical detail obtainable nowhere else. Although the original history is almost unobtainable, it was reprinted with background information on Malcolm and his times by Dr H G Calwell in 1977.

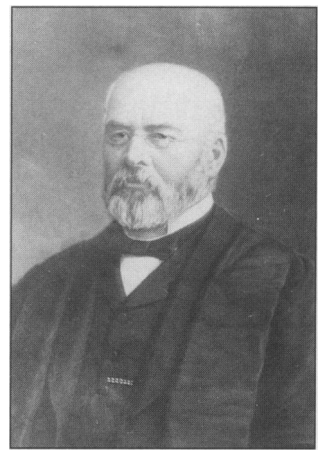


Beginning of the first Charter of the Belfast Royal Hospital dating from 1875

The early eighteen forties (even before the Great Famine) saw a realisation that still more care for the sick and destitute was needed and the Belfast Workhouse, Union Infirmary and Union Fever Hospital were all opened on the site where the Belfast City Hospital now stands. These had a different constitution from voluntary hospitals like that in Frederick Street and really had to take in all who appeared at the doors. The Fever Hospital was able to concentrate on general medicine and surgery and changed its name in 1847 to the General Hospital. At the same time extensions were built on either side of the main block, one of which contained a theatre, which doubled as operating theatre and lecture theatre.

The advent of anaesthesia (which reached Ireland in 1847) also meant that surgery could develop steadily, though fewer than 100 operations were performed annually until after 1857. During the 19th century the main anaesthetic used was chloroform given largely by the open - drop technique and always by the casual medical staff available at the time.

Further ward extensions were opened in the eighteen sixties funded by the great linen families of Mulholland and Charters and in 1875 the hospital obtained a Royal Charter as the Belfast Royal Hospital. This period also saw the physicians and surgeons obtaining a much broader education in Europe and beyond and contributing more formally to the education of medical students. Pupils were admitted to the hospital on an apprenticeship basis from 1820 and there were at least some lectures from the time of Dr James McDonnell who gave the first clinical lecture in 1827. This is regarded as the forerunner of the annual winter oration, although this did not become regular until the 1880's. There had been a medical school at "Inst" since 1835 but the new Queen's College took over medical education in 1849 and established definitive and continuing chairs in the major branches of medicine. The professors were in private practice like other doctors, but most of them were distinguished and are well worth remembering to this day. There were Professor John Creery Ferguson, first Professor of Medicine and inventor of the foetal stethoscope and his successor Professor James Cuming, a tireless worker for the building of the present Royal Victoria Hospital. Perhaps the most distinguished in the last century was Sir William Whitla, Professor of Materia Medica, and the proceeds from his text book of *Materia Medica* and his *Dictionary of Treatment* helped to fund generous benefactions to the Royal Victoria Hospital, Ulster Medical Society, Queen's University and Methodist College.



Professor James Cuming, second Professor of Medicine at the Queen's College, Belfast, who worked hard on the planning of the present Royal Victoria Hospital but died in 1899 before it was completed

The attending surgeons were particularly colourful and restless for Joseph Nelson had left in his student days (1860) to fight with Giuseppe Garibaldi in Sicily and Italy. He returned to qualify in medicine and then went off to a tea plantation in India where he developed an interest in ophthalmology. Finally he returned to Belfast and in 1883 was appointed attending surgeon in this field. Mr William MacCormac, son of Inst's Professor of Medicine Henry MacCormac, went off in 1870 to provide help with the Red Cross in the Franco-Prussian war. He had already eloped with the daughter of the wealthy benefactor John Charters and after the war was appointed to the staff of St Thomas's Hospital, London, and given a baronetcy.

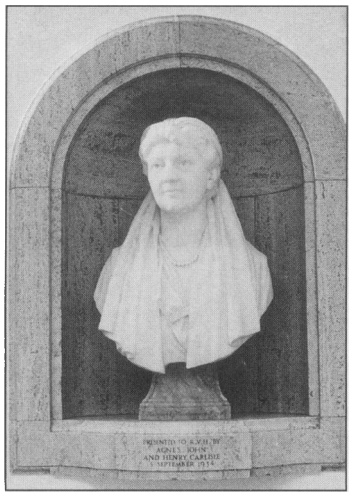
The end of the century saw the need for further expansion and the old site in Frederick Street was now inadequate. After some searching a 4-acre plot in the grounds of the Belfast Lunatic Asylum was obtained in 1898 and plans were prepared for a new building. The architect selected was William Henman who had the original idea of ventilating the entire hospital with clean, warm and humidified air, channelled along a series of ducts by huge fans. To achieve this effectively meant that the hospital should be built with parallel wards coming off a long corridor, below which was the main duct. The necessary funds were raised surprisingly quickly thanks to the Lord Mayor William Pirrie and his wife (later Lord and Lady Pirrie) and the hospital celebrated the move by a further name change to The Royal Victoria Hospital.

The new hospital, opened in 1903, had 17 corridor wards but in the inter-war years this number was first increased to 20 and the old wards were increased in length. New names appear on the staff, notably Dr William McQuitty (commemorated by a scholarship), Dr John Morrow (noted for his irritability and earthy-humour) and Professor MacIlwaine (pioneer in the electrocardiograph). New surgeons included the

eccentric Surgeon Kirk, the urologist Professor Fullerton and the orthopaedic surgeon A B Mitchell.

In the new century medical specialisation really developed. Dr John Rankin was placed in charge of the "electrical department" which included both physiotherapy and x- rays, and gradually the latter developed its own specialised staff, notably Dr Maitland Beath, and the pioneer radiographer Mr Ralph Leman. For the first time a specialist anaesthetist, Dr Victor Fielden was appointed, soon to be given "attending" status, and helped by many part-time colleagues. However, the largest expansion was in the field of pathology, started by the surgeon Dr Henry O'Neill in the 1880's, but really developing after World War I with such figures as Professor William Symmers, Sir Thomas Houston and Sir John Biggart. Clinical biochemistry was developed separately in 1922 by Dr Jack Smyth soon after the introduction of insulin for the treatment of diabetes.

For the first time the matrons emerge from obscurity and we have a series of powerful figures, Miss Bostock, Miss Duffin and Miss Elliott, who dominated the field from 1901 to 1966. Their influence was reflected in improvements in the nurses' working and living conditions. In Frederick Street, nurses had lived either in the nurses' home across the road from the hospital or in the damp basement of the hospital building itself, in case they were needed during the night. After 1903 the west wing provided better accommodation and in 1937 the new Musson House even provided hairdressing facilities and a sitting room for entertaining guests.



Bust of Margaret Montgomery Pirrie, Lady Mayoress, the major fundraiser for the new hospital and President 1915-1935

There had been funding problems from the beginning of the hospital since it relied entirely on voluntary donations. Funds came in . earlier times from prosperous merchants, church collections and house and street collections. Inevitably there were occasional crises but Honorary Treasurers like James Girdwood (1854-73) maintained strict economy with vigorous efforts to find new sources of income. Then in 1892 a new concept, the Working Men's Committee, was introduced to ensure that virtually the entire male working population of a wide area round Belfast was tapped. The work of this committee has been well documented and has raised over one million pounds during its first hundred years. In 1930 it actually raised half the hospital's annual income (approximately £26,000) and its necessity was only lessened by the arrival of the National Health Service.

Two of the most prominent figures of the hospital in the early post-war years, Sir Ian Fraser, surgeon, and Miss Florence Elliott, matron, unveiling the commemorative plaque to the Working Men's Committee in 1992

The advent of the National Health Service was received with mixed emotions but in retrospect it must be seen as giving an enormous boost to the hospital service. There could never be as much money as the doctors and patients wanted but at least new buildings, equipment and staff could be obtained without endless fund-raising activities. The expansion in staff - medical, nursing and clerical - was immediate and dramatic, the increase compared with the 1930s being made more apparent because of war- time economies. New buildings were slower to materialise and early expansion was accommodated by adding an extra floor inside the old extern hall and by moving the pharmacy into the basement under the wards. In addition, the earlier additions of this period - Quin House (1952), Metabolic Unit (1957) and the gynaecology huts (1957) were certainly not prestige buildings, so that they are now all due for demolition. Good quality buildings were delayed until 1964 for the x-ray and main operating theatre block, the EENT building opened in 1965 and the outpatient building opened in 1971.

The change in staffing was not only in numbers, but there was a radical change in the role of the senior

physicians and surgeons. In voluntary hospital days they had perhaps only "attended" the hospital for a few hours in the week and the patients often received only a casual examination, being left to the assistants and resident staff for their main care. Now consultants were paid on a sessional basis and, even if a consultant- based service was a long way in the future, the quality and expertise of medical care rose steadily after 1948.

The most striking change was the introduction of whole-time chairs in medicine, surgery, midwifery and the increasing numbers of other medical and dental professorships. Professors, freed from the need to earn their living by private practise, were able to undertake real research for the first time. Of course, they still played a large part in the hospital, both in the teaching and clinical work, but it was the new type of professor, helped by the Royal Victoria research funds, who attracted so many junior doctors into these fields. In the end many of them stayed in hospital rather than university medicine and contributed equally to the advancement of their specialty.

The National Health Service also permitted further specialisation with fields such as intensive care, cardiology and plastic surgery separating off almost completely from their parent discipline. The introduction of accident and emergency medicine virtually coincided with the opening of the new outpatient block and the beginning of the "troubles". This specialisation, together with the dedication of all the hospital staff in meeting recurrent episodes of violence, undoubtedly contributed to the hospital's reputation in the field.

The Pharmacy could be described as the oldest non-medical subdivision within the hospital for as a dispensary it actually preceded the opening of beds. In addition, there was an apothecary throughout most of the nineteenth century. However, the explosion of drug-based therapeutics in the 1950s and thereafter really forced it to expand. Physiotherapists and almoners (social workers) also pre-date the National Health Service, but the other para-medical professions can all be dated from the more generous funding of specialisation after this period.

The Bicentenary Commemoration has allowed us to assess the hospital's contribution to the life of the city and to medicine in general. At the same time we are in a phase of radical upheaval in funding, staffing and the whole provision of care to the sick, though it is too close to us to be sure of the gains and losses. We can only be confident that the building of the new hospital starting in 1998 will enable the hospital to play a major role in the new millennium.

Selected Bibliography

Allison, R S
The Seeds of Time. Belfast, Brough, Cox and Dunn, 1972

Clarke, R S J
The Royal Victoria Hospital Belfast: a history 1797-1997. Blackstaff Press, 1997.

Clarkson, L A & Litvac, M
The Working Men's Committee of the Royal Victoria Hospital, Belfast 1888-1992. Belfast 1996

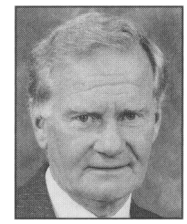
Donaldson, M
Yes, Matron. Belfast, White Row Press, 1989.

Fraser, I
Father and son, a tale of two cities, 1800-1901. Ulster Medical Journal, 1968: 37: 1-39.

Malcolm, A G
The History of the General Hospital, Belfast. Belfast, 1851. Reprinted with a biography of Dr A G Malcolm by H G Calwell as *Andrew Malcolm of Belfast 1818-1856 Physician and Historian.* Belfast, Brough, Cox and Dunn,1977.

Marshall, R
Fifty Years on the Grosvenor Road: An Account of the Rise and Progress of the Royal Victoria Hospital Belfast, during the Years 1903-1953 . Belfast W&G Baird [1953]

The Rise and Fall of the Scalpel in Peptic Ulcer Surgery



George W Johnston OBE, MCh, FRCS

Consultant Surgeon (Retd), Royal Victoria Hospital

In the bicentenary year of the Royal Victoria Hospital this review of the ulcer story will have an unashamedly Ulster bias. Although peptic ulceration was demonstrated pathologically in the 18th century the condition was rarely recognised clinically before the middle of the next century. Gastric ulceration was the commoner form at that time but by the beginning of the 20th century, duodenal ulceration had overtaken it. The incidence gradually increased until the middle of this century and was then followed by a gradual decline. It is reckoned that even now 5-10% of the population will suffer the disease at some time in their lives and 4000-5000 die annually from peptic ulcers in the British Isles as a result.

Prior to the advent of surgery the limited therapies available included bland diets, bedrest and antacids, along with many other less helpful "remedies". Although the first gastrectomy by Billroth in 1881 and the first gastroenterostomy by Wölfer the same year, were for cancer of the stomach, these operations pioneered the way for peptic ulcer surgery. Rydygier in November 1881 did the first gastrectomy for a benign ulcer with pyloric stenosis and subsequently published the report under the title "The first resection for stomach ulcer". An editor's footnote said "and I hope the last". The next few years saw the establishment of the three main operations for benign ulcers, namely gastrectomy, gastroenterostomy and pyloroplasty, all being done initially for the complications of ulceration. Vagotomy was a much later introduction. In the Belfast Royal Hospital in Frederick Street the first gastrectomy for pyloric obstruction was done by Professor Thomas Sinclair in 1886[1]. In the same hospital in 1897 Sir John Campbell and Colonel A B Mitchell both closed perforated duodenal ulcers. At a Belfast meeting of the British Medical Association in 1909 Colonel A B Mitchell read a paper from the Royal Victoria Hospital on twenty eight consecutive operations for duodenal perforations with three deaths, a remarkable achievement at that time by a remarkable surgeont[2].

The rationale for operations done at this time was mechanical and physical rather than a knowledge of aetiology or physiology. In the case of pyloric stenosis a simple gastrojejunostomy was often favoured over gastrectomy because of its simplicity and lower mortality. However about a third of the patients treated in this way developed stomal ulceration and as a consequence gastrectomy again became favoured over the ulcerogenic operation of simple gastrojejunostomy.

Swartz in 1910 coined the phrase "no acid no ulcer" but produced no experimental data to back up his dictum[3]. It was Dr James Adams, a native of Glarryford, Co Antrim, a GP practising on the Ravenhill Road in Belfast, who was the first to document evidence of the association between hyperacidity and duodenal ulceration[4]. His MD thesis of 1911 outlined acid studies over a six year period in 20 patients with duodenal ulcer. Fourteen had hyperacidity, 4 had normal acid and 2 had hypoacidity. He concluded that hyperacidity of the stomach might predispose to the formation of an ulcer. About the same time the Russian physiologist, Pavlov, reported his famous experiments demonstrating the role of the vagus nerves in gastric secretion in dogs. Latarjet, a French surgeon, described the detailed anatomy of the vagus nerves in man and in 1922 published a series of 22 patients treated by vagotomy for relief of abdominal pain[5]. However, the operations were done for a "mixed bag" of conditions and thus vagotomy in the management of peptic ulceration did not acquire respectability until the work of Dragstedt in Chicago in the early 40's[6]. Dragstedt's first vagotomy in January 1943 was on a 35 year old man with severe duodenal ulcer disease and repeated bleeding, requiring transfusion. The patient was offered gastrectomy but refused since his father and brother had had unfortunate experiences with that operation. Dragstedt then told the patient about his experimental work on dogs and a few days later the young man had a trans-thoracic vagotomy with excellent pain relief. Initially Dragstedt performed transthoracic truncal vagotomy without drainage but had to re-operate on 3 of his first 15 patients because of gastric emptying problems. Because of the "post-gastrectomy syndrome", namely problems of dumping, diarrhoea

and bile vomiting together with nutritional disturbances following gastric resection for duodenal ulceration, surgeons were happy to try the new procedure of vagotomy and gastrojejunostomy or vagotomy and pyloroplasty. However, with longer follow-up recurrent ulceration occurred in 5-15% of patients following vagotomy and drainage compared to only 2- 5% following gastrectomy.

Professor John Goligher, an Ulsterman working in Leeds, reported the results of a 5-8 year survey of 565 patients treated for duodenal ulcer, comparing sub-total gastrectomy, truncal vagotomy and antrectomy, truncal vagotomy and pyloroplasty and truncal vagotomy and gastrojejunostomy[7]. Although the trial was not randomised or followed up blindly, vagotomy and antrectomy produced the best results on Visick grading. This "belt and braces" operation, taking care of both the neural and hormonal stimulation of acid, remained popular in the USA because of a low recurrent ulceration rate of less than 2% but it carried a higher mortality than vagotomy and also gave similar post-operative problems as gastrectomy. Modifications of the vagotomy operation were introduced in the 60's. In 1957 Griffith and Harkins published their experimental data on selective vagotomy in dogs[8]. In this operation the hepatic branches to the liver and gallbladder and the coeliac branches to the gut are preserved. Initially it did not catch on but some claimed that it gave a more complete vagotomy because of the meticulous dissection required and that it also produced less diarrhoea than truncal vagotomy. In a randomised controlled double blind trial during 1966 and 1967, comparing truncal vagotomy and pyloroplasty with selective vagotomy and pyloroplasty in elective duodenal ulcer surgery the late Mr Terence Kennedy was able to confirm significantly less diarrhoea and also less recurrent ulceration (though not significant in) the latter operation[9]. However, this operation like truncal vagotomy required a drainage procedure and there were therefore still problems with dumping and bile vomiting because of the "incontinent" stomach. We then set out to compare the two drainage procedures available and in 1968 embarked on a further controlled trial comparing selective vagotomy and pyloroplasty with selective vagotomy and gastrojejunostomy[10]. Although there was no significant difference between the results in the two groups, there were more satisfied patients in the gastrojejunostomy group and less recurrent ulcers. In addition if dumping, diarrhoea or bile vomiting become a problem following a gastrojejunostomy it can be closed without difficulty, whereas pyloric reconstruction is a difficult and often unsuccessful procedure. It has been said that "if gastrojejunostomy is a disease then pyloroplasty is an incurable disease". Thus at this stage of our investigations we favoured selective vagotomy and gastrojejunostomy as the operation of choice. In 1969 Andrup of Copenhagan and Johnston of Leeds independently described highly selective vagotomy (also known as proximal gastric vagotomy) which left sufficient vagal innervation to the antral pump to allow gastric emptying without the necessity for a drainage procedure[11,12]. From 1970-1972 we did a further prospective randomised trial in the Royal Victoria Hospital, comparing selective vagotomy and gastrojejunostomy with the new operation, proximal gastric vagotomy. We found that dumping and diarrhoea were virtually eliminated by the proximal gastric vagotomy but that there was a higher risk of recurrent ulceration[13]. In 1990 we reported the results of 600 consecutive elective proximal gastric vagotomies for intractable duodenal ulceration with a mortality of 0.2%; one patient died in the post-operative period from cerebral haemorrhage[14]. During the 21 year period under review the overall recurrent ulceration rate was 11%, the majority controllable by medication. Ninety-two percent of the patients were Visick grade I or II, that is satisfied patients, which compares well with the "normal" population at large where the figure is 93%. With a view to picking out patients who were more liable to recurrent ulceration following proximal gastric vagotomy, Mr John Hood looked at the pre-operative acid studies in over 260 patients who had had vagotomy[15]. He found that there was a highly significant difference in the basal acid output in recurrence negative and recurrence positive patients. We therefore decided to embark on a further controlled trial on hypersecretors with basal acids above 10 mmol/1, comparing the results of proximal gastric vagotomy with truncal vagotomy and antrectomy in the special group. However, by this time the incidence of duodenal ulceration was on the decline and the numbers of hypersecretors were too small to finish the trial. In addition a further revolution overtook surgical management, namely the development of effective medical therapy.

The discovery of H2 receptor antagonists by Black in 1972 and the subsequent availability of cimetidine in 1976 followed by several similar drugs within a few years, made medical therapy attractive[16]. However, it soon became clear that even on maintenance therapy with these drugs, 20-25% of the patients could expect endoscopic evidence of recurrent ulceration within a year. The development of more powerful proton pump

inhibitors such as omeprazole and its successors added to the pharmacological armamentarium. Perhaps the biggest break through came in 1984 when Marshall demonstrated the ulcerogenic properties of a spiral flagellated bacteria, campylobacter pylori, later known as helicobacter pylori[17]. Ninety per cent of duodenal ulcer patients and 70% of gastric ulcer patients were shown to be infected. Modern eradication therapy with a triple drug regime such as Omeprazole 20 mgs bid, Clarithromycin 250 mgs bid and Metronidazole 400 mgs bid for a period of one week should produce ulcer healing in 90% with only a 1% per annum chance of recurrence. However, there are still problems with patient non compliance, development of drug resistance and the onset of ulcer complications especially in the elderly on NSAID therapy in a few patients. Modern techniques allow bleeding to be controlled in most instances by endoscopic injection therapy, pyloric stenosis by balloon dilatation and perforation by laparoscopic repair. However, some patients will come to open surgery and younger surgeons now have relatively little experience of the operations required. In the past 10 years, prior to retirement, I performed, on average, only one ulcer operation per month and in my last year I operated on only 3 patients with duodenal ulceration and all were for complications.

Is this the end of the ulcer story? Undoubtedly the major role played by surgery in the past has diminished and a whole new chapter is emerging. The new villian, H pylori, is becoming better characterised, and the possibility of new non-antibiotic therapy and a vaccine against H pylori are only two of the new possible therapies being written into the script. Many twists can yet be expected before this story comes to an end.

REFERENCES

1. Irwin JWS. Razors to autoclaves. *Ulster Med J* 1965; **34**: 66-73.
2. Mitchell A B. Perforative duodenal ulcer. *Br Med J* 1909; **11**: 946-948.
3. Schwartz K. Uber penetrierende magen-und jejunal geschwire. *Bruns Beitr Klin Chir* 1910; **67**: 96-128.
4. Baron JH. Duodenal ulcer, hyperacidity and J C Adams of Belfast. *Theor Surg* 1986; **1**: 113-114.
5. Latarjet A. Resection des nerfs de l'estomac technque operatoire; resultats cliniques. *Bullalad Natl Med* 1922; **87**: 681-91.
6. Dragstedt LR, Owens FM. Supradiaphragmatic section of the vague nerves in treatment of duodenal ulcer. *Proc Soc Exp Biol Med* 1943; **53**: 1524.
7. Goligher JC, Pulvertaft CN, Irvin TT, Johnston D, Walker B, Hall R A, Willson-Pepper J, and Matheson T S. Five to eight year results of truncal vagotomy and pyloroplasty for duodenal ulcer. *Br Med J* 1972; **1**: 7-13.
8. Griffith CA and Harkins HN. Partial gastric vagotomy: an experimental study. *Gastroenterology* 1957; **32**: 96-102.
9. Kennedy T, Connell AM, Love A H G, MacRae KD, Spencer EFA. Selective or truncal vagotomy? Five year results of a double-blind, randomized, controlled trial. *Brit J Surg* 1973; **60**: 944-948.
10. Kennedy T, Johnston GW, Love AHG, Connell AM, Spencer EFA. Pyloroplasty verses gastrojejunostomy - results of a double-blind randomized control trial. *Brit J Surg* 1973; **60**: 949-953.
11. Andrup BM, Griffith CA. Selective vagotomy of the parietal cell mass. *Ann Surg* 1969; **170**: 207-14
12. Johnston D, Wilkinson A. Selective vagotomy with innervated antrum without drainage procedure for duodenal ulcer. *Brit J Surg* 1969; **69**: 626-38.
13. Kennedy T, Johnston GW, MacRae KD, Spencer EFA. Proximal gastric vagotomy: interim results of a randomized controlled trial. *Brit Med J* 1975; **1**: 301 - 303.
14. Johnston GW, Spencer EFA, Wilkinson AJ and Kennedy TL. Proximal gastric vagotomy. Follow-up at 10-20 years. *Brit J Surg* 1991; **78**: 20-23.
15. Hood JM, MacRae KD, Kennedy T. The value of peri-operative gastric function tests in predicting the recurrence of duodenal ulcer after vagotomy. *Gut* 1976; **17**: 998-1000.
16. Black JW, Dumcam WAM, Durant CJ, Ganellin CR and Parsons HE. Definitions and antagonism of Histamine H2 receptors. *Nature* 1972; **236**: 385-90.
17. Marshall BJ and Warren JR. Unidentifted curved bacilli in the stomach of patients with gastritis and peptic ulceration *Lancet* 1984; **1**; 1211-4.

The Advance(s) of Cardiac Surgery and Anaesthesia

S Morrell Lyons OBE, BSc, MD, FRCA
Consultant Cardiac Anaesthetist
Royal Victoria Hospital

The introduction of anaesthesia in 1846 opened up completely new fields of endeavour for the surgeons of that day and for their successors. No longer did surgery have to equate with a "smash and grab" approach where speed was of the essence. For the first time it was possible to operate in a considered and deliberate manner with the prospect of more elaborate and reparative procedures becoming a reality.

As surgery became safer with antisepsis, intra-abdominal surgery became possible but operations inside the thorax remained a closed book. The ability to deal with the problems inherent in the creation of the necessary pneumothorax was still a long way off. Despite many attempts, regular intra-thoracic procedures had to await the recognition of the need for and eventually the advent of some form of assisted respiration or intermittent positive pressure ventilation. It was the introduction of muscle relaxants in 1942 which revolutionised how this could be accomplished.

Once the principles were understood, there were several exciting developments. In 1939 a patent ductus arteriosus was ligated, a repair of coarctation of the aorta was carried out in 1945, the Blalock Taussig shunt for palliative treatment of cyanotic congenital heart disease was introduced the same year and mitral valvotomy was successfully carried out before the end of the decade. The first ligation of a patient ductus was done in Northern Ireland by Barney Purce at the Royal Victoria Hospital in 1948, and the first mitral valvotomy was carried out by Tom Smiley also at the Royal in 1950.

All these procedures required minimal interruption of the circulation but they were nevertheless enormous advances. At that time monitoring, if used, was primitive, diathermy unavailable and pacemakers and the defibrillator were still to be invented.

This however was a beginning and as confidence increased, surgeons began to be even more adventurous. There were startling developments in anaesthesia with the introduction of less depressant and less explosive anaesthetic agents and with the gradual introduction of basic monitoring, anaesthesia was ready for the next step forward. Anything but the simplest procedures required the ability to stop the circulation for longer than 1-2 minutes. The advent of the use of moderate hypothermia to 30-32 degrees C allowed periods of circulatory arrest to be prolonged; 5-8 minutes became possible. Success depended on accurate diagnosis. This was not always possible and the risks were considerable.

There was an ever increasing demand for some form of cardiopulmonary bypass to allow time for more prolonged open heart surgery. The 1950s saw the successful culmination of many efforts and technical advances and in 1953 Gibbon and his co-workers in Philadelphia reported the first successful use of a heart lung machine to facilitate the closure of a secundum ASD in a teenage girl who has been a long term survivor. At that they reported the use of the same machine in several other cases but with no survivors. Even so, 1953 showed what was possible.

For an improvement in quality, there needed to be better diagnosis, anaesthesia, surgery, perfusion and intensive care. The rest of the 1950s saw many disasters and other methods such as cross circulation and profound hypothermia were tried but successful cardiopulmonary bypass also became more common. The defibrillator and the pacemaker arrived, monitoring improved steadily, anaesthetic agents appeared which were more suitable for the poor cardiovascular system and, with experience, better overall management was possible.

The first open heart case in the United Kingdom was done in 1958 at the Hammersmith Hospital by Bill Cleland, with the anaesthetist John Beard. Developments were swift and Birmingham reported their experience in 20 cases in 1960. By contrast and at that same time Cooley reported his experience of 450 cases in Houston, Texas.

The 1960s saw the emergence of an interesting time in the development of open heart surgery. Houston was in the forefront of demonstrating how to do large volume work and this was still their forte when I

worked there in 1967/68. At that time Denton Cooley was operating on 8 cases per day in two theatres; later expanded to 25-30 cases per day. At the same time Dwight McGoon in the Mayo Clinic was demonstrating high quality by doing a series of 100 aortic valve replacements with zero mortality. In the United Kingdom Donald Ross and Bill Cleland were establishing cardiac surgery on a firm footing.

New units for open heart surgery were starting in many places in the United Kingdom and the first such operation in Belfast was performed in the spring of 1960 by Tom Smiley, with Maurice Brown as the anaesthetist.

Most centres struggled with problems of apparatus, diagnosis, inadequate experience and lack of any real intensive care. It is fascinating that in Houston the cardiac surgeons came from a vascular surgery training in contrast to this country where the background was thoracic surgery. This probably made the introduction of coronary artery bypass surgery easier in the United States. Whatever these considerations, it became clear that Northern Ireland needed an enlargement of the available skills, a dedicated unit, dedicated personnel and an intensive care unit.

In the late 1960s the Royal and the Northern Ireland Hospital's Authority decided that this was the way forward and a new unit was established in 1968 with Pat Molloy as surgeon, Morrell Lyons as full time anaesthetist with Richard Clarke keeping everyone on the right lines. Pat Molloy had been a consultant in Broad Green, Liverpool, and Frank Pantridge had a lot to do with his enticement here.

The unit started in June 1968 and, in the last 6 months of 1968, a total of 80 operations were done, mostly open with an overall mortality of 12%, which was well within the standards of the day. In 1969 the working pattern for the next few years was established at 5 operations per week, though with a mortality rate of 17%. The work gradually increased as the team expanded with the arrival of Jack Cleland and Jim Morrison. Pat Molloy left for New Zealand in 1973 and was replaced by Hugh O'Kane who then established coronary artery bypass surgery in the province.

The work increased in fits and starts, dictated by finance and personnel rather than need until its present level of 1150 cases per annum. Today's mortality is in sharp contrast to that of 1969 with an overall mortality rate of 2.8%,

This marked improvement has been due to many changes.

1. Surgery and cardiology have vastly improved. Techniques arc better and there are better sutures, better diagnoses, better assistants, better valves, better hardware.

2. Anaesthesia has also improved. After some early disasters it was very evident that adequate preoperative assessment was essential. There are now superior techniques and the introduction of high dose narcotic anaesthesia helped markedly in the decreased myocardial oxygen demands. There has been a revolution in monitoring and much better interpretation of the data. Pulse oximetry was a quantum leap forward and the more intelligent use of inotropes allied to better managed perfusion have played their part. The high quality technical assistance makes this all function smoothly.

3. Perfusion has changed markedly. There are now more efficient and smaller oxygenators and tubing which is less damaging to the blood. The better techniques and the use of arterial filters have helped in the decrease in air emboli and in consequent cerebral damage. The management of perfusion is dependent on highly trained perfusionists and their contribution is vital.

4. Myocardial preservation has been revolutionised by the use of cardioplegia.

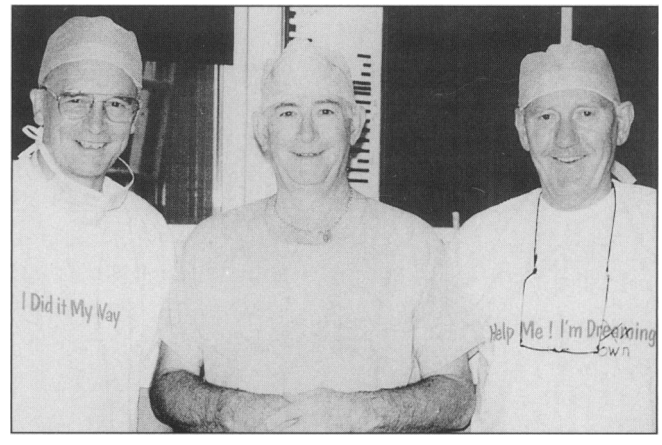


Figure 1 Dr. S Morrell Lyons (Anaesthetist), Mr J Cleland (Surgeon) and Mr E. Stewart (Perfusionist) - doing it their way

5. Intensive care nursing, good physiotherapy, data interpretation and inotropes and the balloon pump have all made major contributions to the improving scene.

6. The applied results of anaesthesia and surgical research have also played their part.

THE FUTURE.

It is always fun to speculate about the future without the responsibility for the outcome.

Valve Surgery

30 years ago it was believed that by the end of this century the need for valve surgery would be minimal. Rheumatic fever was already rare and so a further 30 years would see the disappearance of rheumatic heart disease. However the demand for valve surgery is very little different today than in 1968. Aortic stenosis in the older age groups and mitral valve repair operations secondary to disruption of the valve have come more to the fore so in the next thirty years valve surgery will be very much part of the workload

By that time there will be prostheses available, with a valve more with the characteristics of our own original valves, with better flow pattern, causing no cellular damage and doing away with the need for anticoagulants. With this available then valve replacements will be done before any myocardial or pulmonary damage has occurred and so better results will be obtained.

Coronary Artery Grafts

Will the present preventative measures eliminate the need for coronary artery bypass grafting (CABG) in the next generation? So far I see no signs. Looking at my fellow man, overweight, increasingly sedentary, still smoking, working at pressure, reluctant to take antihypertensive therapy and with no power to select their parents I do not see the need for CABG changing just yet. What will the operation be? Will there be artificial graft material instead of the internal mammary artery and saphenous vein grafts? Or indeed will the operation of choice be a total heart replacement with an allograft? Will we have changed to minimal access surgery or will the operations be by telemedicine?

Congenital Heart Disease

Congenital heart disease may change with social change. The falling birth-rate and abortion are great changes. But will genetic engineering bring change? Will intrauterine treatment have anything to offer? Or again will the allograft be the answer to the most complex problems.

Perfusion

Perfusion apparatus has become smaller and smaller and more and more efficient. Will it become implantable with an arterial assist device or artificial heart in the circulation be the answer?

Anaesthesia

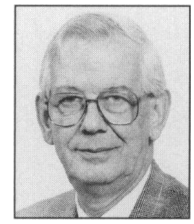
In thirty years anaesthesia will be non pharmaceutical, maybe electrical. Total pain relief without side effects will be available and operative episodes will pass without memory for unpleasantness.

Intensive Care

In intensive care the monitoring will demonstrate full data from non invasive techniques. The management loop will be closed so that the staff will be able to devote more time to the patients themselves. Myocardial preservation will eliminate the need for most inotropes and the better myocardium will decrease the stay needed in the intensive care.

Will these forecasts come true? Who will be around to see? At any rate I wish them good luck.

Imaging, past present and future



Edwin M McIlrath MB, FRCR, FFRRCSI
Consultant Radiologist
Royal Victoria Hospital

Imaging is one of the more recent medical disciplines arising out of Rontgens discovery of X-Rays in 1895. The acquisition of X-Ray equipment by the Medical Committee of the Belfast Royal Hospital in 1896 showed both foresight and a rapid decision making process that we might envy one hundred years later. The glass radiographs were taken and processed by two commercial photographic companies in the city and interpreted by the clinician. In 1903 John Rankin, having gained his MD working with John Symmington in the subject of radiographic anatomy, was appointed to the new Royal Victoria Hospital. Shortly after the first World War Maitland Beath joined the staff and Ralph Leman became the first Radiographer. It should be noted that neither Drs. Rankin or Beath had undergone any formal training. In 1925 Dr. (later Sir) Frank Montgomery was appointed assistant to Dr. Beath, having undergone six months training in Harley Street and acquired the Diploma in Medical Radiology - both Radio Diagnosis, Radio Therapy and Electrology from the University of Cambridge. This examination was later to become the DMRD of the Conjoint Board in London. The Faculty of Radiologists was formed in 1939 and housed as an autonomous Faculty by the Royal College of Surgeons in Lincoln's Inn.

The DMRD, while deemed adequate for a consultant position in the rest of the United Kingdom, was viewed less favourably in Northern Ireland, where MD or other higher qualification was mandatory. Formal training based at the Royal Victoria Hospital commenced around 1950, but local graduates had to go to United Kingdom centres for the extensive physics element of the course, and it was not until 1967 that, with the good offices of the physicists at Belvoir Park, we were able to offer our own and other graduates a fully comprehensive training course. The Fellowship of the Faculty, later the Royal College of Radiologists, had become by 1962 the mandatory qualification for a consultant position in Northern Ireland. The syllabus for the Fellowship has continued to increase since that time with the addition of nuclear medicine, ultrasound, computerised tomographic scanning, magnetic resonance imaging and interventional radiology. The impact of the computer on what was already a highly technological speciality cannot be underestimated and will in my opinion lead inevitably to totally filmless departments, the image being recorded, distributed and viewed using digital technology. This will in turn make expertise, from any major centre in the world, available to our patients

The ability to produce diagnostic information without the use of ionising radiation has major benefits to the population at large but more specifically children and those of child bearing age. The progress that has been made has generated a series of new problems. Sophisticated technology is expensive. The MRI Unit at the Royal Victoria Hospital represented an investment of £1.5 million pounds. Modern screening equipment costs in the region of £400,000 - 30 years ago this would have been approximately £20,000. Small wonder then that in recent years the funding of capital equipment has become very difficult. Public demand and indeed expectation continues to grow frequently, fuelled by irresponsible media coverage and political expediency, not just within the UK but internationally. While the Royal Victoria Hospital continues to function at high professional and economically efficient levels, this has been at the cost of severe pressures on the staff.

In the area of training, the second major function of a teaching hospital, a series of different problems have arisen. As already stated, the content of the syllabus has increased but the period of postgraduate training has diminished. European legislation has influenced medical training without proper consideration of professional requirements, or the vastly differing health care systems within the member states. Many United Kingdom radiologists would look forward to harmonisation with say France, which has 4,500 radiologists for a population similar to that of the United Kingdom, which has a total of 1,500. The Calman recommendations on the period of post graduate training raise interesting questions regarding the adequacy of experience, particularly in the subspecialty areas of paediatric, neuro and interventional radiology. For those trainees who aspire

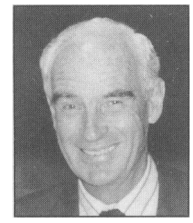
to obtain posts in the teaching hospitals, an overseas fellowship was deemed desirable, but unfortunately, due to changes in American legislation, such research appointments are becoming difficult to obtain. Continuing medical education will become absolutely vital in the future and more resource and less lip service would be welcome.

The future of medical imaging will be the subject of much review and International comparison. In Germany less than 30% of imaging is under radiological control. Japan has virtually no neuro radiologists. In America genito urinary radiology is almost totally in urological hands. In the United Kingdom almost all cardiological imaging is undertaken by cardiologists. It would be almost reflex in Northern Ireland to exhibit the "Not an Inch" syndrome, when faced by this scenario, but the Royal College of Radiologists has taken a more constructive approach. Inter collegiate discussions with obstetricians and general practitioners have formulated consensus on ultrasound. The editorial and letter columns of the College Journal have been filled with conflicting opinions about the training of gastro enterologists in ultrasound.

It is surely fundamental that endovascular surgery will have to be established on a co-operative basis between radiologists and surgeons. What is entirely clear is that 'turf battles' within the profession are not in the best interest of patients. Could it be that the wheel will turn full circle and that by the millennium clinicians will control their own imaging and that with the advent of private finance initiative the production of images will revert to the commercial sector.

To those with foresight a problem becomes a challenge and as radiologists move towards the millennium they must obtain the maximum benefits from the new technologies, not solely within the specialty as it exists now, but in the wider fields of health care. They must accept and plan to supply the requirements arising from greater public knowledge and expectation, particularly in the primary care sector. As a major diagnostic speciality they must become more involved in the education of medical nursing and paramedical trainees, particularly in the area of skill mix as it involves radiographers. They must also make certain that the medical advisory structures to management, and therefore to the politicians of the day, are as effective as possible. It is clear that the effective delivery of Health Care requires a team approach, and to use a football analogy, the squad is large, the stars are many, but without clear objectives we may resemble Middlesborough rather than Manchester United.

The Gallstone Story



R Hermon Dowling MD, FRCP

Director Gastroenterology Unit
Guy's and St Thomas's Medical and Dental School

When the organisers of the RVH Bicentenary kindly approached some expatriate "old boys", inviting us to talk at the celebratory meeting, our brief as we approached retirement was to review some aspect of our professional work. I opted to focus on gallstones and initially, was tempted to begin by reminiscing about our studies of bile lipid composition in patients with ileal disease or resection[1] and our use of the steady-state secretion perfusion technique[2,3] to measure the hour-by-hour output of biliary lipids in control subjects and gallstone patients — with particular emphasis on obesity.[4] I might also have recalled our work on gallbladder motor dysfunction in gallstone disease[5] or our early studies in the use of chenodeoxycholic[6-8] and ursodeoxycholic acids[9-11] as oral treatment for the dissolution of gallstones in symptomatic patients.

In their day, each of these chapters held its own fascination and the research fellows who worked on these projects made valuable contributions to the literature. But rather than wallow in nostalgia, I have chosen to review, briefly, the results of exciting recent studies, performed by my colleagues at Guy's, over the past five years. They began with a collaborative study of acromegalic patients treated with octreotide who develop iatrogenic gallstones[12] - a phenomenon well known at the RVH since one of the first observations on this topic was made by McKnight and colleagues from the Metabolic Unit of the RVH.[13]

We are now close to making the "outrageous assertion" that cholesterol cholelithiasis is an intestinal disease,[14] secondary to changes in large bowel transit.[15] This chapter reviews the evidence behind this assertion and, in keeping with the theme of the meeting, the chapter ends with a discussion of strategies for preventing gallstone formation, in the next millennium.

Clinical Science of Gallstone Formation

The types and composition of gallbladder stones (GBS) are discussed briefly before the classical theory of cholesterol (CH) GBS formation is reviewed. This suggests that, before stones can form, at least three abnormalities (the so-called triple defect)[16] must co-exist: (i) supersaturated GB bile, (ii) abnormal nucleation of CH microcrystals and (iii) stasis due to impaired GB emptying and/or crystal trapping by mucus on the surface of the GB mucosa. However, most of this presentation is based on a modern-day detective story (still evolving) which describes why GBS develop in many acromegalic patients treated with the somatostatin analogue, octreotide (OT).

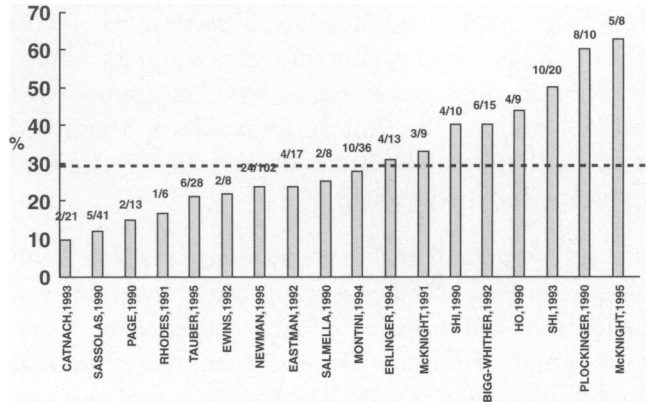


Fig 1 Reported incidence of gallbladder stones (GBS) in acromegalic patients treated with octreotide (OT) in doses ranging from 100-1500 ug /day for periods ranging from 3-70 mo. (Most patients received 100-200 µg tds by sub-cutaneous injection, for approximately 1-2 yr). Since at the start of OT treatment these patients were free of GBS by ultrasound, the results of these 18 studies represent the frequency of OT-induced (rather than OT-associated) GBS. The vertical bars represent the percentage of patients developing cholelithiasis: the numbers at the top of the columns refer to the numbers of patients developing stones, over the numbers of patients treated. The broken horizontal line represents the mean incidence of OT-induced stones (29%) in these 18 studies.

OT is an effective treatment for acromegaly. It acts by suppressing growth hormone and insulin like growth factor-I levels but it also inhibits meal-stimulated cholecystokinin release and GB contraction. We confirmed that OT virtually paralyses the gallbladder[17] but, given the triple defect theory of GBS formation,[16] the first step was to see if OT also affected bile composition and physical chemistry.

Step 1

Studies of fresh GB bile from acromegalic patients with OT-GBS[18] showed that they all have: (i) supersaturated bile, (ii) a high proportion of their biliary CH present in unstable vesicles, and (iii) abnormally rapid nucleation (precipitation) of CH microcrystals. These changes were associated with, and may well be due to, excess biliary deoxycholic acid (DCA % of total bile acids).[18] The hydrophobic DCA is the "bad boy" of bile. (Fig. 2) When present in

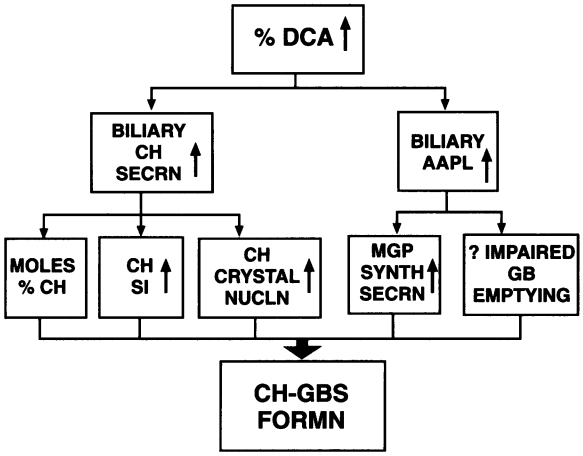


Fig 2 Schematic flow diagram to explain how an increase in the percentage of deoxycholic acid (%DCA) in bile might lead to an increased incidence of cholesterol gallbladder stones (CHGBS). Thus, enrichment of bile with DCA leads to a relative increase in biliary cholesterol secretion (secrn).[19] This may explain why we,[20] and others [33, 34] find that there is a significant linear relationship between the %DCA in bile and: (I) the molar percentage (moles %) cholesterol and (II) the cholesterol saturation index (SI), in gallbladder bile. It may also explain, at least in part, why we find that the mean %DCA in bile is approximately twice as high in patients with abnormally rapid (< 5d) nucleation or precipitation of cholesterol microcrystals, as in individuals with normal (> 10 d) nucleation times[20].

We[35] and others[36-39] also showed that the %DCA in bile was linearly related to the % arachidonic acid-rich phospholipids (AAPL) in bile. In turn, this may explain[40] why mucus glycoprotein (MGP) synthesis by, and secretion into, the gallbladder are increased in gallstone patients[41-43]. An increase in the proportion of AAPLs in GB bile could also contribute to the reduced meal-stimulated gallbladder emptying[5, 44-46] which characterises cholesterol gallstone disease.

excess, DCA induces biliary cholesterol hypersecretion and supersaturation.[19,20] Our results suggest that the increased biliary DCA seen in OT-treated acromegalics is due to the somatostatin analogue treatment, and not to the stones. Thus paired, before-and-during treatment, studies showed that within weeks, OT doubled the percent DCA in bile and induced biliary CH supersaturation - even in the absence of stones.[18]

Step 2

The next step was to determine why OT treatment doubles the % DCA in bile. Previous studies in control subjects had suggested that OT prolongs small bowel transit.[21-23] But would it do the same thing in acromegalics? And, more important, would it also affect large bowel transit (of importance since DCA is formed in the caecum and proximal colon - rather than in the small intestine)?

We confirmed that OT markedly prolongs small bowel transit both in control subjects and in acromegalic patients.[17] We also showed, again in paired before-and-during treatment studies,[24] that OT significantly prolongs large bowel transit time (LBTT). Furthermore, we found that LBTT was linearly related to: (i) the % DCA in serum[25](and, by implication, in bile), (ii) the DCA pool size[26] and (iii) the DCA formation (or "synthesis") rate.[26]

Step 3

If prolonged intestinal transit and altered DCA metabolism play a major role in the pathogenesis of the exotic OT-induced GBS, could these factors also play a similar role in "conventional" GBS disease — that this, GBS unrelated to acromegaly or OT treatment? The results of our own,[14,27] and other,[28-30] studies suggest that they do. Indeed, as noted above, we have even suggested that cholelithiasis is a disease of prolonged large bowel transit.[14]

Step 4

The mechanism whereby prolongation of intestinal transit increases the percentage of DCA in serum and bile, raises several questions. Does prolonged LBTT increase DCA formation by increasing the number of anaerobic bacteria in the right colon? Does it affect the activity of their deconjugating and dehydroxylating enzymes (cholylglycine hydrolase and 7-alpha dehydroxylase) which produce unconjugated (newly-formed) DCA from the glycine and taurine conjugates of cholic acid? Does prolongation of LBTT affect colonic luminal pH - thereby increasing the solubilisation and bioavailability of the newly-formed DCA? Or does a longer than normal LBTT allow more time for DCA absorption from the colon (presumably by passive non-ionic diffusion)?

The answer to these rhetorical questions seems to be - yes, yes and yes.[14] By comparison with "controls", patients with conventional GBS have: (i) significantly prolonged LBTT, (ii) significantly more total anaerobes in the caecum and right colon, (iii)

significantly more gram positive anaerobes, (iv) more deconjugating ($p>0.05$) and 7 alpha-dehydroxylating ($p<0.005$) enzymes per bacterium (or more correctly, per mg protein in the caecal aspirates), (v) a significantly greater colonic luminal pH[31] (probably because the prolonged transit allows more time for absorption of the acidic short chain fatty acids) and, again, (vi) a significant increase in the %DCA in fasting serum.

Thus, there is an intriguing web of complex interactions whereby prolongation of LBTT favours increased DCA: (i) formation, (ii) solubilisation/ bioavailability and (iii) absorption.(Fig. 3)

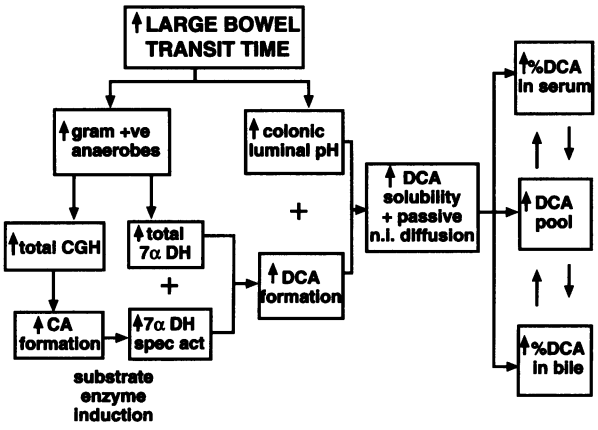


Fig 3 Flow diagram summarising the results of several studies from the authors department[16, 17, 24-27, 31, 32] showing how prolongation of large bowel transit might increase the proportion of deoxycholic acid (DCA) in the bile acid pool, and in serum and bile. Thus, an increase in large bowel transit time favours an increase in the numbers of Gram positive (+ve) anaerobes in the proximal colon. This increase in the numbers of anaerobes leads to increases in the total amounts (masses) of the intestinal bacterial bile acid metabolising enzymes responsible for deconjugation (cholylglycine hydrolase: CGH) and 7a-dehydroxylation (7α-dehydroxylase: 7α- DH) of the conjugated bile acids, in the caecum and colon. The resultant increase in deconjugation means that more cholic acid (CA) is formed in the proximal colon and this, in turn, may increase the specific activity (spec act) of 7α-DH.

The combination of increased total amounts of 7a-DH and increased 7α-DH specific activity, favours enhanced DCA formation. At the same time, the prolongation in large bowel transit time increases colonic lummal pH which ensures that the newly-formed unconjugated DCA is solubilised in, and is therefore made bioavailable for passive non-ionic (n.i.) diffusion from, the colon. This expands the proportion of DCA in the bile acid pool which is in dynamic equilibrium with the %DCA in serum and bile. The consequences of increased proportions of DCA in bile are summarised in Fig 2.

Step 5

If prolonged colonic transit really is important in the development of GBS, can all the resultant abnormalities be prevented or reversed, by the use of commonly-prescribed prokinetic drugs which accelerate intestinal transit? Again, the answer seems to be yes. In a prospective, random-allocation, double-blind, crossover design, controlled trial, we showed that the 5HT4 agonist, cisapride, completely prevented the prolongation of both small and large bowel transit seen in acromegalic patients treated with OT. More important, cisapride "normalised" the % DCA in fasting serum.[32] It remains to be proven, in prospective controlled trials, that the use of colonic prokinetic drugs, such as cisapride, can prevent cholesterol GBS formation in high-risk groups.

This, then, is the challenge for clinical investigators studying gallstone pathogenesis who, as we look BACKWARDS in this century, moved from "the bedside to the bench". As we move FORWARDS to the year 2000, they must now put this process into reverse and translate scientific theory into the clinical practice of gallstone prevention.

ACKNOWLEDGEMENTS

The author is grateful to many colleagues, collaborators and mentors whose work forms the basis of this brief review:

Michael Besser, Gary French, Hyder Hussaini, Paul Jenkins, Tony Mallet, Gerry Murphy, Steve Pereira, Linzi Thomas, Martin Veysey and John Wass.

REFERENCES

1. Dowling RH, Bell GD, White J. Lithogenic bile in patients with ileal dysfunction. *Gut*, 1972; **13**: 415-420.

2. Shaffer EA and Small DM. Biliary lipid secretion in cholesterol gallstone disease. The effect of cholecystectomy and obesity. J. *Clin Invest.* 1977; **59**: 828-840.

3. Northfield TC and Hofmann AF. Biliary lipid secretion in gallstone patients. *Lancet* 1973; **i**: 747-748.

4. Reuben A, Maton PN, Murphy GM, Dowling RH. Bile lipid secretion in obese and non-obese individuals with and without gallstones. *Clin Sci,* 1985; **69**: 71-79.

5. Forgacs IC, Maisey MN, Murphy GM, Dowling RH. Influence of gallstones and ursodeoxycholic acid therapy on gallbladder motor function. *Gastroenterology*, 1984; **87**: 299-307.

6. Bell GD, Whitney B, Dowling RH: Gallstone dissolution in man using chenodeoxycholic acid. *Lancet.* 1972; **ii**: 1213-1216.

7 Iser JH, Dowling RH, Mok HYI, Bell GD. Chenodeoxycholic acid treatment of gallstones: A follow-up report and analysis of factors influencing response to therapy. *New Engl J Med*, 1975; **293**: 378-383.

8. Maton PN, Iser JH, Reuben A, Saxton HM, Murphy GM and Dowling RH. Outcome of chenodeoxycholic acid (CDCA) treatment in 125 patients with radiolucent gallstones. *Medicine (Baltimore)*, 1982; **61**: 85-96.

9. Maton PN, Murphy GM, Dowling RH. Ursodeoxycholic acid treatment of gallstones: dose-response study and possible mechanisms of action. *Lancet*, 1977; **ii**: 1297-1301.

10. Meredith TJ, Williams GV, Maton PN, Murphy GM, Saxton HM and Dowling RH. Retrospective comparison of "Cheno" and "Urso" in the medical treatment of gallstones. *Gut*, 1982; **23**: 382-389.

11. Gleeson D, Ruppin DC, Saunders A, Murphy GM and Dowling RH. Final outcome of ursodoexycholic acid treatment in 126 patients with radiolucent gallstones. *Quart. J Med*, 1990, **279**: 711-729.

12. Dowling RH, Hussaini SH, Murphy GM, Besser GM, Wass JAH. Gallstones during octreotide therapy. *Metabolism: Clinical and experimental*, 1992; **41**: Suppl.2, 22-33.

13. McKnight JA, McCance DR, Crothers JG, Atkinson AB. Changes in glucose tolerance and development of gall stones during high dose treatment with octreotide for acromegaly. *Br Med J*, 1989; **299**: 604-5, 1989.

14. Thomas LA, Veysey MJ, Murphy GM, Dowling RH, King A, French GR. Is cholelithiasis an intestinal disease? *Gut*, 1997; **40** (Suppl 1) A67.

15. Dowling RH, Veysey MJ, Pereira SP, Hussaini SH, Thomas LA, Wass JAH, Murphy GM. Role of intestinal transit in the pathogenesis of gallbladder stones. *Canadian J. Gastro*, 1997; **11**: 57-64.

16. Dowling RH, Gleeson D, Ruppin DC, Murphy GM and the British/Belgian Gallstone Study Group. Gallstone recurrence and post-dissolution management. In: Enterohepatic Circulation of Bile Acids and Sterol Metabolism. Eds: Paumgartner G, Stiehl A, Gerok W. MTP Press Limited, Lancaster. pp361-369, 1985.

17. Hussaini SH, Pereira SP, Veysey MJ, Kennedy C, Jenkins P, Murphy GM, Wass JAH, Dowling RH. The roles of gallbladder emptying and intestinal transit in the pathogenesis of octreotide-induced gallbladder stones. *Gut*, 1996; **38**: 775-783

18. Hussaini SH, Murphy GM, Kennedy C, Besser GM, Wass JAH, Dowling RH. The role of bile composition and physical chemistry in the pathogenesis of octreotide-associated gallbladder stones. *Gastroenterol*, 1994; **107**: 1503-1513

19. Carulli N, Loria P, Bertolotti C, Ponz de Leon M, Menozzi D, Medici G, Piccagli I. Effects of acute changes in bile acid pool composition on biliary lipid secretion. *J Clin Invest*, 1985; **74**: 616-24.

20. Hussaini SH, Pereira SP, Murphy GM, Dowling RH. Deoxycholic acid influences cholesterol solubilization and microcrystal nucleation time in gallbladder bile. *Hepatology*, 1995; **22**: 1735-1744

21. Fuessl HS, Carolan G, Williams G, and Bloom SR. Effect of a long-acting somatostatin analogue (SMS 201-995) on postprandial gastric emptying of 99mTc-tin colloid and mouth-to-caecum transit time in man. *Digestion*, 1987; **36**: 101-107.

22. Møller N, Petrany G, Cassidy D et al. Effects of the somatostatin analogue SMS 201-955 (Sandostatin) on mouth-to-caecum transit time and absorption of fat and carbohydrates in normal man. *Clin Sci*, 1988; **75**: 345-350.

23. O'Donnell LJD, Watson AJM, Cameron D, Farthing MJG. Effect of octreotide on mouth-to-caecum transit time in healthy subjects and in the irritable bowel syndrome. *Aliment. Pharmacol. Therap*, 1990; **4**: 177-182, 1990.

24. Veysey MJ, Arraton SRD, Mallet A, Jenkins P, Murphy GM, Wass JAH, Dowling RH. Long-term octreotide treatment increases large bowel transit time (LBTT), the proportion of deoxycholic acid (%DCA) in serum and the risk of gallstone formation. *Gut*, 1996; **39** (Suppl. 3): A134, (Abstr).

25. Veysey MJ, Arraton SRD, Gilani SS, Mallet A, Jenkins P, Murphy GM, Wass JAH, Dowling RH. The relationship between large bowel transit time (LBTT) and the proportion of deoxycholic acid (%DCA) in serum. *Gut*, 1996; **38;** (Suppl 1); A53, (Abstr).

26. Veysey MJ, Mallet A, Murphy GM, Dowling RH.Deoxycholic acid pool size and input rate, measured by stable isotope dilution, are increased in patients with slow transit constipation. *Clin Sci*, 1997; **92**: 3P (Abstr).

27. Thomas LA, Veysey MJ, Murphy GM, Dowling RH, King A, French GL. Bile acid metabolising intestinal bacterial enzyme activity: a novel factor in cholesterol gallstone pathogenesis. *Gut*, 1997; **40** (Suppl 1) A67 (Abstr).

28. Heaton KW, Emmett PM, Symes CL, Braddon FEM. An explanation for gallstones in normal-weight women: slow intestinal transit. *Lancet*, 1993; **341**: 8-10.

29. Shoda J, He B-F, Tanaka N, Matsuzaki Y, Osuga T, Yamamori S, Miyazaki H, Sjövall J. Increase of deoxycholate in supersaturated bile of patients with cholesterol gallstone disease and its correlation with de novo syntheses of cholesterol and bile acids in liver, gallbladder emptying, and small intestinal transit. *Hepatology*, 1995; **21**: 1291-1302.

30. Azzaroli F, Mazzella G, De Vegori E, Festi D et al. Sluggish gallbladder and small bowel motility are associated with cholesterol gallstones. *Gastroenterol*, 1997; **112**: A499 (Abstr).

31. Thomas LA, Bathgate T, Veysey MJ, King A, French GL, Murphy GM, Dowling RH. Do changes in colonic luminal pH explain the increased proportions of serum and biliary deoxycholic acid seen in patients with cholesterol gallbladder stones (GBS)? *Gut*, 1997; **41** (Suppl 3)**:** A32 (Abstr).

32. Veysey MJ, Arraton SRD, Mallet A, Jenkins P, Murphy GM, Wass JAH, Dowling RH. Cisapride reverses the effects of octreotide (OT) on intestinal transit and the proportion of deoxycholic acid (%DCA) in bile and serum. *Gut*, 1996; **39** (Suppl. 3): A103 (Abstr).

33. Berr F, Schreiber E, Frick U. Interrelationships of bile acid and phospholipid fatty acid species with cholesterol saturation of duodenal bile in health and gallstone disease. *Hepatology*, 1992; **16**: 71-81.

34. Hofmann AF, Grundy SM, Lachin JM, Lan SP, Baum RA, Hanson RF, Hersh T et al. Pre-treatment lipid composition in which patients with gallstones in the National Cooperative Gallstone Study. *Gastroenterology*, 1982; **83**: 738-52.

35. Pereira SP, Hussaini SH, Cassell TB, Murphy GM, Wass JAH, Dowling RH. Biliary phospholipids and mucin glycoprotein are altered in octreotide-induced gallstones. *Gut* 1995; **36:** (Suppl 1), A47 (Abstr)

36. Angelico M, Corradini GS, Masella R, Alvaro D, Cantafora A, Capocaccia L. Molecular composition of biliary phosphatidylcholines, as related to cholesterol saturation, transport and nucleation in human gallbladder bile. *J Hepatol*, 1992; **15**: 59-66

37. Hatsushika S, Tazuma S, Kajiyama G. Nucleation time and fatty acid composition of lecithin in human gallbladder bile. *Scand J Gastroenterol*, 1993; **28**: 131-136.

38. Cantafora A, DiBiase A, Alvaro D, Angelico M, Marin M, Attili AF. High performance liquid chromatographic analysis of molecular species of phosphatidylcholine-development of quantitative assay and its application to human bile. *Clin Chim Acta.* 1983; **134**: 281-295.

39. van Berge Henegouwen GP, van der Werf SDJ, Ruben AT. Fatty acid composition of phospholipids in bile in man: promoting effect of deoxycholate on arachidonate. *Clin Chim Acta.* 1987; **165**: 27-37.

40. Carey MC and Cahalane MJ. Whither biliary sludge? *Gastroenterology*, 1993; **95**: 508-523.

41. Lee SP. Lessons from experimental cholelithiasis: gallbladder and mucosa, nonsteroidal antiinflammatory drugs, and gallstones. *Gastroenterology*, 1991; **101**: 85760.

42. Marks JW, Bonorris GG, Albers G, Schoenfield LJ. The sequence of biliary events preceding the formation of gallstones in humans. *Gastroenterology*, 1992; **103**: 566-70.

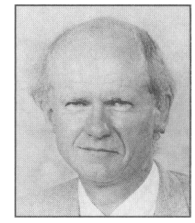
43. Shiffman ML, Sugarman HJ, Kellum JM, Moore EW. Changes in gallbladder bile composition following gallstone formation and weight reduction. *Gastroenterology* 1992; **103**: 214-21

44. Fisher RS, Stelzer F, Rock E, Melmud LS. Abnormal gallbladder emptying in patients with gallstones. *Dig Dis Sci.* 1982; **27**: 1019-1024

45. Pomeranz IS, Shaffer EA. Abnormal gallbladder emptying in a subgroup of patients with gallstones. *Gastroenterology.* 1985; **88**: 787-791.

46. Thompson JC, Fried GM, Ogden MD, Fagan CJ, Inoue K, Wiener J, Watson LC. Correlation between release of cholecystokinin and contraction of the gallbladder in patients with gallstones. *Ann. Surg.* 1982; **145**: 670-676.

Imaging of the Heart



Norman PS Campbell MD, FRCP

Consultant Cardiologist,
Royal Victoria Hospital

Most people from time to time become aware of the regular or irregular beat of the heart. As this is often during moments of high emotion or stress, the heart has featured greatly in popular culture and the arts. It is widely mentioned in poetry and literature. In the 1989 Oxford Dictionary of Quotations references to the heart far exceed those to lung, brain, liver or spleen[1]. Endocrinologists will note with dismay the complete absence of quotable remarks about pituitary, thyroid or pancreas.

TABLE 1

Quotations to the Body Organs in the Oxford Dictionary of Quotations (1989)

Organ	Quotations
Heart	227
Brain	25
Liver	6
Lungs	5
Spleen	2
Pancreas, Pituitary, Thyroid	0

An Egyptian papyrus from the 16th century BC - now in a museum in Brussels - shows one of the earliest visual representations of the heart. The heart was thought to represent conscience; after death it was placed in scales. If it proved heavier than a statue of truth the signs were thought favourable; and the fortunate deceased was led towards Osiris rather than to the nether regions. Where there was doubt about the probity of the dead man, the odds could be improved by using an ostrich feather instead of the statue. The heart seems less than impressive in the papyrus, but perhaps something has been lost by the passage of 3,500 years and by the quality of reproduction.

In medical texts of the middle ages representations of the heart and circulation were also somewhat fanciful. More anatomically accurate pictures were to follow with the work of Vesalius, Leonardo da Vinci and others during the 16th century. By the 19th century the morbid anatomy of cardiac disease was well established, but it was not until this century that it became possible to look at the beating heart in vivo.

At the time I started cardiology in 1971, diagnosis was made by a combination of clinical symptoms and signs, the electrocardiogram, the chest X Ray and in highly selected cases information from cardiac catheterisation and angiocardiography. In the last 25 years minimally invasive techniques of viewing the heart have become available. Tables 2 and 3 indicate some of the relative merits of 3 techniques discussed in this paper.

TABLE 2

Features of imaging techniques used in cardiac assessment.

Feature	Technique: Ultrasound	Radio Nuclear	MRI
Safety	++++	+++	+++
Expense	+	++	++++
Bed side Studies	++++	+	0
Time for study	+++	++	+++
Operator Skills	++++	+++	+++
Possible in all Patients	++	+++	+++
Convenience	++++	+++	++

(Each feature is gauged on a scale of 0 - ++++: for example in terms of convenience, ultrasound is straightforward, MRI (Magnetic Resonance Imaging) is relatively inconvenient)

ECHOCARDIOGRAPHY

Echocardiography has probably been the most widely available of these techniques and the one which has made the greatest impact on the practice of cardiology. The first cardiac ultrasound pictures in man were published by Edler in 1954[2], but it was not until the 1970's that echo techniques became widespread in clinical cardiology. Ultrasound is entirely safe, and its high temporal resolution permits beat to beat analysis of the heart.

Developments in technology allowed the progression

TABLE 3

Cardiac imaging methods - relative value in various disease categories

Feature	Technique Ultrasound	Radio Nuclear	MRI
Ischaemic	+++	++++	++
Valve	++++	++	+++
Congenital	++++	+	++++
Cardiomyopathy	++++	++	+++
Pericardial	+++	0	++++
Endocarditis	++++	0	++
Tumours	++++	0	++++

(Adapted from: Heart Disease: Edited by E. Braunwald)

from single to two dimensional images; these were later complemented by Doppler wave form analysis and colour display. Doppler techniques add the ability to look at blood flow within the central circulation. In 1980 Hatle and co-workers described the simple modified Bernoulli equation:

Pressure difference (mmHg)
$= 4 \times \text{peak velocity } (m.sec^{-1})^2$,

allowing the conversion of velocity measurements into pressure[3]. With colour coding of Doppler signals it is possible to detect and partially quantify abnormal valvular regurgitation or shunt. A transoesophageal approach allows high quality images to be obtained of structures relatively invisible to a probe on the anterior chest wall.

Echocardiography has resulted in a greatly improved ability to diagnose and understand a whole range of clinical conditions including congenital heart disease, pericardial disease, ventricular size and function and the cardiomyopathies. In the field of adult cardiology the assessment of valvular disease has been of great importance. For example, in a patient with rheumatic valvular disease it is possible to assess mitral and aortic valve areas, the degree of regurgitation through each valve, chamber size and function, and obtain information about intra-cardiac pressures. Such a complete picture results that it is often possible to avoid invasive evaluation. Recent developments include the use of stress echocardiography to diagnose and guide management of the patient with coronary artery disease, and intra-vascular ultrasound catheters to aid coronary intervention by angioplasty and stents.

Echocardiography has some disadvantages - it is relatively time consuming to perform an examination, it requires a skilled operator and in some-patients it is simply not possible to get high quality images.

NUCLEAR CARDIOLOGY

Nuclear imaging of the heart overcomes some of these difficulties, though presents other methodological problems. The first camera suitable for medical imaging was designed by Anger in 1958, but as in the case of ultrasound, it was not until the 1970's that the technology began to make a major impact.

Two major uses have evolved; the assessment of ventricular function and the analysis of myocardial blood flow and perfusion. One of the great advantages of nuclear techniques is that the information is in digital form, and can be readily manipulated by computer to produce quantitative information. For example, left ventricular ejection fraction - a measure of left ventricular function - can be calculated with ease. Digital imaging also permits tomographic reconstruction - this is now used routinely in many centres in the assessment of perfusion.

Ventricular Function

The most widely used technique is that of blood pool imaging. An isotope (usually 99m technetium) is tagged on to an intravascular structure (red cell or albumen). Because, during each cardiac cycle the heart will contain only a small amount of isotope, the technique of gating was developed - with this, acquisition of data is synchronised to the R wave of the ECG. The data from successive cardiac cycles are summated, the starting point being each R wave - at the end of the study, a composite or average heart beat is obtained containing information from perhaps up to 300 cycles.

The ejection fraction is calculated from the isotopic activity (scintillations counted) within the final images after correction for 'contamination' from background structures using the formula:

$$\text{Ejection fraction} = \frac{\text{End diastolic - end systolic activity}}{\text{End diastolic activity}}$$

Function may be assessed from the passage of a bolus of isotope through the heart - *first pass imaging*. During its transit through each chamber it is possible to make an estimate of function.

We have been fortunate to have had the opportunity of investigating this technique using a novel imaging device - the multi-wire camera. This camera, different in concept from the traditional 'Anger' camera, may be used successfully with a low energy isotope

(tantalum 178) which has also a short half life. High quality images may be obtained with a low radiation exposure for the patient. We have used this technique to study the response of the left ventricle to maximum stress in a wide rnge of clinical conditions including patients with recent myocardial infection, heart failure and congential heart disease[4,5].

By whatever method it is measured, radio-nuclide ejection fraction at rest of after stress is a powerful predictor of long term prognosis especially in patients with ischaemia heart disease.[6,7] Data from the Mayo Clinic in patients with known or suggested coronary artery disease have shown that an exercise ejection fraction of less than 0.30 is associated with a cardiac event rate of almost 50% over a 4 year period.[7]

Perfusion Imaging

Perfusion imaging of the myocardium was initially done with thallium - an analogue of potassium - but more recently technetium has been favoured because of its better imaging characteristics. Only metabolically active heart muscle will take up the isotope. The amount that is taken up is directly related to blood flow. Tissue that is dead or ischaemic and has a reduced blood supply (usually because of coronary artery disease) will acquire little isotope and will appear as an area of reduced activity.

In most perfusion scans the isotope is injected at peak excercise or after a pharmacological stress (dipyridamole, adenosine). The pictures that are obtained are then compared with a study at rest - either a second injection of the isotope at rest, or where thallium is used, a repeat series of pictures 4 hours after the first injection. Comparision of the 2 sets of images allows the areas of reduced uptake to be classified as fixed or transient defects. In general terms, the former are more likely to represent infarction, the latter ischaemic tissue.

When the technique was first described, the heart was in imaged in various 2 dimensional planes, this has been superseded in most centres by 3 dimensional tomographic reconstruction - so called SPECT (Single Photon Emission Computed Tomography). Analysis of the scans may be in a visual qualitative fashion, though interpretation of the data is often enhanced by quantitation of the results.

Perfusion imaging can aid the non-invasive dignosis of coronary artery disease. Table 4 shows a summary of some of the studies in which perfusion imaging has been used to diagnose the presence of ischaemic heart disease. Quantitative planar imaging yields a

TABLE 4

Ability of quantitative perfusion imaging to detect the presence of coronary artery disease

Method	Sensitivity(%)	Specificity(%)	Normalcy(%)
Perfusion Planar	**89**	**68**	**88**
Perfusion SPECT	**89**	**89**	**88**

(Adapted from reference (8))

sensitivity of 89% and a specificity of 68%. Improved results are obtained when SPECT imaging is used. The rather low specificity probably reflects referal bias. This is supported by the high normalcy rates for both methods.

Perfusion imaging may also help in the detection of viable myocardium. A non-contractile area of the heart may represent scar tissue of potentially viable muscle in a state of 'hibernation' - restoration of blood supply to a hibernating zone by by-pass surgery may allow return of muscle function. Detection of 'hibernating' tissue by nuclear and ultrasound methods has become an increasingly important isue in clinical cardiology.

MAGNETIC RESONANCE IMAGING

The technique which has most recently been applied to cardiology is that of Magnetic Resonance Imaging (MRI). Protons in a strong magnetic field are exposed to radiofrequency pulses. The protons subsequently emit a radiofrequency signal which can be detected. The first picture - a human finger - was obtained in 1976 and since then development has been rapid. The method allows high quality structural data as well as 'cine' sequences to be obtained - as in the case of nuclear cardiology, acquisition of a study may require 'gating' with the ECG.

In cardiology it has found application in the diagnosis of aortic aneurysms both dissecting and nondissecting and pericardial disease. Excellent pictures can also be obtained of cardiac tumours, regurgitant and stenotic lesions and chamber size and function. It is also possible to identify flow within coronary vessels though the quality is not as yet good enough to show coronary anatomy reliably. The exact place of MRI in imaging of the heart is still being evaluated.

FUTURE TRENDS

Predictions about the future direction of cardiac imaging remain guess work. Echocardiography will remain a valuable technique being relatively inexpensive, safe and quick. There will be continued improvements in image quality and 3-dimensional reconstruction of images. There are likely to be considerable advances in the assessment of myocardial perfusion especially with the use of contrast agents injected peripherally.

The long term future of nuclear methods in cardiology is perhaps less certain. Developments in echocardiography and MRI may take over some of the functions of the nuclear laboratory. However, it is likely that nuclear methods will remain as the most convenient for assessing myocardial perfusion and new isotopes should make determination of myocardial metabolism more readily available.

I suspect that over the next one or two decades there will be a great expansion in the use of MRI in cardiology. The noninvasive nature of the method, its safety, and the ability to reconstruct and quantify the data are all important features. At present the method is quite slow and may be difficult to perform in the acutely ill patient. In the years ahead, new methods of analysis, faster acquisition times and reduced cost will probably ensure a considerable expansion of cardiac MRI.

This has been of necessity a short and comparatively superficial survey of some of the developments in cardiac imaging over the last 30 years. Having the ability to perform accurate and reliable tests puts an onus on the clinican to use the investigations wisely - to order them appropriately and to interpret them correctly. In 1933, Sir Thomas Lewis wrote in the preface to his textbook of cardiology:

'It has been important to try to achieve a proper perspective of values so as not to place undue weight on this or that, because its novelty attracts or because it has a strong personal interest.'

In most cardiology units, including our own, there has been a major increase in the number of tests being requested, with an inevitable effect on waiting times and costs. Thus, since 1922, the number of ECGs performed each year has increased by 20% and the current waiting time has increased from 3 to 9 months. Not all of these tests may be necessary, and no test, however good, should be permitted to be a substitute for clinical judgement.

The same 'proper perspective' of Lewis is still required today.

REFERENCES.

1. Oxford Book of Quotations; Third Edition. Oxford University Press; 1989
2. Edler I and Hertz CH. Use of ultrasonic reflectoscope for continuous recording of movement of heart walls. *Kungl. Fysiogr. Sallsk. i Lund. Forhandl.* 1954; **24**:40.
3. Hatle L, Angelsen BA, Tromsdal A. Non-invasive asessment of aortic stenosis by Doppler ultrasound. *Br. Heart J*, 1980; **43**: 284.
4. Vallely SR. Radionuclide Angiocardiography using a Multiwire Camera and Tantalum-178. Thesis for Doctor of Medicine: Queen's University: Belfast. 1993
5. Moore AM: Beta-adrenergic Receptor Antagonists and Exercise Radionuclide Angiocardiography in Patients with Proven Coronary Artery Disease. Thesis for Doctor of Medicine Queen's University; Belfast. 1997
6. Lee KL, Pryor DB, Pieper KS et al. Prognostic value of radionuclide angiography in medically treated patients with coronary artery disease. *Circulation*, 1990; **82**, 1705.
7. Taliercio CP, Clements IF, Zinsmeister AR et al. Prognostic Value and limitations of exercise radionuclide angiography. *Mayo Clin. Proc*, 1988; **63**: 573.
8. Maddahi J: in Cardiac Imaging. A Companion to Braunwald's Heart Disease: ed Skorton DJ: Chapter 63: WB Saunders Company: 1996.

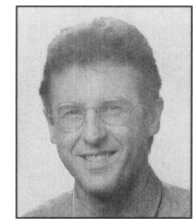
AA Jennifer Adgey MD, FRCP, FRCPI, FACC Introducion of the Calvert Lecture

Cecil Armstrong Calvert was well known to many and tragically in 1956 he was killed in a road accident in this country. In 1922 he graduated from this medical school with first class honours. His phenomenal yet effortless capacity for sustained mental and physical activity commanded respect and affection from all those who worked with him. He established the first neurosurgical department here in Northern Ireland in the Royal Victoria Hospital and became its first director. At his funeral service, in St. Anne's Cathedral, approximately 1500 people gathered, he was described as the best loved doctor in Ulster; surely there could be no more fitting an epitaph. He was one of the most outstanding men that this Belfast school has produced, for only the best would satisfy him. His diagnostic powers and surgical skill perpetuated by his gentle patience and compassion for his patients were known to all. He had both a national and international reputation as one of the foremost neurosurgical surgeons in the world at that time.

The Royal Victoria Hospital Research Committee allocate an annual award to scholarships given to the two persons who, judged by the committee, have carried out the best research in their fellowship year with us - the Calvert and Purce Lectures.

On the Trail of a New Virus

THE CALVERT LECTURE 1997



Jonathan R Kerr MD, DSc, MRCPath
Honorary Senior Lecturer in Virology
University College London Medical School

Human parvovirus B19 was discovered in 1975[1]. The first clinically significant illness associated with B19 infection was hypoplastic crisis in children with sickie-cell anaemia[2]. Development of specific serological assays showed that patients with fifth disease (erythema infectiosum) also had acute B19 infection[3]; an aetiology that is now widely accepted.

Human parvovirus B19 is a member of the genus Erythrovirus of the family Parvoviridae. B19 is a small single-stranded DNA virus, whose genome is a single linear molecule of only 5596 nucleotides; composed of an internal coding sequence of 4830 nt, flanked by the terminal repeat sequences of 383 nt each. The major nonstructural protein, NS1, is encoded by the left side of the genome, and is essential for viral replication. Structural proteins, VP1 and VP2, are encoded by the right side of the genome and form the viral capsid. Parvovirus B19 has not been shown to infect other animals, and the other animal parvoviruses have not been shown to infect humans.

B19 infection is common in humans, with a seroprevalence in developed countries of 5% in children, 60% in blood donors and 85% or more in the elderly. In temperate climates, there is an increased prevalence from late winter to early summer and increased infection rates every four to five years. B19 is transmitted in the community by the respiratory route causing infection both sporadically and in outbreaks, which are apparent in schools. Transmission has also occurred among medical laboratory staff working with native virus. B19 virus can also be found in donated blood, the incidence of which is estimated between 1:3300 and 1 :50,000, and infection has been transmitted by clotting factor concentrates. Although nosocomial transmission and resultant outbreaks in both paediatric and adult wards have been documented, this is infrequent [4].

B19 infection may be asymptomatic or may result in a wide range of clinical manifestations depending on host factors such as age, presence of anti-B19 antibody, immunocompetence and red cell fragility. B19 is the aetiological agent of erythema infectiosum, transient aplastic crisis in patients with shortened red cell survival, acute and chronic arthritis and chronic anaemia in immunocompromised patients. B19 infection has also been associated with fetal hydrops, congenital red cell aplasia, vasculitis syndromes, glomerulonephritis with nephrotic syndrome, meningitis, encephalopathy, peripheral neuropathy, myocarditis, hepatitis, systemic lupus erythematosus, necrotising histiocytic lymphadenitis (Kikuchi's disease), pulmonary disease following paediatric heart transplantation, conjunctivitis, Kawasaki disease, congenital abnormalities and chronic fatigue syndrome[4].

An outbreak of B19 infection in Northern Ireland

My work began with the description of an outbreak of B19 infection in Northern Ireland. Testing patient serum using an in-house enzymeimmunoassay assay (EIA) for anti-B19 IgM, 133 cases of acute B19 infection were diagnosed by the Regional Virus Laboratory from 1984 to July 1991. An increased prevalence (103 of 133 cases) occurred during 1989-1990. Of the total 133 cases, the ratio of female to male was 3.4:1. The age range was 4-63 years with a mean of 28 years. Clinical manifestations of infection from 1984 - 1991 included rash (n=22), arthralgia (n=35), rash and arthralgia (n=70), aplastic crisis in patients with shortened red cell survival (n=3), fetal death following maternal infection (n=1), Henoch-Schonlein purpura (n=1), and lymphadenopathy (n=1). This outbreak coincided with an outbreak in England and Wales[5].

Study of the incidence of fetal death in B19-infected pregnant women.

Although B19 was known to cause fetal death, the incidence of this following maternal B19 infection was unknown. During 1989, the outbreak year, we collected and later tested the serum from 2400 pregnant women at 12 weeks gestation for the presence of anti-B19 IgM by enzymeimmunoassay. Eight of these were positive. We followed these pregnancies and found that one resulted in spontaneous abortion at 26 weeks. The incidence of fetal death following maternal infection was therefore 12.5%, in general agreement with the major UK study of 186 pregnancies which showed a 9.2% incidence of fetal death. No congenital abnormalities were noted in the 7 surviving infants, either at birth or at 3 years of age[5].

TABLE

Clinical details and results of serum PCR for B19 DNA from seven patients with persistent B19 infection at acute infection and at follow-up assessment. Genotyping of these B19 isolates is shown in Figure 2. (see reference numbers 16 & 17).

Patient number	Age onset	Sex	Symptoms at onset	B19 DNA at onset	Follow-up interval (months)	Duration of symptoms (months)	Symptoms at follow-up	B19 DNA at follow-up
24	10	F	Rash	NT	55	<1	-	+
39	49	F	Arthralgia in knees	+	61	<1	-	+
40	29	F	Arthralgia in knees	+	61	61	Arthralgia in knees	+
41	54	F	Rash	+	60	<1	-	+
46	22	F	Rash	NT	50	<1	-	+
50	29	F	Aplastic crisis	+	26	26	Chronic haemolytic anaenia	+
51	17	F	Arthralgia in knees and shoulders	NT	65	65	Arthralgia in knees and shoulders, Chronic fatigue syndrome	+

NT not tested.

Production of a monoclonal antibody to B19 capsid proteins

A highly conserved B19 epitope is known to be encoded by amino acids 328 - 344 of B19 viral Protein 2. Antibody attachment to this epitope neutralises the virus in erythroid culture.

Using avidin-biotin immunohistochemistry, 3H8 labelled erythroid cells with and without viral inclusions in lung sections from 4 fetuses with histology suggestive of intrauterine B19 infection. No staining was observed in other cell types or fetal lung sections from negative controls. The isotype of 3H8 was IgG1[6].

Study of the cellular distribution of blood group P and B19 antigens in B19 infected bone marrow

In 1993, blood group P antigen was implicated as the cellular receptor for parvovirus B19[7]. In response to this, we examined the bone marrow of 61 AIDS patients and selected 3 bone marrow biopsies which were positive for B19 DNA by nested PCR and B19 capsid proteins by avidin-biotin immunohistochemistry using monoclonal antibody, 3H8. These sections were then stained by a double-fluorescent labelling technique using 3H8 linked to Texas Red followed by a monoclonal antibody to P antigen linked to fluorescein. In all 3 cases an identical pattern of cellular distribution of the two antigens was seen, providing further evidence for P as the virus receptor (Figure 1)[8].

Study of the molecular epidemiology of parvovirus B19

The dominant influences on the clinical manifestations of B19 infection are those of the host. Namely, age, presence of anti-B19 antibody, immunocompetence, red cell fragility, and blood group P antigen status. However, it is possible that the make-up of a particular B19 strain may also contribute[9]. To study the molecular epidemiology of B19 infection, we developed a viral typing method using PCR - single-stranded conformational polymorphism (SSCP) assay. A nested PCR method was developed using oligonucleotide primers specific for a region within the B19 non-structural gene. The first reaction amplified a 369 bp fragment, and the second amplified an internal 284 bp fragment (B19 nucleotides 1399-1682). This 284 bp fragment, after visualisation on agarose gel electrophoresis was then typed using SSCP. The principle of SSCP is that electrophoretic mobility of a DNA molecule in a gel is sensitive to both its size and shape. Therefore, a mutated sequence causes altered folding which is detected as a change in mobility. And in general, the method has a higher sensitivity for short fragments of 100 - 200 bases[10]. The method was optimised to 100% sensitivity, and was able to detect a single mutation in the 284 bp fragment. The method was then applied to 50 virus isolates from patients with different symptoms and geographical locations.

Five types were demonstrated, each of which had a unique nucleotide sequence. In all, 6 mutations were detected, all of which were silent, consistent with the

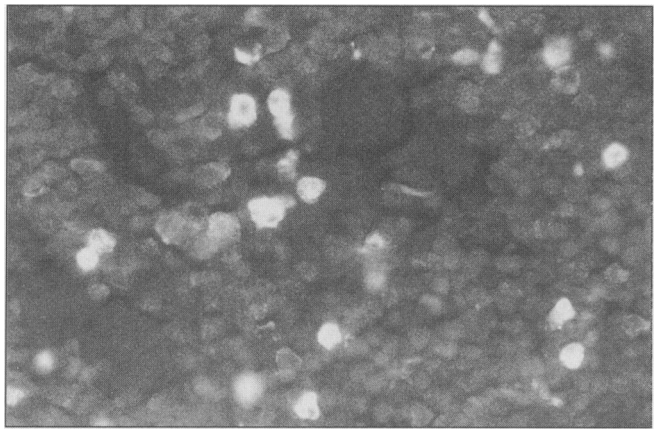


Figure 1a

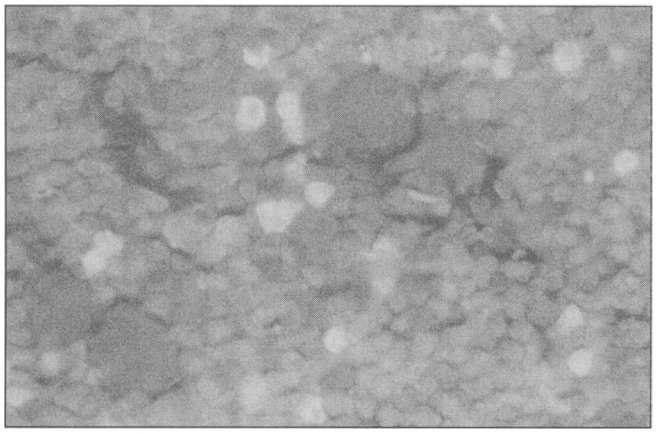


Figure 1b

Figure 1a. B19 infected bone marrow. stained sequentially with monoclonal antibody to B19 antigen (3H8) linked to fluorescein and monoclonal antibody to blood group P antigen (a-P) linked to texas red. Figures 1a and 1b were viewed with filters of emission wavebands at 515nm (to detect bound Streptavidin - FITC) and 615nm (to detect bound Streptavidin - Texas Red), respectively. Both monoclonal antibodies show the same pattern of cellular distribution (see reference number 8).

conserved nature of this region and its crucial role in B19 replication. Among the 50 isolates, types 3 and 4 accounted for 92%. A correlation was seen between SSCP type and country of origin. Type 3 predominated in Japan and the UK, whereas type 4 predominated in the USA. Also, type 3 strains predominated among females, whereas there were approximately equal numbers of strain types 3 and 4 among males, a finding which remains to be explained. Within the Japanese group, although type 3 strains predominated overall, strains isolated from 1981 to 87 consisted of types 1,2, 3, and 4, whereas strains isolated from 1990 to 94 consisted almost entirely of type 3. There was no correlation between SSCP type and clinical illness [11].

Study of the role of B19 in the pathogenesis of rheumatoid arthritis

B19 arthralgia occurs in up to 80% of infected adults, affecting the hands, wrists, knees, and cervical spine. Most patients are women, and rheumatoid factor may be present or may rise following B19 infection. B19 DNA has been detected in the synovial fluid, cells, and tissue of patients with serologically proven B19 infection. On this basis, B19 was implicated in the pathogenesis of RA.

First, we hypothesised that if B19 plays a role in RA, then rheumatoid synovium would contain B19 DNA significantly more frequently than controls. We examined 52 patients undergoing elective orthopaedic surgery; 26 test patients with RA and 26 controls with osteoarthritis (OA)

All synovia were negative for both antigens. Using nested PCR to detect B19 DNA, all sera were negative. However, in synovium,10 of 26 RA patients and 9 of 26 OA patients were positive (P = 0.77). All patients with B19 DNA in synovium had serum anti-B19 IgG[12].

Second, we hypothesised that if B19 plays a role in RA, then RA patients at the time of acute joint swelling may exhibit B19 DNA in the serum, synovial fluid and synovial fluid cells significantly more frequently than controls. A total of 29 patients with acute joint swelling requiring knee joint aspiration were assessed; 18 test patients had RA, and 11 control patients had non-rheumatoid (non-RA) disease.

Serum and synovial fluid from au patients from both groups were anti-B19 IgM negative. Serum, synovial fluid and synovial fluid cells from all patients tested negative for serum B19 DNA[13]. From, these 2 studies, we concluded that a role for B19 in the pathogenesis of RA was not supported.

Presence of viral DNA in synovium is not indicative of viral replication unless intracellular B19 protein is also identified. P antigen was looked for in synovial sections as it might act as the viral receptor in synovial cells, as it does in erythroid cells. However, since P was not detected in any case, the mechanism of viral entry into these cells is unclear. In addition, in vitro cultures of human synovial cells are resistant to B19 infection. There are therefore two theories which may account for a persistent arthropathy following B19 infection and possibly also the presence of B19 DNA in synovium. First, as the joint symptoms coincide with appearance of specific IgG, viral persistence may occur in an extraarticular site such as the bone marrow, with prolonged symptoms being generated by immunopathological mechanisms. Intermittent viraemia may contaminate synovium and explain positive PCR results. However against this, in the present study all 52 sera were PCR-negative. Second, local viral replication may occur in another cell type, for example the macrophage, with excretion of a factor causing synovial inflammation. The B19 non-structural protein, NS1, would be a candidate as it is cytotoxic in vitro[12].

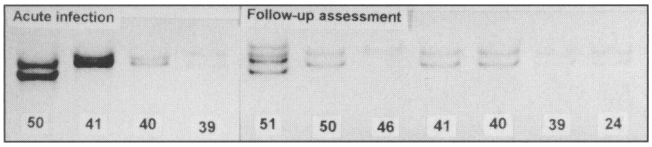


Figure 2. SSCP analysis of PCR products from the serum of 7 patients with persistent B19 infection (Table). Each specimen showed double—stranded DNA of 284bp (nt 1399 to nt 1682) on conventional agarose gel electrophoresis. PCR products were denatured at 90°C in formamide and subjected to electrophoresis in a Mutation Detection Enhancement acrylamide gel (AT Biochem) in 90mM Trisborate, pH 8.3 / 4mM EDTA at a constant power of 20W for 5 hours at 23°C in a vertical gel electrophoresis apparatus (Bio-Rad). The gel was stained by a silver staining method (Promega), and viewed and photographed on a light box (see reference numbers 16 and 17). Reproduced with permission of Scandinavian University Press.

Follow-up study of acute B19-infected persons

In immunocompetent persons, prompt viral clearance and disease resolution is the rule. However, reports have described persistent B19 infections in apparently normal persons and an association with autoantibody production and autoimmune disease. These reports prompted us to perform a follow-up study in 53 persons with confirmed B19 infection and without a known immune defect, to determine the natural history, immune response, and incidence and significance of autoantibody production and virus persistence. Fifty-three patients testing positive for serum anti-B19 IgM were followed for approximately 4 years. At follow-up, clinical symptoms were recorded and blood taken. A control group was included, matched for age and sex.

Seven patients presenting with rash had resolved within a month. Of 42 cases of arthralgia, 19 had resolved within a month, and 23 persisted for 1-7 years. In two cases with persistent arthralgia, chronic fatigue syndrome (CFS) was also present. Of 3 patients presenting with aplastic crisis, 2 were asymptomatic at follow-up and one required occasional blood transfusion for a chronic anaemia. There was one case of fetal death following maternal infection. Apart from one patient with persistent arthralgia who had been diagnosed as having rheumatoid arthritis, there were no cases with other symptoms suggestive of autoimmune disease. At follow-up, all test and control patients were serum anti-B19 IgM negative. All 53 test patients and 45 controls were IgG positive (2-tailed P value = 0.008)[14].

These sera were then tested for antibodies to the unique region of B19 VP1. B19 structural proteins, VP1 and VP2, form the viral capsid in a ratio of 1:25, respectively. They are identical, except for an additional 227 amino acids at the amino-terminal of VP1. This so-called unique VP1 region projects from the virus surface and its recognition by the human immune system is crucial in disease resolution. Serum was tested for antibodies to this region by immunoblot, using 11 synthetic overlapping peptides incorporated onto nitrocellulose strips. At follow-up all test and control patients were negative for antibodies to this region. Serum from the time of acute infection was available for 33 test patients, 16 of which were positive. However, presence or absence of these antibodies did not predict particular symtoms of their duration. Of the 11 peptides, 3 were variably recognised; numbers 2, 8 and 9. These peptides correspond to 2 regions, which encode neutralising viral epitopes. Although, immune recognition of this region is crucial in disease resolution surprisingly all patients tested negative for these antibodies at convalescence. The most likely explanation may be that while antibody binding of these linear epitopes may neutralise the virus, the most important neutralising epitopes are conformational and therefore undetectable in an immunoblot[14].

Seven test and no control patients had serum autoantibody at a titre greater than or equal to 160. These antibodies consisted of antinuclear, gastric parietal cell, antireticulin, antmitochondrial and rheumatoid factor. Only one of these patients had clinical illness at follow-up; a 48 year old woman with serum rheumatoid factor of 1920 iu/ml and a 4 year history of polyarthritis, who had been diagnosed as having RA. In conclusion, in most cases it would seem that these autoantibodies did not have clinical relevance[15].

Serum was then tested for B19 DNA by nested PCR. Seven Test and no control patients were positive (2-tailed P value = 0.016). All seven with persistent infection were women, only 3 of which were symptomatic with arthralgia, arthralgia and CFS and chronic anaemia, respectively (Table). There was no obvious relationship between B19 persistence, autoantibody production and immune recognition of the unique region of VP1. For the 7 persistently infected patients, serum from the time of acute infection was available for four, all of which contained B19 DNA. SSCP assay (Figure 2) showed identical types in 5 of 7 follow-up isolates, suggesting an advantage to the virus of this particular type. In 2 of the 4 cases for which both acute and follow-up PCR product was available patient numbers 40 and 41, the SSCP type at follow-up was different from that at presentation, demonstrating nucleotide substitution occurring during persistent infection. In addition, 2 virus types were shown to co-exist in patient 51, with chronic fatigue syndrome (Figure 2). This is a phenomenon not previously demonstrated for B19 but known to occur with Aleutian mink disease parvovirus, which is also prone to persistent infections. We speculated that as B19 non-structural protein is required for replication, DNA sequence

changes in this region may modify viral replication, possibly promoting persistence[16,17].

Study of the role of B19 in chronic fatigue syndrome

Results of the follow-up study indicated that 2 of 53 patients with acute B19 infection developed CFS, which was still present after 4 years. One of these patients was shown to be persistently infected, and SSCP assay showed the co-existence of 2 virus types. In view of this we examined serum from 22 cases of CFS, according to the diagnostic criteria of the Centers for Disease Control, and 12 normal controls. Regarding serum ant-B19 IgM, 3 of 22 test and 2 of 12 control cases were positive; a surprising result, although not statistically significant. Regarding serum anti-B19 IgG, 15 of 22 test and 8 of 12 control cases were positive; again not significant. All test and control cases were PCR-negative.

We also tested muscle biopsies from 6 patients with CFS and 6 control persons for B19 DNA by nested PCR; one of each group was positive, a non-significant difference[18]. From these 2 studies, we concluded that a role for B19 in the pathogenesis of CFS was not supported.

Study of B19 infection in HIV-1 infected patients

Acute B19 infection in AIDS patients may lead to persistent infection and bone marrow suppression. Persistent B19 infection is typically manifest by pure red cell aplasia, and is associated with a lack of humoral responsiveness to the unique region of VP1. Human immunoglobulin, containing these antibodies, is the only specific treatment. To determine the incidence and significance of B19 infection in AIDS, we tested the bone marrow and assessed the clinical status of 61 HIV infected patients. Reasons for bone marrow biopsy were investigation of anaemia, various cytopenias and suspected lymphoma. The bone marrow of 23 control patients assumed to be HIV negative was also examined. Bone marrow biopsy had been performed in these patients for investigation of lymphoma, leukaemia, anaemia, platelet abnormalities, multiple myeloma, and raised serum IgM.

13 test and no control patients had B19 DNA detected in bone marrow by nested PCR (2-tailed P value = 0.016). Of the 13 infected patients, 11 were CDC group 4, reflecting the known correlation between B19 persistence and level of immunosuppression. However surprisingly, only 2 of these 13 had a haemoglobin below 9g/dl.

One explanation may be that the virus is present at very low concentration in bone marrow, as in all cases it was detected only by nested and not by one—step PCR. The sensitivity of the nested PCR was of the order of 10 genome copies per ml. While the sensitivity of the one—step PCR was of the order of 100,000 genome copies per ml. Unfortunately, serum from the time of bone marrow biopsy was unavailable. Our conclusion, which is consistent with studies using serum, is that low titre B19 persistence in the bone marrow may be common and frequently subclinical in AIDS patients [19].

ACKNOWLEDGEMENTS

I would like to acknowledge the support of Dr Peter Coyle, Dr Percy Ferguson, Professor Tadasu Nunoue and Professor Peter Behan. For financial support, I would like to thank the Royal Victoria Hospital for a one year research fellowship, the Department of Health, the British Council in Japan, The Royal Society, and the Persistent Virus Disease Research Foundation.

REFERENCES

1. Cossart YE, Field AM, Cant B, Widdow D. Parvovirus-like particles in human sera. *Lancet* 1975;**1**:72-73.

2. Pattison JR, Jones SE, Hodgson J, Davis LR, White JM, Stroud CE, Murtaza L. Parvovirus infections and hypoplastic crisis in sickle-cell anaemia. *Lancet* 1981; **1** :664-665.

3. Anderson MJ, Jones SE, Fisher-Hock SP, Lewis E, Hall SM, Bartlett CL, Cohen BJ, Mortimer PP, Pereira MS. Human parvovirus, the cause of erythema infectiosum (fifth disease). *Lancet* 1983;**1**:1378.

4. Kerr JR. Parvovirus B19 infection *Eur J Clin Microbiol Infed Dis* 1996;**15**:10-29.

5. Kerr JR, O'Neill HJ, Coyle PV, Thompson W. An outbreak of parvovirus B19 infection; a study of clinical manifestations and the incidence of fetal loss. *Irish J Med Sci* 1994;**163**(2):65-7.

6. Kerr JR, O'Neill HJ, DeLeys RJ, Wright C, Coyle PV. Design and production of a target-specific monoclonal antibody to parvovirus B19 capsid proteins. *J Immunol Meth* 1995;**180**:101-106.

7. Brown KE, Anderson SM, Young NS. Erythrocyte P antigen: cellular receptor for B19 parvovirus. *Science* 1993;**262**:114-117.

8. Kerr JR, McQuaid S, Coyle PV. Expression of P antigen in parvovirus B19-infected bone marrow. *N Engl J Med* 1995;**332**(2):128.

9. Kerr JR, Umene K. The molecular epidemiology of parvorvirus B19. *Rev Med Microbiol* 1997;**8**(1):21-31.

10. Kerr JR, Cunan MD. PCR-SSCP; applications to microbiology. *Clin Mol Pathol* 1996;**49**:315-320.

11. Kerr JR, Curran MD, Moore JE, Erdman DD, Coyle PV, Nunoue T, Middleton D, Ferguson WP. Genetic diversity in the non-structural gene of parvovirus B19 detected by single-stranded conformational polymorphism assay (SSCP) and partial nucleotide sequencing. *J Virol Meth* 1995;**53**:213-222.

12. Kerr JR, Cartron JP, Curran MD, Moore JE, Elliott JRM, Mollan RAB. A study of the role of parvovirus B19 in rheumatoid arthritis. *Br J Rheumatol* 1995;**34**:809-813.

13. Kerr JR, Ferguson WP, McMillan SA, Bruce IN, Bell AL. Parvovirus B19 and acute joint swelling in rheumatoid arthritis patients. *Ann Rheum Dis* 1996;**55**:648-9.

14. Kerr JR, Coyle PV, DeLeys RJ, Patterson CC. A follow-up study of clinical and immunological findings in patients presenting with acute parvovinus B19 infection. *J Med Virol* 1996;**48**:68-75.

15. Kerr JR, Boyd N. Autoantibodies following parvovirus B19 infection. *J Infect* 1996;**32**:41 -47.

16. Kerr JR, Curran MD, Moore JE, Coyle PV, Ferguson WP. Persistent parvovirus B19 infection. *Lancet* 1995;**345**:1118.

17. Kerr JR, Curran MD, Moore JE, Murphy PG. Parvovirus B19 infection; persistence and genetic variation. *Scand J Infect Dis* 1995;**27**:551-557.

18. Kerr JR, Barrett AM, Curran MD, Behan WMH, Middleton D, Behan PO. Parvovirus B19 and chronic fatigue syndrome. *J Chronic Fatigue Syndrome* 1997; **3**: 101-107.

19. Kerr JR, Kane D, Crowley B, Leonard N, O'Briain S, Coyle PV, Mulcahy F. Parvovirus B19 infection in AIDS patients. *Int J Sexually-transmitted diseases and AIDS* 1997;**8**:184-6.

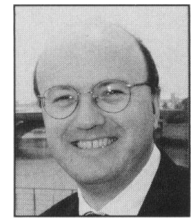
Peter G Toner DSc, FRCPG, FRCPath
Introduction of the Patrick Watt Memorial Lecture.

I first met Patrick in 1984 when I joined the Department as Musgrave Professor of Pathology. He was already recognized as a phenomenon far beyond the ordinary. He was an accomplished and dedicated clinical surgeon who nevertheless found himself content in the laboratory study of disease. Working with Jimmy Sloan, Patrick established and developed a programme of pathological investigation based on the quantity of analysis of histological images. Through his personal efforts and through the recruitment of a young and exceptionally able assistant, Peter Hamilton, who is now a senior lecturer in our department, quantitative pathology became firmly established in Belfast and has since developed into one of our most successful methodologies with applications and collaborations in numerous fields of clinical medicine.

As a practising pathologist, Patrick was also an innovator and an professional leader. By combining his professional skills in surgery and pathology he played a key role in developing in Belfast a clinic-based service in fine-needle aspiration cytology on which modern surgical practice has come increasingly to rely.

Finally, as a person Patrick was the finest of colleagues, he was gentle and considerate in all his personal dealings, yet forceful and determined in pursuing the interests of his patients and of his research. I count myself privileged at having enjoyed his acquaintance. Patrick himself is irreplaceable but his legacy to pathology will live on for many years to come, this lecture today is one small attempt to commemorate Patrick's memory and to highlight his association with scientific pathology in the clinical context.

Wound Healing - Scar Wars



Mark WJ Ferguson BSc, PhD, FFDRCSI
Professor of Biological Sciences
University of Manchester

Scarring following wounding is a major medical problem. In skin wounds or burns scarring often leads to adverse cosmesis and consequent psychological problems, adverse function particularly over joints and retardation of growth especially in children. Scarring in muscle adversely affects movement and can cause ankylosis. In abdominal and pelvic organs scarring can lead to life threatening strictures and adhesions. In the eye, scarring can cause blindness, whilst in the central nervous system scarring inhibits neuronal reconnection and hence restoration of neuronal function. In almost every organ and tissue, scarring following injury or trauma is a major problem, for which there are no good preventative or therapeutic regimens.

Several years ago, we and other researchers observed that skin wounds made in early embryos/fetuses of reptilian, avian and mammalian species healed without scarring. My laboratory subsequently embarked upon a detailed analysis of the cellular and molecular basis of scar-free healing in embryos compared to scar forming healing in adults. Investigations using embryonic and fetal mice revealed that incisional wounds made in embryos and fetuses, up to approximately the first half or 2/3 of gestation, healed without scarring. Wounds made during the last trimester of pregnancy or in early postnatal life showed progressively worse scarring. Thus, there is a temporal cut off for scar-free healing during late embryonic or early fetal life.

The phenomenon of scar-free embryonic healing does not depend on the special intra uterine environment e.g. warm, sterile, uniform 37°C, bathed in the amnoitic fluid. At least two lines of experimentation indicate that the fetal environment is unimportant for scar-free healing. First, adult skin grafted onto a fetus and subsequently wounded heals with a scar, whereas corresponding control fetal grafts heal without scarring. Conversely, embryonic skin grafted into subcutaneous locations in the adult heals without scarring. Second, experimentation on new born marsupials indicated that incisional wounds made within the first four days of the embryo attaching to the nipple on the marsupial, heal without scarring. The new born marsupials are not bathed in aminiotic fluid, are frequently in a microbiologically rich environment (from maternal faeces and urine) but like the late embryo or early fetus, have a very poorly developed immune system, however unlike the eutherian embryo or fetus, they have highly differentiated skin.

There are many cellular and molecular differences between scar-free embryonic healing and scar forming adult healing. One critical difference is the inflammatory response. Embryos mount a poor inflammatory response to wounding with the recruitment of only small inflammatory cells e.g. monocytes and macrophages to the wound site and even smaller numbers of mature activated cells. Consequently, the types and quantities of growth factors present in the embryonic wound compared to the adult wound are quite different. Embryonic wounds have a very low levels, for example, of transforming growth factors beta-1 and beta-2 whereas adult wounds have a very high early levels of TGFß1 and TGFß2 (released from degranulating platelets and subsequently from recruited monocytes and macrophages).

Using the information gleaned from these molecular and cellular investigations comparing scar-free embryonic healing and scar forming adult healing, we have experimentally manipulated adult rodent, porcine and human wounds in an attempt to ameliorate or prevent scarring.

In the first series of experiments, we demonstrated that neutralising antibodies to transforming growth factor beta-1 and beta-2 (TGFß1 and TGFß2) injected intradermally at the wound site could prevent subsequent scarring. Dose response and time response experiments showed that the neutralising antibodies had to be applied immediately before, at the time of, or immediately after wounding to achieve maximum effect. In fact the timing of any scar preventing therapy is critical. The best results are obtained if the therapy is applied before, at the time of, or immediately after wounding. This is a real biological phenomenon. All growth factors such as TGFß1 and TGFß2 operate as auto inductive cascades. A small initial amount of TGFß1 released from degranulating platelets is chemotactic to monocytes and

macrophages which migrate to the wound site and secrete further TGFß1 and 2. TGFß1 is also autocatalytic, binding it to its own promoter and upregulating its own synthesis. There, thus exists a large amplification cascade. Consequently, neutralisation of a small amount of the growth factor early in the wound healing process leads to major effects later on. Moreover, in the early phases of wound healing, many key processes are regulated by a small number of growth factors, such as those released from degranulating platelets. However, within a few days of wounding, complex interacting networks of cytokine responses are established, such that it is much more difficult to obtain effects out of manipulating one or two cytokines: effects that can be produced early in the wound healing response before the interacting redundant cascades become established.

Neutralising antibodies to TGFß1 and TGFß2 markedly decrease scarring, such that there is no microscopic evidence of where the incisional wound was made and the dermal architecture is restituted to a normal basket weave pattern. Neutralising antibody therapy also reduces the number of monocytes and macrophages at the wound site, decreases the numbers of blood vessels and also decreases the early wound fibronectin content: effects which are consistent with low levels of transforming growth factor beta-1 and beta-2. By using isoform specific antibodies, we have determined that neutralisation of transforming growth factors beta-1 and beta-2 is required to give optimal anti-scarring effects. Neutralisation of TGFß3 has no anti-scarring effect at best and makes the scar worse in some instances. Conversely, addition of exogenous TGFß3 at the time of, or immediately after, wounding results in a marked improvement in scarring. It is therefore the ratio between TGFß3 on the one hand and TGFß1 and TGFß2 on the other which is important for scar formation. Decreasing the levels of TGFß1 and TGFß2 relative to TGFß3 appears to be the key to the anti-scarring therapy. This conclusion is supported by wound healing studies in transgenic mice, which either under or over-express TGFß1 or TGFß3. Antisense oligonucleotides to TGFß1 and TGFß2 administered before wounding also prevent subsequent scarring. For the antisense oligonucleotide therapy it is essential to deliver the antisense oligonucleotides before wounding and therefore this therapy is only applicable to elective surgery (the most common form of trauma). The antisense oligonuclcotide technology takes advantage of the transient permeabilisation of cells which occurs during wounding to achieve very high loading of the antisense oligonucleotides into target cells.

These studies have led to new therapeutic regimes which have been tested in experimental rodents and pigs and are now entering human clinical trial. Reagents in human clinical trial for anti-scarring e.g. in the central nervous system, the eye or the skin, currently include recombinant human phage neutralising antibodies to TGFß2 and TGFß1, antisense oligonucleotides to TGFß1 and 2, TGFß3 and plasmids expressing TGFß3 for gene therapy.

Transforming growth factor beta family members like most growth factors, are made as an inactive precursor. This precursor is subsequently activated by proteolytic cleavage to produce the active growth factor. Activation is therefore a key biological regulatory step. In the case of TGFß1, it is initially secreted as an inactive precursor associated with a larger protein transcribed from the same gene entitled 'the latency associated protein' (LAP). This LAP has three carbohydrate chains on two of which the terminal residues are the sugar Mannose-6-Phosphate. Activation of transforming growth factor beta is complex but depends in part on bonding of the Mannose-6-Phosphate /TGF-2 receptor, followed by a conformational change in the molecule, exposure of a protease sensitive site and cleavage of the active TGFß1 from the inactive LAP precurser. We have demonstrated that exogenous administration of Mannose-6-Phosphate can competitively inhibit binding of the TGFß latency associated peptide at the Mannose-6-Phosphate receptor, thus preventing activation of TGFß1 and hence inhibit scarring. The mode of delivery of the Mannose-6-Phosphate is crucial as the molecule is rapidly metabolised and appropriate vehicles have to be used to achieve the requisit tissue levels over the post-wounding period. However, single applications of Mannose-6-Phosphate in an appropriate vehicle at the time of wounding can markedly prevent scarring. These applications also reduce the number of monocytes and macrophages, blood vessels and early fibronectin content of the wounds similar to the effects seen with neutralising antibodies to TGFß1 and TGFß2. Mannose-6-Phosphate as an anti-scarring agent is currently in human clinical trial.

Manipulation of the levels of other growth factors, such as platelet derived growth factor and several interleukins early in the wound healing cascade can also have a scar modulating effect.

In parallel with the development of these novel antiscarring therapies, we have also devised both clinical and histological quantitative scales for the

assessment of scarring. These scales include validated visual analogue scales for the assessment of the macroscopic features of scarring, together with similar scales for the assessment of histological scarring and the development of three dimensional image analysis to quantitate changes in the structure of the dermis in man and animals.

Interestingly, our studies of ageing rodents and humans have demonstrated that the maximum inflammatory response and hence cytokine profile is present in young adults who scar worst. Conversely, in old age, the inflammatory response is reduced. The growth factor profile differs both quantitatively and qualitatively (with decreased levels of TGFß1 and TGFß2 and increased levels of TGFß3) and the quality of scarring is markedly improved. There are major differences in healing speeds and quality between males and females with age and between pre and post-menopausal females, indicating the importance of the hormonal milieu.

We hypothesise that acute wounds are phylogenetically optimised for speed of healing under dirty conditions. The evolutionary response is to maximise the inflammatory response and put into overdrive the cytokine cascade. This ensures that the wound heals very quickly and has multiple redundant mechanisms. This is doubtless important to prevent further bleeding from minor trauma or septicaemia from a slowly healing wound. However, this massive inflammatory response swamps out the endogenous regenerative capacity of the dermis and results in scarring. With contemporary hygiene, we can modulate this early cytokine profile, changing the ratios of various growth factors and cytokines. Such manipulated wounds heal just as quickly with no evident signs of infection but with markedly improved scarring. Such studies indicate that there is a wide therapeutic window for the control of scarring in man, as this is something which evolution has not optimised. Interestingly, similar mechanisms appear to operate in chronic fibrotic disorders, such as pulmonary fibrosis, liver cirrhosis, glomerular nephritis, indicating that fundamental investigations of the basis of dermal scarring and how it might be prevented may have a more widespread application in many common human fibrotic disorders.

Further Reading

Whitby DJ & Ferguson MWJ. Immunohistochemical studies of extracellular matrix growth factors in fetal and adult wound healing' In "Fetal Wound Healing: A Paradigm for Tissue Repair (eds. N.S. Adzick & M.T. Longaker), Elsevier Science Publishing Co., New York, 161-175, 1991.

Longaker M T, Whitby D J, Ferguson M W J, Harrison M R, Stern R. Studies in fetal wounds healing III. Early Deposition of Fibronectin distinguishes fetal from adult wound healing. *J. Pediatric. Surgery,* 1989; **24**: 799-805.

Longaker MT, Whitby DJ, Adzick NS, Crombleholme TM, Langer, JC, Duncan HW, Bradley SM, Stern R, Ferguson MWJ & Harrison MR Studies in Fetal Wound Healing, VI. Second and Early Third Trimester Fetal Wounds Demonstrate Rapid Collagen Deposition Without Scar Formation. *Journal of Pediatric Surgery*, 1990 **25**: 63-69.

Longaker MT, Whitby DJ, Jennings RW, Duncan BW, Crombleholme TM, Harrison MR, Ferguson MWJ and Adzick S Adult skin in the fetal environment heals with scar formation, *Surg. Forum*, 1990; **41**: 639-641.

Whitby DJ, Longaker MT, Adzick NS, Harrison MR, Ferguson MWJ Rapid epithelialisation of fetal wounds is associated with the early deposition of tenascin. *Journal of Cell Science*, 1991; **99**: 583-586.

Whitby DJ, Ferguson MWJ The extracellular matrix of lip wounds in fetal, neonatal and adult mice. *Development,* 1991; **112**(2), 651-668.

Longaker MT, Whitby DJ, Jennings RW, Duncan BW, Ferguson MWJ, Harrison MR, Adzick NS Fetal diaphragmatic wounds heal with scar formation. *Journal of Surgical Research*, 1991; **50**, 375-385.

Longaker M., Whitby DJ, Ferguson MWJ, Jennings EW, Lorenz HP, Harrison MR, Adzick NS Adult skin wounds in the fetal environment heal with scar formation. *Annals of Surgery*, 1994; **219**, 65-72.

Whitby DJ, Ferguson MWJ Immunohistochemical localisation of growth factors in fetal wound healing. *Developmental Biology*, 1991; **147**: 207-215.

Ferguson MWJ, Whitby DJ, Shah M, Armstrong J, Siebert JW, Longaker MT Scar formation: the spectral nature of fetal and adult wound repair, *Plastic and Reconstructive Surgery*, 1996; **97** (4), 854-860, 1996.

Shah M, Whitby DJ, Ferguson MWJ Fetal wound healing and scarless surgery In: Recent Advances in Plastic Surgery No. 5, Eds I.T. Jackson and B.C. Sommerlad, Churchill Livingstone, Edinburgh, 1-12, 1996.

Shah M, Foreman DM, Ferguson MWJ Control of

scarring in adult wounds by neutralising antibodies to transforming growth factor beta (TGFß) *Lancet*, 1992; **339**: 213-214.

Chamberlain J, Shah M, Ferguson MWJ The effect of suramin on healing adult rodent dermal wounds *Journal of Anatomy*, 1995; **186**, 87-96.

Shah M, Foreman D M, Ferguson MWJ Neutralising antibody to TGFß1, 2, reduces scarring in adult rodents *Journal of Cell Science*, 1994; **107**: 1137-1157.

Shah M, Foreman DM, Ferguson MWJ Neutralisation of TGFß1 and TGFß2 or exogenous addition of TGFß3 to cutaneous rat wounds reduces scarring. *Journal of Cell Science*, 1995; **108**: 985-1002.

Ferguson MWJ, Whitby DJ, Shah M, Armstrong J, Siebert JW, Longaker MT Scar formation: the spectral nature of fetal and adult wound repair, *Plastic and Reconstructive Surger,* 1996; **97** (4), 854-860.

Bardsley WG, Sattar A, Armstrong JR, Shah M, Brosnan P, Ferguson MWJ The Quantative Analysis of Wound Healing. *Wound Repair and Regeneration,* 1995; **3**(4), 426-441.

O'Kane S, Ferguson MWJ Transforming Growth Factor ßs and Wound Healing, *International Journal of Biochemistry and Cell Biology*, 1997; **29**, 63-78.

Ashcroft GS, Horan MA, Ferguson MWJ The effect of ageing on cutaneous wound healing, *Journal of Anatomy*, 1995; **187**: 1-26.

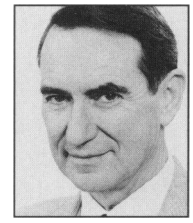
Ashcroft GS, Horan MA, Ferguson MWJ Ageing is associated with reduced deposition of specific extracellular matrix components, an upregulation of angiogenesis and an altered inflammatory response in a murine incisional wound healing model, *Journal of Investigative Dermatology*, 1997; **108**, 430-437.

Ashcroft GS, Horan MA, Ferguson MWJ The effects of ageing on wound healing: immunolocalisation of growth factors and their receptors in a murine incisional model. *Journal of Anatomy*, 1997; **190**, 351-365.

McCallion RL and Ferguson MWJ Fetal wound healing and the development of anti-scarring therapics for adult wound healing in The Molecular and Cellular Biology of Wound Repair 2nd ed Ed R.A.F. Clarke. Plenum Press, New York 561-600, 1996.

External Beam Radiotherapy in the management of subfoveal choroidal neovascular membranes of the eye:

A new treatment for an old disease



Desmond B Archer MB, BCh, DO, FRCS, FRCOphth
Professor of Ophthalmic Surgery, Royal Victoria Hospital

The exudative form of Age-Related Macular Degeneration (ARMD) is associated with a particularly poor visual prognosis and accounts for 88% of ARMD sufferers who are registered blind.[1] In this disease, characteristic changes occur in the posterior pole of the eye within the confines of the macula which is the region of the retina responsible for central vision. When visual loss results from progressive degeneration of the retinal pigment epithelium and photoreceptors the condition is known as dry macular degeneration. In a significant proportion of eyes there is invasion of the sub-pigment epithelial and sub-retinal spaces by new blood vessels originating from the choroid. The infiltrating vessels are enmeshed in fibrous inflammatory tissue constituting a choroidal neovascular membrane (CNVM).[2] The natural history of a CNVM is one of rapid expansion with increasing leakage of fluid and blood associated with progressive severe visual loss. The neovascular channels within the membrane eventually stop perfusing and involute with the development of a fibrous disciform scar. The morphogenesis of the scarring process destroys the retinal pigment epithelium and the photoreceptors and is incompatible with normal central visual function.

Laser photocoagulation has been used for many years to ablate those choroidal neovascular membranes which are located outside the foveal avascular zone.[3] Laser photocoagulation of the foveal avascular zone will of necessity destroy the foveal photoreceptors resulting in complete loss of the central 5° of visual field and an immediate fall in visual acuity. In 1991 the Macular Photocoagulation Study Group (MPS) showed that well-defined sub-foveal membranes no larger than 3.5 disc areas benefit from laser photocoagulation.[4] In this study, patients treated with laser photocoagulation showed on avèrage a 3.3 line fall in acuity from baseline while controls showed a 3.7 line drop at 12 months; a difference of 0.4 lines. With continuing follow up, at 18 months and at 24 months, treated patients had visual acuities which were one line or two lines of vision better than that which was found in the no treatment group.[4] However as already stated, treatment destroys the fovea and there is an immediate marked fall in visual acuity (on average a fall of 3 lines on the Snellen chart).[5] It is therefore questionable whether a long-term marginal visual benefit at the cost of an immediate significant deterioration in vision is worthwhile. Understandably alternative treatment modalities are being sought.

It has been known for a long time that ionising radiation can limit cell growth and division, with rapidly dividing cells showing a greater degree of susceptibility to the lethal effects of ionising radiation.[6] Ionising radiation has been used to limit contraction and scar formation in surgical wounds for over 40 years and the elegant studies of Grillo and Potsaid were the first to shed light on the primary role of fibroblasts in wound repair and their inhibition by radiation.[7] In our laboratories, studies carried out in the experimental animal have shown that low dose ionising radiation applied focally at the site of an ocular perforation causes a marked reduction in the vascularity of the granulation tissue with an associated decrease in the proliferation of scar tissue and traction retinal detachment. Focal radiotherapy did not adversely affect the adjacent healthy retina and choroid as evidenced by histological examination.[8] We have also determined the radiosensitivity of retinal microvascular endothelial cells in vitro and in vivo and the results indicate that a single dose of radiation in the region of 500 cGy is sufficient to arrest division in 99% of irradiated endothelial cells. [9]

In addition to the high degree of radiosensitivity of vascular endothelial cells, the use of radiation has other theoreticae advantages. Following laser, recurrent neovascularisation has been identified as the principal cause of continuing visual loss. It has been suggested that, the inflammatory element of the CNVM appears to be an important component in the formation of the membranes, release of enzymatic products and its remodelling.[10] Treatment of CNVM by laser photocoagulation results in damage to tissue which can evoke an inflammatory response with

further recruitment of macrophages. These inflammatory cells are potent inducers of neovascularisation through the production of cytokines and angiogenic growth factors.[11] As inflammatory cell recruitment is inhibited by low doses of ionising rays, treatment of the CNVM by this modality is unlikely to provoke recurrent neovascularisation. Thus the studies carried out in our laboratories have provided the theoretical basis for the use of low-dose ionising radiation as a suitable treatment modality in the management of sub-foveal CNVM of ARMD. The next logical step was a phase I/II Clinical trial to determine whether low-dose radiation to the macular region could influence the natural course of age-related sub-foveal neovascularisation. These phase 1/11 trials were commenced in 1990 and the results of these studies have been reported extensively in the scientific literature.[12-14]

Overview of results

Fifty three patients with sub-foveal neovascularisation on fluorescein angiography were identified for inclusion into the study. The angiograms of all these patients showed early leakage of dye seen as hyperfluorescence which increased in intensity and area and which involved the foveal avascular zone. The patients were fully counselled on the nature of their condition and treatment options available. From January 1992 those patients who fitted the MPS criteria for foveal ablation[4] were offered this treatment but all declined. Any patient with pre-existing ocular disease (eg. glaucoma, high myopia, chronic inflammatory or neoplastic disorders) was excluded as were those with systemic disorders (diabetes, uncontrolled hypertension) or a known life-threatening disease at enrolment into the study. Informed consent to participate in the radiotherapy study was obtained in all treated cases. Those patients who declined radiotherapy were followed up as a non-randomised comparison group (A total of 41 eyes received radiotherapy and 13 eyes of 12 patients were followed up as controls).

In the initial stages of the study (first 19 patients) two treatment regimes were used with patients receiving either lOGy (2Gyx5 fractions) or l5Gy (3Gyx5 fractions).[12] The analysis of the initial results showed stabilisation of central visual function in treated patients which was accompanied by regression of the neovascular membrane which was documented angiographically. By contrast central vision in the comparison group deteriorated significantly and the neovascular membrane was seen to expand. The long-term follow up data on 41 treated and 13 controls for periods up to 60 months confirmed that radiotherapy appeared to induce regression of CNVM which was associated with maintained visual acuity (Table 1). In those patients who received IOGy, the rate of regression of the neovascular membrane was slower than that observed in those who received 15Gy although final visual acuity was similar between groups. The lack of statistical significance in visual outcome between these two groups may have been due to the small size of the pilot study or the absence of any real difference between the two doses of radiotherapy.

3Gy fractions are known to be associated with a higher risk of optic neuropathy hence a new treatment regime was instituted consisting of 12Gy delivered as 2Gy fractions x 6. In order to allow for the radiobiological effectiveness of these fractionation schedules the nominal standard dose (NSD) which is expressed in rets was calculated for each treatment regime. In a seminal piece of work Harris and Levene[15] have shown that there was a significant increase in the risk of visual loss not only with fraction sizes exceeding 2 Gy but also when the NSD exceeded 1500rets. In practice the majority of radiotherapists do not prescribe in fraction sizes in excess of 2Gy particularly when the field of radiotherapy includes the brain and the eye. These are important considerations as ARMD is a non-life-threatening condition and since central vision is already poor in ARMD sufferers, it would be questionable clinical practice to compromise optic nerve function by any therapeutic intervention. In this context it should be noted that at least one investigator has reported sight-threatening retinopathy in a patient with dysthyroid ophthalmopathy treated with external beam radiation at a total dose of 20Gy given in 10 fractions over periods of 10 to 14 days.[16] Our calculations based on the information provided in this paper show that the NSD in these patients was in the region of 1120 to 1160 rets and thus we feel it prudent to restrict the dose and fraction size to ensure a ret value below 1000. In our study the NSD which is expressed in rets did not exceed 1000 rets in the 10 or 12Gy group and 1200 rets in the 15Gy group. On the basis of our clinical impression we are now electing to treat all subsequent patients with 12Gy each as the NSD is kept to below 1000 rets, giving us a wider margin of safety than a dose of 15Gy.

Throughout the duration of the study, our patients were monitored for any possible adverse side effects which could be attributed to radiotherapy. Transient conjunctival irritation was reported by one patient with resolution within three weeks from radiotherapy

TABLE 1

Summary of Published Phase I/II studies

Group	Radiation	Dose	Fraction	NSD	No. Treated	Cont	Reference	Results
Chakravarthy et al	6 MV P	10 15	5 x 2 5 x 3	571 857	19	7	BJO 1993;77:265-273	Stabilisation of VA in 63% at 12 months
Bergink et al	16MVP	8 12 18 24	Ix8 2x 6 3 x 6 4 x 6	900 952 1224 1417	17	none	Graefes. Arch 1994; 232: 591-598	Stabilisation of VA with doses in excess of 12Gy in 48% at 12 months
Bergink et al	16 MV P	8 12 18 24	1x 8 2x 6 3 x 6 4 x 6	900 952 1224 1417	40	none	Doc Ophthal 1995;90: 67-74	Stabilisation of VA with doses in excess 12Gy in 57% at 18 months
Finger et al	6 MV	14.4	8 x 1.2 10x 1.44	695 642	75	none	Ophthalmol 1996; 103: 878-889	Stabilisation of VA in 48% at 9 months
Berson et al	6 MVP	14 15	8 x 1 75 1 x 1.88	G86 735	52	none	Int. J Radiat Oncol. Biol, 1996;36:861-865	Stabilisation of VA in 79% at 7 months
Freire et al	Not stated	14.4	8 x 1.8	685	39	none	Int. J. Radiat Oncol. Biol, 1996;36:857	Stabilisation of VA in 92% at 3 months
Valmaggia et al	6 MeV E	5 8	4 x 1.25 4 x 2	409 493	46	none	Klin. Monats 1996; 208:315-317	Stabilisation of VA with doses in excess of 8Gy in 72% at 6 months
Hart et al	6 MV P	10 15	5 x2 5 x 3	571 857	41	13	BJO 1996; 80:1046-1050	Stabilisation of VA in 65% at 48 months

and thereafter this patient has remained asymptomatic. Another patient suffered transient alopecia areata involving an area 2cm diameter at the beam exit point. Both these patients received 15Gy. Significant progression of cortical and posterior subcapsular lens opacities with accompanying loss of acuity was observed in the treated eyes of two patients (both had received 15Gy) after 36 months post-treatment. Cataract extraction and intraocular lens insertion has been carried out in both these patients. Post-surgery, vision returned to the level measured prior to the onset of lens opacities. Radiation induced retinal

vasculopathy (microvascular abnormalities, leakage and cotton wool spots) or optic neuropathy (disc pallor) were not observed clinically. Angiograms were scrutinised for evidence of retinal microvascular abnormalities and none was found.

Discussion and Summary

Various novel treatments have been proposed in recent years for the management of CNVM untreatable by laser. Interferon α 2a which is a potent inhibitor of vascular endothelial cell proliferation and migration in culture has been used systemically in the treatment of sub-foveal CNVM.[17] To date this treatment option has not proved significantly effective and it is also associated with severe secondary effects which may be local or systemic. Other experimental therapies involve the use of thalidomide, retinoids, and amiloride[19] all of which are known to possess antiangiogenic properties. The results of such treatments are as yet unavailable. Surgical excision of CNVM has been attempted[20] but the outcome is significantly better in younger patients with presumed ocular histoplasmosis rather than ARMD.[21] Transposition of the retina has also been considered, however these are all highly invasive procedures and it is doubtful whether central visual function can be preserved or improved by such drastic surgery.

Radiotherapy is attractive as it can be delivered to a precise location, it is non-invasive and has no systemic side effects at low doses. Since the publication of our original studies on radiotherapy in ARMD there has been increasing interest in this treatment modality .External beam radiation as employed by other centres in the management of CNVM has included dose regimes ranging from 8Gy to 24Gy (Table 2). The fractionation schedules varied considerably and fraction sizes as large as 8Gy have been used.[22-23] Where cyclotron facilities were available proton beam irradiation has been used which with its highly collimated beam and sharply defined Bragg Peak effect has theoretical advantages in the treatment of CNVM.[24] Alternatively brachytherapy rather than teletherapy has also been tried with some investigators using Pd 103 or Sr 90 plaques (beta emitters) designed to deliver doses between 12.5 and 15Gy to the region of the CNVM.[25-26] Most of these recent reports suggest a positive treatment effect in the short term. Although no adverse effects have been reported in any of these studies it should be noted that the follow-up times have in general been less than one year.

In summary the basis for the use of ionising radiation to inhibit growth of CNVM of ARMD has been underpinned by many years of information gleaned from basic laboratory studies. These studies are now quoted extensively in the literature by researchers worldwide as the rationale for commencing clinical trials of this treatment modality in ARMD. Our preliminary phase I/II trials are also enshrined in

TABLE 2

Distribution of Visual Acuity in Treated Eyes Between O and 48 months post Radiotherapy

	O	3	6	12	18	24	36	48
LogMar (Snellen)	n=41	n=41	n=41	n=41	n=30	n=29	n=25	n=9
O.O 0.6 (6/6 - 6/24)	27%	29%	39%	26%	23%	21%	20%	45%
0.78 - 1.1 (6136 -5/60)	49%	46%	46%	42%	47%	38%	56%	33%
1.2-1.78 (4/60 -1/60)	24%	25%	15%	32%	36%	41%	24%	22%

Distribution of Visual Acuity in Control Eyes Between 0 and 48 months post Radiotherapy

	O	3	6	12	18	24	36	48
LogMar (Snellen)	n=13	n=13	n=13	n=13	n=12	n=l0	n=8	n=4
0.0- 0.6 (6/6 6/24)	47%	31%	31%	8%	0%	0%	0%	0%
0.78 - 1.1 (6/36 -5/60)	38%	54%	31%	46%	58%	40%	38%	50%
1 3 -1.78 (4/60 -1/60)	15%	15%	38%	46%	42%	60%	62%	50%

the literature as they were the first to explore the potential of radiotherapy in the management of subfoveal CNVM. A number of multicentre randomised controlled studies are now progressing and a more definitive answer should be available very soon.

ACKNOWLEDGEMENT

These studies have been supported by the Wellcome Trust, UK and the Medical Research Council UK.

REFERENCES

1. Kahn HA, Moorehead HB. Statistics on blindness in the model reporting area 1969 1970. United States Department of Health, Education and Welfare Publication No (NIH) 73-427, Washington DC, US Government Printing Office, 1973.

2. Gass JD. Pathogenesis of disciform detachment of the neuroepithelium. III. Senile disciform macular degeneration. *Am J Ophthalmol*, 1967; **63**:617-644.

3. Macular photocoagulation study group. Argon laser photocoagulation for neovascular maculopathy. Three year results from randomised clinical trials. *Arch. Ophthalmol*, 1986; **104:** 694-701.

4. Macular photocoagulation study group. Laser photocoagulation of subfoveal neovascular lesions in age-related macular degeneration. *Arch. Ophthalmol*, 1991; **109**:1220-1231.

5. Macular Photocoagulation Study Group. Visual outcome after laser photocoagulation for sub-foveal choroidal neovascularisation secondary to age-related macular degeneration. The influence of initial lesion size and initial visual acuity. *Arch Ophthalmol*, 1994;**112**:480-488

6 Arlett C.F and Harcourt S.A. Survey of radiosensitivity in a variety of human cell strains. *Can. Res*, 1980; **40**:926-932

7. Grillo HC, Potsaid MS. Studies in wound healing. Retardation of contraction by local x-irradiation and observations relating to the origin of fibroblasts in repair. *Ann Surg*., 1961; **154**:741-753

8. Chakravarthy U., Biggart JH., Gardiner TA., Archer DB. & Maguire CJF. Focal irradiation of perforating eye injuries with Iodine-125 plaques. *Curr. Eye. Res.* 1989; **8**:1241-1250

9. Chakravarthy U & McQuaid M. Radiosensitivity of retinal capillary endothelial cells and pericytes. 30lh Meeting of the Association for Eye Research, Montpellier. p89 1989

10. Lopez PF, Grossniklaus HE, Lambert HM, AaberEg TM, Capone A, Sternberg P.Jr & L'Hernault N. Pathologic features of surgically excised subretinal neovascular membranes in age-related macular degeneration. *Am. J. Ophthalmol*, 1991;**112**:647-656.

11. Schultz GS & Grant MB. Neovascular growth factors. *Eye* 1991; **5**: 170-180

12. Chakravarthy U, Houston RF & Archer DB. Treatment of age-related sub-foveal neovascular membranes by teletherapy: A pilot study. *Brit. J. Ophthalmol*, 1993; **77**:265- 273

13. Hart PM, Archer DB, Chakravarthy U. Asymmetry of disciform scarring in bilateral disease when one eye is treated with radiotherapy. *Brit J Ophthalmol*, 1995; **79**:562-568

14. Hart PM, Archer DB, Houston RF, Chakravarthy U. Teletherapy for choroidal CNVM. The results of prolonged follow up. *Brit. J. Ophthalmol*, 1996;**80**: 1046-1050

15. Harris JR & Levene MB. Visual complications following irradiation for pituitary adenomas and craniopharyngiomas. *Radiology*; 1976; **120**: 167-171

16. Miller ML, Golberg SH, Bullock JD. Radiation retinopathy after standard radiotherapy for thyroid-related ophthalmopathy. *Am. J. Ophthalmol*, 1991;**112**:600-601

17. Kirkpatrick JNP, Dick AD and Forrester JV. Clinical experience with interferon alpha 2a for exudative age-related macular degeneration. *Brit. J. Ophthalmol*, 1993; **77**:766-770

18 Tang Y. Interferon friend or foe. *Arch. Ophthalmol*, 1995; **113**:987

19. Guyer DR. Experimental therapies for exudative age-related macular degeneration American Academy Abstracts 1995 p60-67

20. Thomas MA, Grand G, Williams DF, et. al Surgical management of sub-foveal choroidal neovascularisation. *Ophthalmology*, 1992; **99**: 952-968

21. Berger AS, Kaplan AG. Clinical experience with the surgical removal of sub-foveal neovascular membranes. *Ophthalmology*, 1992; **99**:969-976

22. Bergink GJ, Deutman AF, van den Broek JFCN, van

der Maazen RWM. Radiation therapy for subfoveal choroidal neovascular membranes in age-related macular degeneration. Graefes Arch. Clin Exp. *Ophthalmol*, 1994; **232**:591-598

23. Bergink GJ, Deutman et al. Radiotherapy for age-related sub-foveolar choroidal neovascular membranes. *Docum. Ophthalmol*, 1995; **90**:67-74

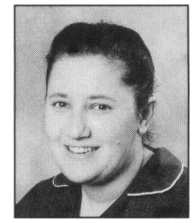
24. Slater JD, Ln Loredo, LT Yonemoto et al. Proton beam irradiation of subfoveal choroidal neovascularisation in age-related macular degeneration. *Invest Ophthalmol.* 1995; **36**:1020

25. Immonen I, Jakkola A, Heikkonen. Treatment of subfoveal choroidal neovascular membranes using strontium 90 plaques irradiation. *Invest Ophthalmol*, 1995; **36**:1022

26. Finger PT Radiotherapy for subretinal neovascularisation. *Invest Ophthalmol,* 1995, **36**:1021

Wound Healing - from poultices to maggots.

(A short synopsis of wound healing throughout the ages).



Jean Donnelly BSc (Hons) Health Studies, RGN, O.N.C.
Tissue Viability Nurse, Royal Hospitals

Pictographs, ancient surgical tools and fossilised bodies bare witness to the fact that wound care is one of the earliest forms of medicine practised by man. Unfortunately, early scientific knowledge existed alongside religious and superstitious ideas. In some societies chronic wounds such as leg ulcers were viewed as an outward manifestation of evil. Treatments often involved making the body uninhabitable to demons, e.g. by beating, starving and torturing the patient.

As societies became more civilised they began to study the effects of various medicaments on wound healing. In China, the colourful Yellow and Red Emperors compiled the first book of herbal treatments. In Egypt, a 100 page encyclopaedia of medicine (found within the Ebers papyrus) records the fact that various salves and dressings could be made from resin, honey, lard and beef. By around 600 BC surgery in India had advanced to the point that Sasruta was able to describe rhinoplasty and the cauterisation of wounds. This was particularly useful as 'nasal amputations' were a frequent punishment of the time.

Unfortunately, wound management remained something of a hit or miss affair. Those fortunate enough to be treated by the followers of the great physician Hippocrates would have had their wounds bathed in warm sea water and bound in olive leaves - with a little stretch of the imagination this regime could be likened to the modern practice of cleansing a wound with normal saline and applying a moist, non-adherent dressing. The less fortunate suffered immeasurable harm through,

> *"balsams, astringent gums, ointments and other idle inventions for mundifying, incarning, or cicatrizing of wounds" (Dictionary of Arts and Sciences, 1815)*[1]

As we approach the Millennium one would expect doctors and nurses to have a clear understanding of modern wound care practices. However, section 1 of the Oxford Textbook of Surgery (1995), opens with a quote[2] which states that,

> *'Nowhere is the gap between basic research and clinical application more glaring than in the biology of wound healing'*

Despite the plethora of research into modern wound management many practitioners continue to treat wounds with products which can harm healing tissues. For example, it is still common practice to pack cavity wounds with gauze. Electron micrographs have shown that newly formed capillary loops can grow through the weave of the gauze mesh. When the dressing is removed, the newly-formed granulation tissue can be literally ripped apart. In addition, fibres from the gauze are shed into the wound bed and have the potential to act as a foci for infection. Interestingly, saline soaks (in the form of 'wet to dry' dressings) are used as a method of debridement in some areas of America and the Third World. One can only wonder why practitioners in the UK continue to use them as a primary contact layer for a clean granulating wound.

An anonymous surgical treatise dated 1446 was recently discovered in the British library. Bound within, is a 9000-word manuscript on ulcers which showed that medieval leg ulcer management was systematic and logical. This manuscript highlights the importance of classifying the ulcer and of using bandages to treat venous ulcers. It also highlights the importance of holistic care and makes great reference to the importance of treating other illnesses, giving analgesia (albeit in the form of cannabis and alcohol) and improving the patients nutritional status. In view of the fact that many modern day patients with leg ulcers have not had their ulcers diagnosed and therefore appropriately treated, it would seem that we still have a lot to learn from our ancestors.

Most practitioners will be aware that the use of antiseptics as an aid to modern wound healing is the subject of heated debate. Antiseptics were developed in the latter half of the 19th Century and the early part of the 20th Century by Lister, Fleming and others. A review of the literature of 1915 showed that the surgeons of the day believed that antiseptics were responsible for saving the lives of many people,

particularly the wounded soldiers of the Great War[3]. Indeed, whilst lecturing on war wounds, Bowlby, Surgeon in Ordinary to the King, said,

> *".... and if I am told that the antiseptics I have employed to the skin and to the wound have played no part, and that sterilised water would have done as well, I should reply that I know by experience that until we did use antiseptics very thoroughly we did not get these results, and that the wounds which have been treated in the manner described have done consistently better than those of previous years."*

Despite this glowing testimony modern research has questioned the ritualistic use of antiseptic solutions. For example, a much quoted paper by Leaper and Simpson[4] indicates that hypochlorites, e.g. Eusol (Edinburgh University Solution of Lime) were particularly toxic to fibroblasts, granulation tissue and permanently damaged the micro circulation. They, therefore, suggested that all topical antiseptics should be used with caution[5,6]. It is interesting to note that Fleming was very aware of the side effects of antiseptics. He stated that,

> *".. It is necessary, in the estimation of the value of an antiseptic, to study it's effect on the tissue more than it's effect on the bacteria".*

Although some research would appear to support the fact that antiseptics are cytotoxic, unequivocal, empirical evidence on the use of the same is not available. However, most wound care experts feel that the evidence is strong enough for them to recommend physiological saline (0.9%) as the cleansing agent of choice.

Prior to the invention of the 'Gamgee' dressing (1880) most wounds were dressed with oakum - a fibrous mass of unpicked old rope. Thomas states[7] that this,

> *"must have represented a significant hazard to the patient from prior contamination by chemical, physical and microbiological agents."*

Although cotton wool was readily available the greases present in its natural state rendered it virtually non absorbent. Samson Gamgee discovered that he could remove the hydrophobic components of cotton wool through a bleaching process. Gamgee tested the clinical effectiveness of his invention by applying it to one small wound[8].

Nearly 120 years later Gamgee-type dressings are still used in the treatment of large and or heavily exudating wounds. Although these dressings are relatively cheap their cost effectiveness can be questioned on two counts. The first is that they are not an 'ideal' primary wound contact layer (see Table), i.e they adhere to and shed fibres into the wound bed and they do not maintain a moist wound healing environment. The second is that they readily allow 'strike-through' of exudate which effectively creates a path for organisms to colonise or infect healing tissue.

TABLE

Key Components of the Ideal Dressing[27]

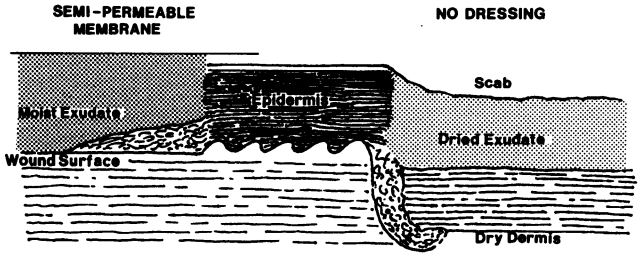
- Maintains a high humidity at the wound - dressing interface
- Removes excess exudate and toxic components
- Allows gaseous exchange
- Allows no leakage of exudate
- Maintains wound temperature
- Impermeable to bacteria
- Free from particulate and toxic contaminants
- Does not disintegrate when moist
- Allows trauma-free dressing change
- Comfortable for the patient

During World War I Lumiere developed 'tulle gras' (paraffin gauze). As paraffin is an excellent carrier for medicaments, e.g. antibiotics, medicated variations soon appeared. Common examples include Sofra-Tulle and Fucidin-Intertulle. Early studies indicated that medicated tulles could reduce the risk of sepsis and promote healing. However, later studies began to highlight serious side effects such as contact dermatitis and the emergence of resistant strains of micro-organisms[9,10].

Although paraffin gauze is sold as a low adherent primary contact material, most nurses would argue to the contrary. Unless changed frequently Paraffin gauze dries and become incorporated into the granulating tissue. It is not uncommon for patients to suffer considerable pain as the dressing is gently prised from the wound bed (irrigating the dressing with water or saline is of limited benefit as paraffin is hydrophobic in nature). In some instances the pain can be severe enough to warrant the use of narcotic analgesia or Entonox[11]. If the dressing has adhered its removal will inevitably result in the removal of new granulation or epithelial tissue. Visible evidence of trauma includes the characteristic criss-cross pattern which is present

on the wound bed and bleeding[12]. In the light of these problems and the emergence of more sophisticated wound management products the use of tulle is in general decline.

The concept of moist wound healing is commonly attributed to the work of Dr. George Winter in 1962[2]. Winter's research unequivocally proved that wounds heal two to three times quicker in a moist environment. Under dry conditions the bed of an open wound rapidly dries out and forms a scab. New epidermal cells burrow under this scab until they locate a moist environment, so extending the healing phase. Once they find a moist environment they will migrate across the wound. Today a moist environment can be created by a rapidly expanding array of modern wound care products. These include hydrocolloids, alginates, hydrogels and hydropolymer foams. The type of product chosen usually depends on the depth of tissue damage, the type of tissue in the wound bed and the level of exudate.



Necrotic tissue in the wound bed will significantly delay and in some cases prevent healing. If the limb is viable, the necrotic matter must be removed. Sharp debridement is the quickest method. However, in instances where sharp debridement is not appropriate various topical applications can be effective. These include hypochlorites, enzymatic agents, hydrogels and larvae.

Hypochlorites, e.g. Eusol, are non selective. They will remove viable as well as non viable tissue. Despite this and the pre stated adverse effects some surgeons find hypochlorites useful in the preparation of an area for grafting. However, the Welsh Centre for the Quality Control of Surgical Dressings in Bridgend[13] calculated that it would take about 100 ml of Eusol to dissolve 1 gram of slough. In their opinion this can be achieved more effectively by modern wound care products, e.g. hydrogels.

Enzymatic products such as streptokinase/ streptodornase act to liquefy slough. However, the topical application of streptokinase has been shown to result in a significant production of anti-streptokinase antibody. The production peaks at one month and then declines over a six month period. It is suggested that it may be prudent to avoid the use of topical streptokinase in patients who are at risk of coronary artery thrombosis. It is also suggested that if a thrombolytic agent is required within six months of administrating topical streptokinase/ streptodornase, intravenous streptokinase should be withheld in favour of an alternative thrombolytic agent[14,15].

Hydrogels actively rehydrate devitalised tissue by donating water to the desiccated matter. The rehydration process creates a moist environment which facilitates autolysis. The efficacy of hydrogels is reduced in the presence of excess exudate. In this instant it is better to use a product such as an alginate which will use (absorb) the exudate to produce a gel.

Although the use of larvae (Biotherapy) may seem radical to some, the use and effectiveness of the same has been known for hundreds of years. Indeed in the 1st quarter of this century larvae of the common green-bottle (Lucilia Sericata) was widely used in the management of infected and necrotic wounds. Their use simply declined with the advent of the widespread use of antibiotics in the 1940s[16]. The first therapeutic use of maggots is credited to J. F. Zacharias, a Confederate medical officer during the American Civil War. Zacharias reported that,

"Maggots in a single day would clean a wound much better than any agents we had at our command" [17,16].

During World War I Baer, an orthopaedic consultant, had occasion to treat two wounded soldiers who had been left lying on the battlefield for a week. Baer found that although the soldiers' compound fractures and abdominal wounds swarmed with maggots the wounds were granulating and free from infection. Later, as a clinical professor of orthopaedic surgery, Baer decided to use maggots to treat several cases of intractable osteomyelitis. The wounds healed in six weeks[18].

The use of larvae became very popular in the 1930's, so much so that the larvae of the green-bottle fly were produced commercially by Lederle. Many papers highlighting their therapeutic effectiveness, particularly in the management of oestomyelitis, appeared in the medical journals[19,20,21].

Although the use of antibiotics resulted in a decline in the use of larvae, papers reporting the beneficial effects of myiasis appeared from time to time[22,23]. In latter years the emergence of antibiotic-resistant strains of bacteria has lead to a renewed interest in larvae.

Larvae are thought to combat wound infection in one of two ways. The most popular theory is that they ingest micro-organisms which are then destroyed in their gut. However, a few of the early papers refer to the fact that larvae exude a broad spectrum antibacterial substance known as allantoin[24,25]. Unfortunately, the clinical significance of allantoin has not been fully investigated[16].

Sterile larvae, which are approximately 2 mm long, are introduced into the wound using an aseptic technique. The larvae produce a powerful mix of proteolytic enzymes which liquefy necrotic debris. The liquefied material is then re-absorbed and digested. Under favourable conditions, larvae rapidly increase in size, reaching 8 - 10 mm when fully grown. The larvae are removed after a maximum of 3 days. Thomas[16] states that larvae are a potent therapeutic tool and must be used with caution. The main contraindications would appear to be wounds with a tendency to bleed.

In the past dressing materials were used to clean and protect wounds, today they are used to enhance wound healing by creating the ideal environment for the natural wound healing processes to take place. Futuristic dressings offer something different. Through a process known as Tissue Engineering, dressings containing growth factors, extracellular matrix proteins (collagen, fibronectin and tenascin) and human dermal fibroblast cells are being developed. Some of these dressings actually seed fibroblasts into non healing wounds. As one would suspect these dressings are expensive - approximately £300.00 per piece. However, they can be applied on an out patient basis and the subsequent saving on a hospital admission may make them a very cost effective option.

Of course, in Ireland we do not need 'fancy' dressings as many people possess 'the cure'! Unfortunately, the cure can range from a poultice of poteen, cow dung, lard, grass, and marshmallow to the application of linen taken from a corpse. The fact that well educated people with chronic wounds choose to undertake 'the cure' would indicate that some aspect of modern practice (or some modern practitioners) is failing to meet their needs.

Plato stated that,

> *"the cure of the part should not be attempted without treatment of the whole"* [26]

This statement embodies the philosophy of many past and present wound management strategies. In other words wound management is more than poultices and maggots, it means ensuring the physical and psychological comfort of the patient, treating underlying disease, ensuring appropriate pain relief and applying an evidence based wound care product.

REFERENCES

1 Ryan TJ. Stick or stitch. *Wound management* 1993; **4**: (2) 58.

2 Cherry GW, Hughes MNA, Kingsworth AN, Arnold FW. The Oxford Textbook of Surgery. 1995; Oxford University Press: New York.

3 Sinclair RD, Ryan TJ. A great war for antiseptics. *Wound Management.* 1993; **4**: (1) 16-18 .

4 Leaper DJ, Simpson RA. The effect of antiseptics and topical antimicrobials on wound healing. *Journal of Antimicrobial Chemotherapy* 1986; **17**: (2) 135-137.

5 Tantnall FM, Leigh IM, Gibson JR. Comparative study of antiseptic toxicity on basal keratinocytes, transformed human keratinocytes and fibroblasts. *Skin Pharmacol* 1990; **3**: (3) 157-163.

6 Lawrence JC. The use of antiseptics in wound care. *Journal of Wound Care.* 1996; **5**: (1) 44-45.

7 Thomas S. Absorbent dressings. *Journal of Wound Care.* 1997; **6** :(2) 60.

8 Gamgee J. Absorbent and medicated surgical dressings. *Lancet* 1880; **1**: 127.

9 Kirton V, Munro-Ashman D. Contact dermatitis from neomycin and framycetin. *Lancet* 1965; **2**:138-139.

10 Reynolds JEF. (ed.) Martindale; The Extra Pharmacopoeia. (1989) Pharmaceutical Press: London.

11 Thomas S. Pain and Wound Management. *Community Outlook* 1989; **85**: 11-15.

12 Thomas S. Low adherence dressings. *Journal of Wound Care.* 1994; **3**: (1) 27-30.

13 Welsh Centre For The Quality Control of Surgical Dressings. *The dressing times.* 1990; **3**:(1) 3-4 .

14 Green C. Antistreptokinase titres after topical streptokinase. *Lancet* 1993; **341**: 1602-1603.

15 Bux M, Baig MK, Rodrigues E, Armstrong D, Brown A. Antibody response to topical streptokinase. *Journal of Wound Care.* 1997;**6**: (2) 70-73.

16 Thomas S, Jones M, Shutler S, Jones S. Using larvae in modern wound management. *Journal of Wound Care*. 1996; **5**: (2) 60-69.

17 Chernin E. Surgical maggots. *Southern Medical Journal*. 1986; **79**: (9) 1143-1145.

18 Baer WS. The treatment of chronic osteomyelitis with the maggot (larva of the blowfly). *Journal of Bone and Joint Surgery*. 1931; **13**: 438 - 475.

19 Liningstone SK. Maggots in the treatment of chronic osteomyelitis, infected wounds and compound fractures. *Surg. Gyn. Obst.* 1932; **54**: 702-706.

20 Wilson EH, Doan CA, Miller DF. The Baer maggot treatment of osteomyelitis; preliminary report of 26 cases. *JAMA*. 1932; **98**: 1149-1152.

21 Buchman J. The rationale of the treatment of chronic osteomyelitis with special reference to maggot therapy. *Ann Surg*. 1934; **99**: 251-259.

22 Bunkis MD, Ghernis, Walton R. Maggot therapy revisited. *West J Med* 1985; **142**: 554-556.

23 Morgan D. Myiasis: the rise and fall of maggot therapy. *Journal of Tissue Viability*. 1995; **5**:(2) 43-51.

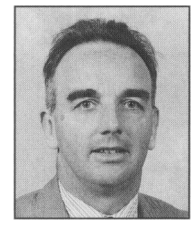
24 Robinson W. Stimulation of healing in non-healing wounds by allantoin occurring in maggot secretions and of wide biological distribution. *Journal of Bone and Joint Surgery* 1935; **17**: 267-271.

25 Pavillard ER, Wright EA. An antibiotic from maggots. *Nature* 1957;**180**: 916-917.

26 University of Dundee. The wound programme. Centre for Medical Education, Dundee 1992; in conjunction with Perspective: London.

27 Turner TD. Which dressing and why. In Westby, S (ed.) 1985; Wound Care. Heinemann Medical: London.

The Space Time Continuum of Neurorehabilitation



John P McCann MD, FRCP

Consultant in Rehabilitation Medicine
Royal Victoria Hospital

BACK TO THE FUTURE ?

It is apposite as we approach the third millennium, and celebrate the beginning of a third century of medical care in the Royal Victoria Hospital, that we consider the place of the "third phase of medical care" both now and in the future. This was the term applied by Howard A. Rusk to rehabilitation in the period immediately following the Second World War[1]. Rusk is regarded as the pioneer of medically led rehabilitation expounding the philosophy:

> *"medical care can not be considered complete until the patient with a residual physical disability has been trained to live and work with what he has left".*

Although the terminology and emphasis has changed in the intervening years, this remains the central principle underpinning the practice of neurorehabilitation today. Neurorehabilitation is indeed the application of the principles and practice of rehabilitation to those persons disabled as a result of neurological illness or injury. It's practice is not new, although it has advanced.

In 1949 Dr. Rusk described a report of neurorehabilitation in treating 130 patients with chronic neurological disease all but two of whom were veterans of the First World War. Many of these had been bed-bound for ten years and after nine months of physical medicine rehabilitation all but ten had shown worthwhile permanent improvement[2]. While the nature of their physical disability is not detailed, this unblinded and uncontrolled study does demonstrate that even at a late stage,that rehabilitation is effective. We are still having to prove the benefits of rehabilitation as we seek to achieve service development, despite such evidence being available.

SERVICE DEVELOPMENT

Following World War Two, two separate models of service delivery were developed. Rusk pioneered general rehabilitation facilities where people disabled due to various conditions were treated by a therapy team under the direction of a specialist in Physical Medicine and Rehabilitation. Indeed in 1947, he was the Chief of Physical Medicine and Rehabilitation Service at Bellevue Hospital in New York, the first comprehensive total Medical Rehabilitation Program in America. This has formed the basis for similar units and programmes throughout USA, UK and Europe.

An alternative concept, which for at least one group of patients has been fully accepted, is the specialist unit dealing with all phases of care for persons with a specific cause for their disability. Sir Ludwig Guttman[3] pioneered the specialised Spinal Injuries Unit, incorporating acute medical and surgical care with specialised rehabilitation for a single condition. The success of this model is apparent, with centres such as Stoke Mandeville Hospital developing a world wide reputation and the concept gaining acceptance worldwide. The concept of pure specialist Spinal Injuries Units treating a single condition is under critical review and Spinal Injuries specialists perceive themselves as being under threat from Rehabilitation Medicine. Already in some centres, there is a shift towards integration of service under the heading of Neurorehabilitation Units. The integrated acute care and rehabilitation service has now gained acceptance in management of Stroke with the development of acute Stroke Units and Stroke Rehabilitation Units being shown to influence both mortality and morbidity[4,5,6].

BRAIN INJURY REHABILITATION

The development of specialised services for brain injured patients has, surprisingly given the size of the problem, lagged behind those services outlined above. Gradually, however, recognition of their problems, again following war - namely the Seven-Day War in Israel in 1975, and the use of appropriate therapeutic interventions for cognitive and behavioural dysfunction stimulated the development of brain injury rehabilitation[7].

During the 1980s there was a very rapid expansion in specialised brain injury programmes in the United States and this has to a lesser degree been mirrored in

the United Kingdom. Supraregional highly specialised units such as the Kelmsley Unit at St.Andrew's Hospital in Northampton and The Royal Hospital for Neurodisability Putney have been to the fore in head injury management in Great Britain with many other facilities and services now being established throughout the country. Most of these are in the private sector with as yet no network of head injury units to match the network of spinal injuries units despite the much greater incidence of brain injury and the greater complexity of problems that it presents.

The lack of such a network, with an agreed approach to care by those involved, means that few areas of the country, if any, have an integrated programme of care for people with brain injury. Not only must such a programme of care deal with the acute and sub-acute periods, but a range of services within the community setting are required for long term problems, mainly of cognition and behaviour, but also physical disability.

MODELS OF SERVICE DELIVERY

Cope[8] has defined the elements of comprehensive brain injury rehabilitation as:

1. Expert medical and nursing care in directing and providing the rehabilitation process
2. The prevention of secondary deterioration
3. Maximisation of natural recovery processes
4. Facilitation of incremental functional gain through specific (rehabilitation) intervention
5. Provision of an optimal environment for neurological recovery
6. Provision and teaching of compensatory techniques including cognitive strategies
7. Provision of appropriate equipment
8. Provision of adaptive environmental modifications

These various elements are required throughout the space time continuum of brain injury rehabilitation.

Burke[9] has reviewed the range of models of brain injury rehabilitation including the comprehensive centre, cognitive rehabilitation; behaviour rehabilitation, slow-stream rehabilitation; coma arousal programme, acute, outpatient, transitional and vocational rehabilitation programmes. The evidence indicates that, apart from coma arousal the efficacy of which remains unproven, all these programmes have a place in brain injury rehabilitation services.

It is axiomatic that understanding of the physical, cognitive and behavioural problems and the use of specific rehabilitation measures for them will be required in the temporally separate rehabilitation programmes to ensure their success. It appears self evident that the earlier rehabilitation is begun the more likely it is to be effective.

EARLY REHABILITATION

Delay into rehabilitation programmes has been shown to be associated with the development of avoidable complications, which by their presence further impede progress in rehabilitation[10]. Although this paper is almost thirty years old, the complications of "frozen shoulders", joint deformities, decubiti and indeed poor nutritional status remain an issue for patients who do not gain early access to an inpatient rehabilitation programme.

Cope and Hall[11] have demonstrated that delay of patients into a specialised rehabilitation programme leads to both an increase in the length of time within the programme and the patients total length of stay. Mackay et al[12] have studied the provision of rehabilitation therapies at an earlier stage again. They report that when therapy was begun for patients while they were still in coma there was a significant improvement on a range of outcome measures. The benefits of early rehabilitation for these patients are reduced length of stay and improved functional status at discharge. In the Cope and Hall study continuing benefits were noted in terms of level of disability and social functioning on long term follow-up. A further study[13] suggests that there is a positive correlation between the length of stay, intensity of treatment and the outcome of a brain injury rehabilitation programme.

POST-ACUTE REHABILITATION

Post-acute rehabilitation may be provided on an outpatient or residential basis. In those patients receiving outpatient rehabilitation improvements in physical, functional and cognitive status have been reported and these have occurred independently of the time from injury to commencing outpatient treatment[14,15].

Similar benefits were reported by Johnston and Lewis[16] in 82 patients entered into residential community re-entry programmes. Highly significant decreases in need for supervision and care with an improvement in independent living and productive

activities were noted. Improvements occurred independently of the time from injury demonstrating a benefit of the programme rather than spontaneous improvement. Similar benefits are reported by Cope et al[17] in their analysis of comprehensive rehabilitation within a co-ordinated system of post acute programmes.

A small number of studies have reported some success in vocational rehabilitation programmes for brain injured patients. This remains one of the most difficult areas with a high post injury rate of unemployment.

The role of neurobehavioural rehabilitation was initially reported by Eames and Wood in 1985[18,19]. Such as been its success that their methods are incorporated into many rehabilitation programmes today,

'NO MAN IS AN ISLAND"

It must be remembered that none of the above interventions or programmes cures the patient and that long term problems will persist. No patient exists entirely in isolation and the occurrence of brain injury has effects on all family members. Some recent studies highlight this. Gervasio and Kreutzer[20] in a study of 116 family members of a sample of outpatients with brain injury report that they feel alienated, isolated, overwhelmed and mentally preoccupied, with spouses experiencing most distress. This is probably implicated in the 49% divorce/separation rate in a sample of 131 couples with one partner brain injured as reported by Wood and Yurdakul[21]. It is of note that there was an association between duration from injury and separation/divorce indicating the cumulative nature of stress on the uninjured partner.

BACK TO THE FUTURE !

When taken as a whole, these studies demonstrate the positive benefits of a specialised neurorehabilitation service for brain injured patients. Similarly, neurorehabilitation has proven benefits in patients suffering from stroke and spinal cord injury. Patients with a variety of other neurologically disabling conditions, both progressive and non-progressive, can benefit from neurorehabilitation. Its principles should, therefore, be incorporated into Paediatric, Adult and Geriatric medical practice with the development of specialist programmes crossing these age related boundaries.

I have deliberately avoided discussion on specific therapy and pharmacologic developments. These while, in themselves, of value contribute to the totality of the rehabilitation process rather than transform it by their actions. When we look at the number of individual professions who may be part of the Rehabilitation Team we can see that the whole is indeed greater than the sum of its parts. (Table 1)

TABLE

Professions involved in Neurorehabilitation team

Doctors
Physiotherapists
Occupational Therapists
Speech & Language Therapists
Nurses
Dieticians
Psychologists
Orthotists
Rehabilitation Engineers
Social Workers
Recreational Therapists
Chaplins
Podiatrists

As the Royal Victoria Hospital enters it's third century it will be faced with more challenges. Advancing medical and surgical practice has improved the survival of patients following trauma and other conditions such as stroke. Unfortunately, the day when acute intervention will provide a cure for disabling conditions such as brain injury, spinal cord injury and stroke still seems some way off. The demands for rehabilitation will increase and planning for such a service should be central.

REFERENCES

1. Rusk H A. Advances in Rehabilitation. *Practitioner* 1959; **183**:505-512

2. Rusk H A. Rehabilitation. *J.A.M.A.*1949; **140**:286-292

3. Guttman L. Spinal Cord Injuries. Comprehensive Management and Research (Blackwell Scientific Publications, Oxford), pp 1-21:1973

4. Dennis M, Langhorne P. So Stroke Units save lives: Where do we go from here? *Br.Med J* 1994; **309**:1273-1277

5. Kalra L. The influence of Stroke Unit rehabilitation on functional recovery from stroke. *Stroke* 1994; **25**:1-821- 825

6. Stroke Unit Trialists' Collaboration. Collaborative systemic review of the randomised trials of organised inpatient (Stroke Unit) care after stroke. *Br.Med J* 1997;**314**:1151-59.

7. Boake C. A history of cognitive rehabilitation of head injured patients, 1915-1980. *J.Head Trauma Rehabil* 1989; **4**:1-8

8. Cope D N. The effectiveness of traumatic brain injury rehabilitation: A review. *Brain Inj* 1995; **9**:649-670

9. Burke D C. Models of brain injury rehabilitation. *Brain Inj* 1995; **9**:735-744

10. Rusk H A, Block J M, Lowman E W. Rehabilitation following traumatic brain damage. *Med Clin North Amer* 1969; **53**:677-684

11. Cope D N, Hall K. Head injury rehabilitation: Benefit of early intervention. *Arch Phys Med Rehab* 1982; **63**:433-437

12. Mackay L E, Bernstein B A, Chapman P E, Morgan A S, Milazzo L S. Early intervention in severe head injury: Long term benefits of a formalized program. *Arch Phys Med Rehab* 1991; **73**:635-641

13. Spivack G, Spettle C M, Ellis D W et al. Effects of intensity of treatment and lengths of stay on rehabilitation outcomes. *Brain Inj* 1992; **6**:419-434

14. Sscherzer B P. Rehabilitation following severe head trauma.. Results of a three-year program. *Arch Phys Med Rehab* 1986; **67**:366-374

15. Mills V M, Nesbeda T, Katz D I, et al. Outcomes for traumatically brain-injured patients following post-acute rehabilitation programmes. *Brain Inj* 1992; **6**:219-228

16. Johnston M V, Lewis F D. Outcomes of community re-entry programmes for brain injury survivors. *Brain Inj* 1991; **5**:141-154

17. Cope D N, Cole J R, Hall K M, Barkan H. Brain injury: Analysis of outcome in a post-acute rehabilitation system. *Brain Inj* 1991; **5**:111-126

18. Eames P, Wood R. Rehabilitation after severe brain injury: A special unit approach to behaviour disorder. *Int Rehab Med* 1985; **7**:130-133

19. Eames P, Wood R. Rehabilitation after severe brain injury: A follow up study of behaviour modification approach. *J Neurol Neurosurg Psychiatry* 1985; **48**:613-619

20. Gervasio A H, Kreutzer J S. Kinship and family members' psychological distress after traumatic brain injury: A large sample study. *J Head Trauma Rehabil* 1997; **12**:14.26

21. Wood R H, Yurdakul L K. Change in relationship status following traumatic brain injury. *Brain Inj* 1997; **11**:491-502

The Development of Physiotherapeutic Intervention with the Head Injured Patient

Carrie Spence BSc, MSCP
Superintendent Physiotherapist,
Joss Cardwell Centre, Belfast

Head injury has often been described as the 'silent epidemic of the twentieth century', for whilst it is estimated that about one in every three hundred families will be affected by the condition[1], the public as a whole knows relatively little about it. Furthermore as an increasing number of the more severely brain injured are now surviving due to advances in medical and scientific technology, both the skills and resources of the rehabilitationists are being stretched to new limits.

The physical problems that may result from injury are frequently diverse and complex in their presentation, the situation often being further compounded by cognitive deficits, as well as orthopaedic and respiratory complications. However, in general terms and particularly in the early stages, the problems that pose the most significant obstacles in rehabilitation are due to the presence of abnormal tonus and the development of severe spasticity[2]. These can be summarised broadly as follows:

- Contracture and deformity (fig 1)
- Establishment of abnormal spastic patterns of movement with consequent loss of
- postural control and selectivity
- Myositis Ossificans
- Pain and trauma due to joint mar-alignment and superimposed trauma

In order to control, as far as is possible the development of these problems, therapy has necessarily undergone a significant evolution in recent years. Intervention is now a much more dynamic and positive process and the outcome, therefore, more optimistic.

Some of the more important developments both in philosophy and also therapeutic modality will now be briefly considered.

EARLIER INTERVENTION

As Goldspink[3] reported - dramatic changes occur in

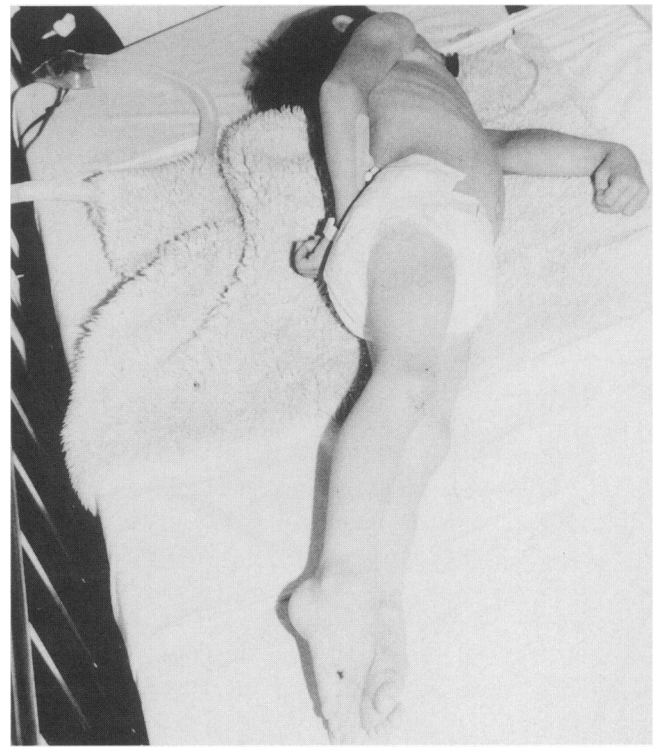


Figure 1 Typical decerbrate posturing demonstrating areas of potential contracture

muscle tissue when it is immobilised for periods in a shortened position, as would occur in the presence of severe hypertonicity. In particular, there is muscle atrophy, loss of sarcomere numbers, protein degradation and an increase in the proportion of connective to muscle tissue. Significantly, these alterations may start to develop within as little as 72 hours. Furthermore, as Nash[4] highlighted, muscle shortening would seem to potentiate the stretch reflex so that a vicious circle is set up whereby spasticity leads to muscle contracture and muscle contracture in turn increases spasticity.

Certainly contracture and deformity can develop in the head injured with amazing rapidity during the first few days and weeks post-trauma. Although malalignments may establish at any joint, planter flexion contracture of the ankle seems to be the most prevalent with an estimated incidence of about 76%[5]. Loss of normal foot contact with the ground significantly interferes with the ability to stand and transfer weight and will

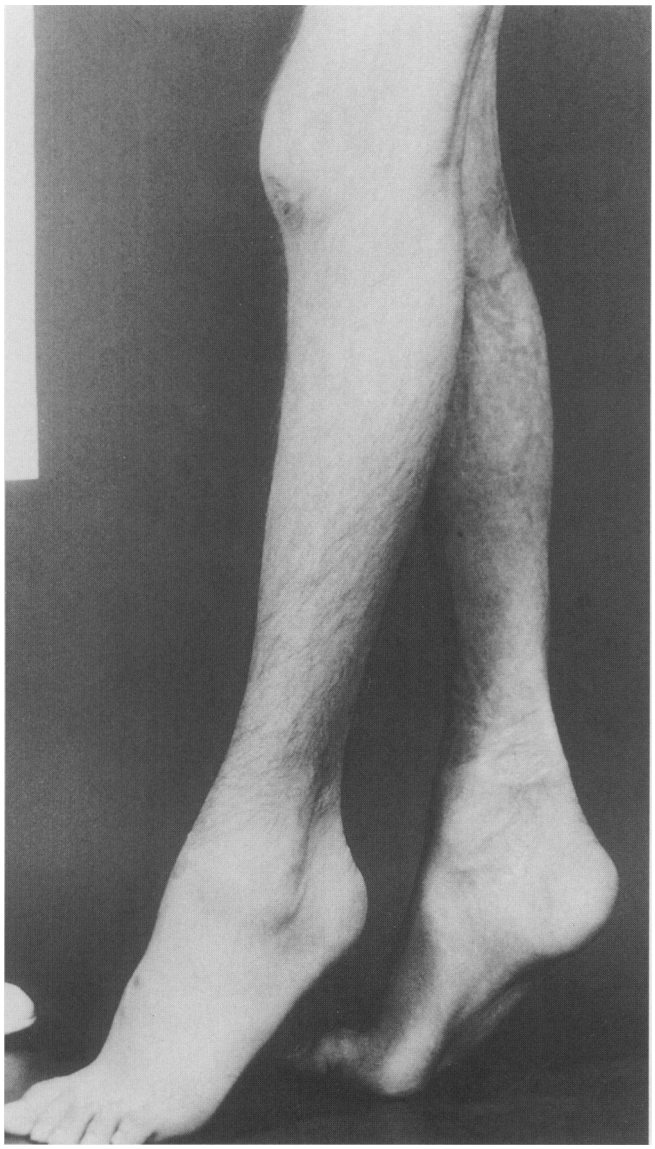


Figure 2

Figure 3

ultimately limit mobility (Figs 2 & 3)

The establishment of abnormal mass patterns of movement further interferes with the recovery of function and independence. As highlighted by Kidd[6] the more these abhorrent synergies are 'practiced' the quicker they become learnt and established into the neuronal circuitry of the CNS. Once assimilated, as every Therapist is all too aware, it is extremely difficult to fractionate these mass patterns into their component parts to achieve selective movement and, therefore, 'choice' in function. However, if plastic adaptation can be channelled towards normality from the start then the outcome will naturally be more favourable. Consequently, rehabilitation must commence as soon as the patient arrives at the Intensive Care Unit (ICU), and as McMillen[7], emphasises it must be 'proactive rather than reactive in it's delivery'. Furthermore daily intervention is frequently essential so that the traditional Monday to Friday therapy routine can no longer be regarded as entirely adequate or ethically acceptable in these instances. The extent and severity of the injury are obviously vital factors in determining prognosis, however, as Lynch[2] emphasises the patient is exquisitely sensitive to his, environment and the way in which he is handled and treated. Essentially what happens to the patient in this initial stage may determine the whole nature and quality of his future life.

Therapists in the Royal Hospitals Trust have embraced this concept in a dynamic and committed fashion and are now regarded by many throughout the United Kingdom as leaders in the management of the head injured. The primary benefits of their programme of early intervention can be summarised as follows:

1. A reduction in the incidences of contracture and, therefore, in the numbers of patients later requiring surgery.
2. A reduction in the appearance of myositis ossificans.
3. A reduction in the incidence of painful shoulder.
4. A reduction in the intensity of treatment required following transfer to the sub-acute ward.

DEVELOPMENT OF NEW THERAPEUTIC INNOVATIONS;

Over the last two decades in particular many new and exciting therapeutic modalities have been successfully implemented and some of the most influential will now be described.

a) Dynamic Standing

The facilitation of selective movements in a weight bearing position to maintain the integrity of the calf musculative and prevent contracture has been advocated by many clinicians[8,9]. The effect is partly mechanical, but Therapists also exploit the use of proprioceptive input to augment descending inhibitory control, thereby achieving a reduction in tone.[10] The influence on hypertonicity can be so pronounced that patients demonstrating typical severe decorticate posturing may quickly become low toned and easily mobilised so that joint range can be effectively maintained. The effect is most obvious when the procedure is carried out on a more 'dynamic' basis, between two or possibly three Therapists, who can adjust their handling appropriately in response to changes in the patient's level of tonus(Fig 4). Tilt tables may occasionally have to be used, particularly if it is necessary to bring the patient more gradually into the vertical position, however, they hold the patient more 'statically' and are consequently less effective in influencing tone. (Fig 5)

Standing of the unconscious ventilated patient in the ICU is even possible providing the cranial pressure and other medical factors permit.

b) Plastering Techniques

The use of 'static' serial plastering techniques to increase joint range with the head injured as described by Conine[11], and Sullivan[12], and many others represents a significant development in the management of contracture. (Fig 6) Its use, however, on a prophylactic basis as suggested by Frank[13], is proving to be even more beneficial. For example, head injured patients in the ICU of the Royal Hospitals Trust now routinely have bilateral plasters applied to maintain their ankles at 90° dorsiflexion, as soon as they begin to demonstrate any increased tone and potential loss of range of movement. Experience has shown that this is best done in conjunction with dynamic standing. In the past surgical lengthening of the tendoachilles was a relatively common requirement post head injury, however, today largely through the use of both the casts and weight bearing strategies it is rarely necessary.

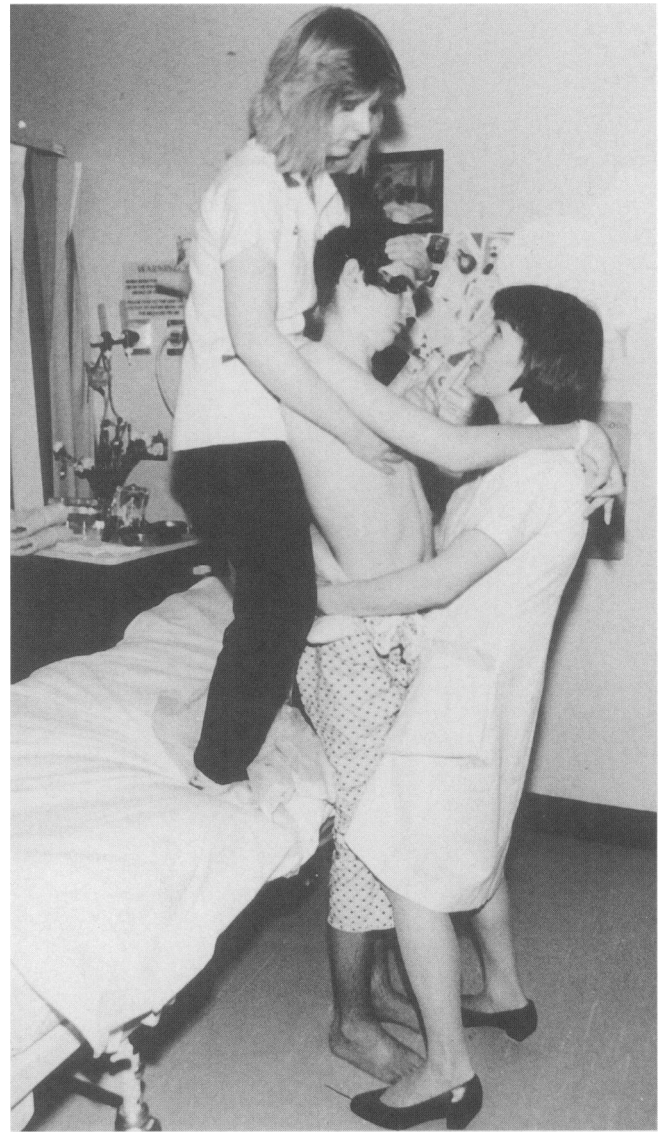


Figure 4 "Dynamic Standing" of a head injured patient between two therapists

More recently Therapists have introduced a new form of 'dynamic' plastering as described by

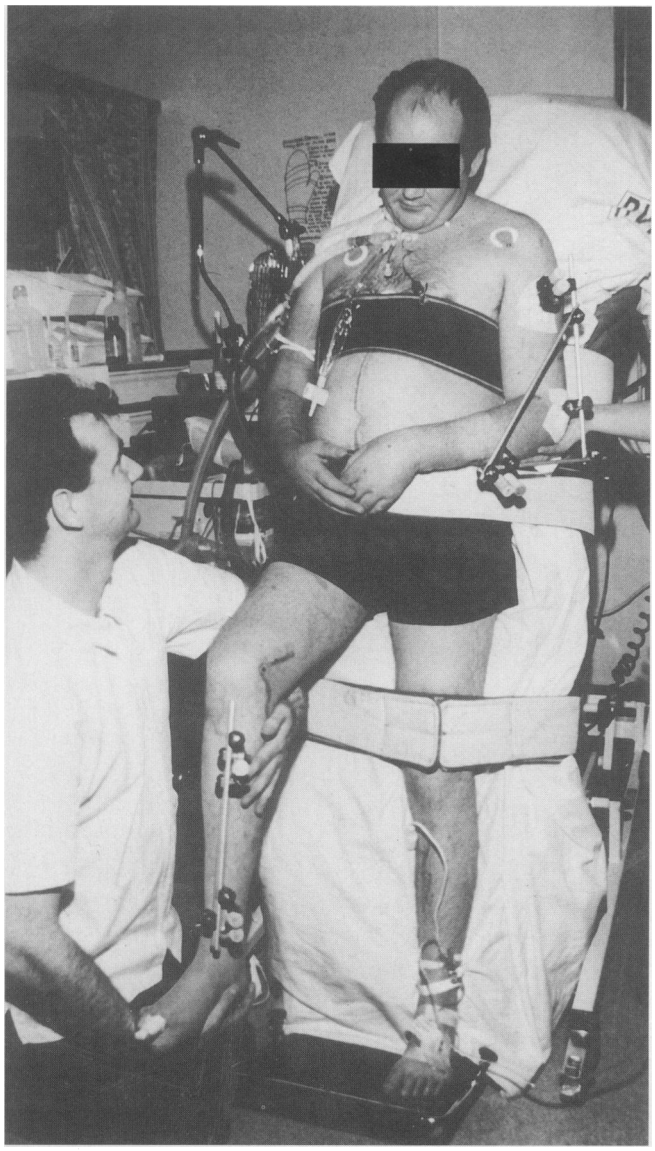


Figure 5 Use of the tilt table in the intensive care unit with an early head injured patient

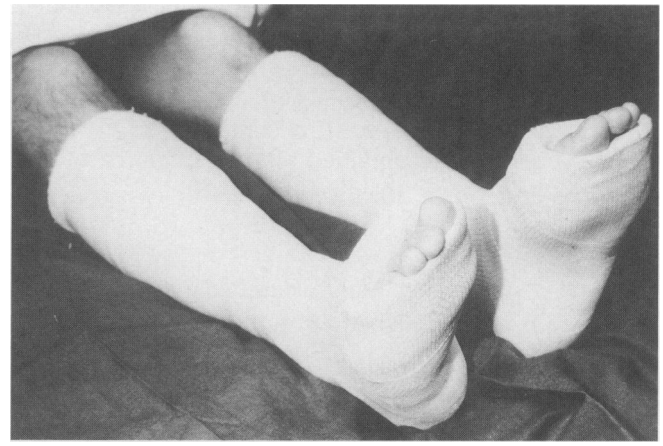


Figure 6 Static plastering in the intensive care unit

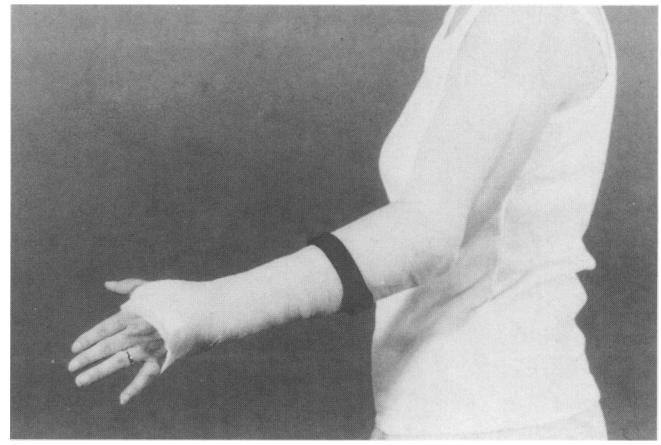


Figure 7 Dynamic "drop-out" splinting

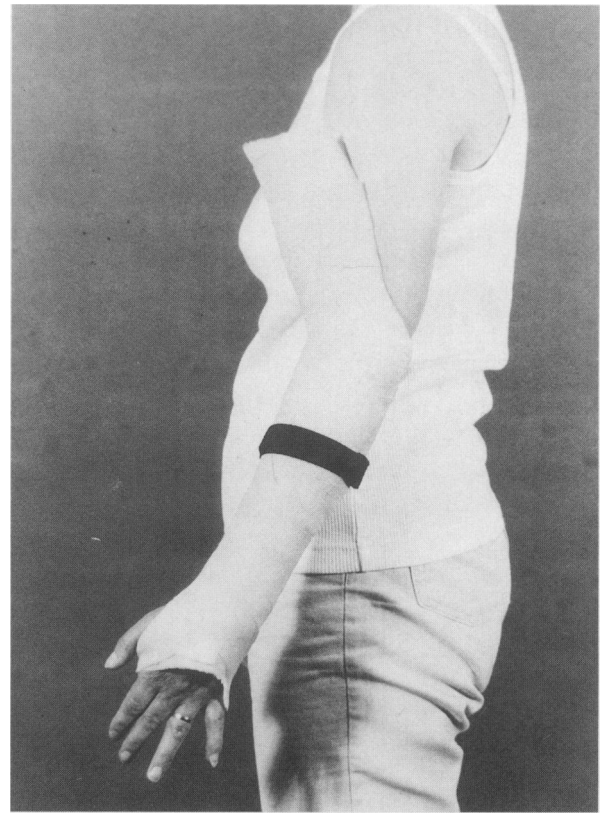


Figure 8

Edwards[9]. Essentially, these 'drop-out casts' are a less forceful means of regaining joint range allowing some degree of movement as the tone gradually reduces and the limb 'drops out' of the cast. They have been found to minimise effectively the problems of joint stiffness and effusion that are so often observed following removal of the static splints, particularly at the elbow and knee. (Fig 7 & 8)

c) Botulinum Toxin

Botulinum toxin is a potent neurotoxin which produces temporary muscle paralysis by presynaptic inhibition of acetylcholine release[14]. It has been used very effectively in the management of dystonia but more recently has played as increasing role in the treatment of severe localised

spasticity in the early head injured patient.

From cases reviewed to date at the Royal Hospitals Trust the general consensus has been as follows:

- Best results are obtained when the source of the problem can be localised to one or two specific muscles
- The drug is best administered early, i.e. before there is an established or 'static' contracture
- The drug is used in conjunction with dynamic plastering techniques
- A back up programme of intensive physiotherapy is implemented following injection in order to maximise the new potential for the recovery of selective muscle function

Generally only one dosage of the botulinum was required in the early stages as the initial severe tonal problems tend to settle to some degree after about six to eight weeks.

It's use in later stage rehabilitation is currently being explored in various centres and certainly at Joss Cardwell Centre it has proved to be very effective in certain cases where the contracture is of a more dynamic nature. Much more work, however, is required to evaluate objectively it's efficacy.

d) Specialised Handling Skills

In years gone by rehabilitation was built on the premise that the neuron Al circuitry was a static and fixed entity incapable of change or adaptation. Treatment, therefore, simply encouraged compensatory strategies, i.e. the overuse of unaffected parts, and established spasticity was regarded as an inevitable consequence of brain damage. However, in the last decade or so the dynamic and plastic nature of the CNS has been revealed and its ability to reorganise after damage in respect of both its molecular form and muscle function has been recognised[6].

Therapists trained in the 'Bobath Concept' endeavour to exploit this latent potential, using both their expertise in the analysis of movement and specialised handling skills to direct plastic adaptation towards normality. Treatment essentially involves the inhibition of abhorrent motor activity and the recreation of a framework of balance control and selective movement for functional recovery. This contrasts with certain other approaches which naively see re-education as merely the strengthening of 'weak' muscles'; a concept which is neither physiologically accurate or clinically effective

The use of mobilisation and movement etc. to change tone, which is part of the Bobath concept, has to a large extent also superseded the mindless routine of passive movement in the more proactive units. Indeed as reported by Silver[15] and David[16], although passive movements may have some limited value, when performed overenthusiastically or without proper care to realign the joint (particularly the shoulder girdle), they may be responsible for precipitating myositis ossificans, joint pain and trauma.

HOLISTIC TEAM APPROACH

As highlighted by Cope[17] the diverse and complex problems that characterise head injury necessitate a 'fully integrated multidisciplinary team approach'.

In the acute stage, for example, appropriate 'positioning' of the patient is particularly important as certain postures may actually markedly exacerbate the hypertonicity and thus promote further joint malalignment. Consequently nurse and therapist need to work closely together to use positioning to the patients advantage rather than his detriment. Uniform handling is equally vital in preventing joint trauma and similarly requires the co-operation of all those involved in the patients management.

Furthermore, the needs of the patient and family need to be kept central throughout the whole process of the rehabilitation continuim. At Joss Cardwell Centre the use of the 'Key Worker' strategy and case conference format have been successfully introduced whilst the recent implementation of 'family conferences' and peer discussion groups etc has greatly enhanced overall effectiveness and patient satisfaction. The importance of the team approach is perhaps best summarised by Nieuwenhuis[18], who stated that "it is a waste of time putting effort into a rehabilitation programme unless it has the wholehearted co-operation of all the members of staff."

CONTINUITY AND REVIEW

Unlike stroke - where evidence would seem to suggest that most functional recovery occurs within the first six to twelve months, significant changes in the head injured are well recognised two years or more after

injury[19]. Therefore, as Greenwood[1] stresses "if recovery is to be maximised rehabilitation may be required for some years after injury".

Recovery of function may also be a relatively discontinuous process characterised by intermittent progress and treatment plateaus, which Bethune[20] terms "periods of consolidation". Deterioration may of course also occur if the problems of spasticity have not been effectively controlled. Therefore, as Bach-y-Rita[21], suggests episodes of more intensive rehabilitation should be provided to optimise periods of acquisition or indeed to counter any loss of function whilst the consolidation process may require only home management.

This perspective is centred to the philosophy at Joss Cardwell Centre, where fragmentation of responsibility is avoided by an ongoing patient review system led by the Consultant in Rehabilitation Medicine. In this way patients who have been discharged may be re-referred for reassessment or further therapy as deemed necessary.

In conclusion, therefore, whilst it is clear that therapeutic intervention has undergone a considerable metamorphosis in recent years it should also be emphasised that the actual service provision is by no means totally comprehensive. In contrast to the network of NHS Centres for spinal cord injury, even though there are only a few hundred such cases in the United Kingdom annually, service facilities for the head injured are either woefully inadequate or absent. In Northern Ireland, in particular, outside of the immediate Belfast area, many of the young brain injured are merely transferred from acute wards to geriatric units - an utterly deplorable situation for all concerned; the need for a centralised brain injury unit in the province has never been greater.

Therefore, in looking to the year 2,000, while we can celebrate advances made, there is ever increasing responsibility to demand more for those shattered by head injury in order to give them a better chance of 'life' rather than mere existence.

REFERENCES

1 Greenwood R, McMillan T, Models of Rehabilitation Progammes for the Brain Injured Adult 1: Current provision, efficacy and good practice. *Clinical Rehabiliation* 1993; **7**: 248-255.

2 Lynch M, Grisogono V, 1991Strokes and Head Injuries - A Guide for patients, families friends and carers. John Murray.

3 Goldspink C, Williams P, 1990 Muscle Fibre and Connective Tissue Changes Associated With Use and Disuse. In Canning: C, (eds) Key Issues in Neurlogical Physiotherapy: Physiotherapy Foundations for Practice: Butterworth - Heinemann, Oxford.

4 Nash J, Neilson PD, 0'Dwyer NJ Reduction of Spasticity for Control of Muscle Contracture in Children with Cerebral Palsy. Dev. *Md. Child Neurol* 1989; **31** (4): 471

5 Moseley AM. The effect of casting combined with stretching on pasive ankle dorsiflexion in adults with traumatic head injures. *Physical Therapy* 1997; **77** (3): 240-247

6 Kidd G, Lawes N, Musa I, 1992 Understanding Neuromuscular Plasticity: A Basis for Clinical Rehabilitation, Edward Arnold, London.

7 McMillen T, Greenwood RJ. Models of Rehabilitation Programmes for the Brain Injured Adult (11) Model Services and suggestions for change in the U.K. *Clinical Rehabilitation* 1993; **7**: 346-355

8 Ada L, Canning C, 1990 Physiotherapy: Foundations for Practice - Key Issues in Neurological Physiotherapy. Butterworth - Heinemann.

9 Edwards S. 1996 Neurological Physiotherapy: A problem solving Approach. Churchill Livingstone

10 Muse I. The Role of Afferent Input in the Reduction of spasticity: *An hypothesis. Physiotherapy* 1986; **72** (4): 179-182.

11 Conine T, Sullivan T, Mackie J, Goodman M, Effects of Serial Casting for the Prevention of Equinus in-patients with Acute Head Injury *Archives of Physical Medicine and Rehabilitation* 1990; **71** (5): 310 - 312.

12 Sullivan I, Conine J, Goodman M, Mackie, I Serial Casting to Prevent equinus in aucte head injury. *Physiotherapy Canada* 1988; **40**(6): 346-350

13 Frank C, Akeson WM Woo S, Amiel D, Coutts RD. Physiology and Therapeutic Value of Passive Joint Motion. *Clinical Orthopaedics and Related Research* 1984; **185**: 113-125.

14 Anderson J, Rivest J, Stell R, Steiger MJ, Cohen H, Thomspon PD, Marsden CD. Botulinum Toxin Treatment of Spasmodic Torticollis. *Journal of the Royal Society of Medicine* 1992; **85**: 524 - 529.

15 Silver JR Heterotopic Ossification - A Clinical Study of its possible relationship to trauma. - *Paraplegia* 1969; **7**: 220

16 David O, Sett P, Burr RG, Silver JR. The relationship of heterotopic ossifican to passive movement in paraplegic patients. *Disability and Rehabilitation* 1993; **15**: (3) 114-118

17 Cope DM, Hall K Head Injury Rehabiliation: Relatively early intervention. *Arch Phys. Med Rehabil.* 1982; **63**: 433-37

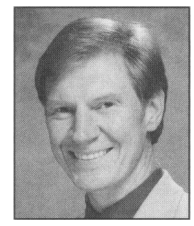
18 Neiuwenhuis R. Teamwork in Neurology (Therapy in Practice 40) - Chapman and Hall, 1993.

19 Hall K, Cope DN, Rappaport M, Glasgow Outcome Scale and Disability Rating Scale: Comparative Usefi~lness following Recovery in Traumatic Head Injury. *Arch Phys Med Rehabil* 1985; **66**: 33-37

20 Bethune D. Another Look at Neurological Rehabilitation. *Australian Journal of Physiotherapy* 1994; **40**: (4) 255-261.

21 Bach-y-Rita P, Lazarus JC, Boyeson MG, Balliet R, Meyers TA. (1988) Neural Aspects of Motor Function as a Basis of Early and Post-Acute Rehabilitation - In De Lisa J., (Ed) Rehabilitation Medicne Principles and Practice. Philadelphia: J. Lippincott PP 175- 195.

Great Medicine - Pity about the Cost



Jonathan Cooke PhD, MRPharmS

Director of Pharmacy
South Manchester University Hospitals NHS Trust

The cost of healthcare is increasing inexorably in all countries in the world. Many governments have focused their activities on promoting the effective and economic use of resources allocated to healthcare. Medicines form a small but significant proportion of total healthcare costs and one that has been increasing consistently as new medicines appear into the market place. The writing of a prescription is the most common therapeutic intervention in medicine and yet there is much evidence to suggest that this simple task is not conducted optimally.

Healthcare spending contributes to around 14% of growth domestic products in the US economy compared to 7% in the United Kingdom. The UK, spends around £50 billion on healthcare, mainly in the public sector, which represents around £900 per person per year. The amount spent on medicines has consistently been around 10% with around 550 million prescriptions being dispensed annually.

Each patient receives on average 9.4 items but this tends to be skewed towards the elderly population. However the proportion spent on medicines is starting to rise and is currently 13% of the total. Medicines expenditure in the UK has increased by an average of 12% per year in the last five years. 81% of the costs are incurred in primary care and this constitute up to 50% of the primary care revenue costs. Within average general hospitals 3% to 5% of the total revenue expenditure is spent on medicines. This increase in expenditure was recently picked up in an independent report produced by the Audit Commission which identified potential for savings of £450 million by promoting good prescribing by general practitioners[1]. A House of Commons Select Committee enquiry into medicines expenditure was recently convened to examine these increases in costs of medicines[2].

There are a number of reasons why costs are increasing. These include:

- Demographic changes in the population. As the average age in the population becomes older and as the proportion of elderly patients becomes greater their pharmaceutical needs increase
- Health screening programmes which have been particularly targeted at the elderly have uncovered previously non-identified diseases which subsequently require treatment.
- Improved diagnostic techniques have again uncovered more treatable diseases in these patients.
- New medicines are entering the market place on a regular basis frequently offering more effective and less toxic alternatives to existing agents. Invariably these are more costly

Pharmacoeconomics has been defined as the measurement of both the costs and consequences of therapeutic decision making. Pharmacoeconomics provides a guide for resource allocation but does not offer a basis on which decisions should be made. Pharmacoeconomics can help to provide a solution for dilemmas for decision makers where, for example, medicines with a worse outcome may be available at a lower cost and medicines with better outcome and higher cost can be compared.

Costs and consequences of therapeutic decision making can be described in a number of ways. Costs can be *direct* to the organisation, ie. acquisition costs of medicines, consumables associated with drug administration, staff time in preparation and administration of medicines, laboratory charges for monitoring for effectiveness and adverse drug reactions. *Indirect* costs include lost cost to the economy and taxation system as well as economic costs to the patient.

Consequences can be measured in terms of the total cost associated with a programme where both costs and consequences are measured in monetary terms *(cost benefit analysis). Cost effectiveness* can be described as an examination of the costs of two or more programmes which have the same clinical outcome. Treatments with dissimilar outcomes can also be analysed by this technique. *Cost utility* provides a method for estimating patient preference and quality of life measurements within the economic

setting. The dilemmas faced by decision makers on the introduction of a new treatment is indicated in figure1.

FIGURE 1

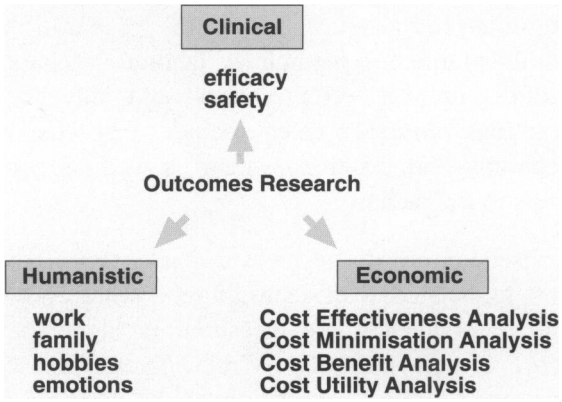
Decision matrix for a new treatment

	lower cost	**same cost**	**higher cost**
worse outcome	?	reject	reject
same outcome	consider (CMA)	optional	reject
better outcome	dominant	adopt	?

Outcomes research is now examining the value of medicines in society by seeking their clinical effectiveness in terms of efficacy and toxicity but, as importantly, the humanistic outcomes in terms of quality of life and health gain which are patient specific (Figure 2). The third dimension of cost effectiveness can help society through governments make priorities in healthcare decision making. The use of evidence based medicine is becoming a sought after goal and medicines, by virtue of the licensing process and use of formularies, are one of the only group of clinical interventions which have been subjected to health technology assessment.

FIGURE 2

The three dimensions considered in outcomes research which examine the overall and relative effectiveness of a particular health care intervention.



The costs associated with adverse drug reactions can be considerable. eg. The cost for each case of nephrotoxicity of aminoglycosides was calculated to be $2500 per case in 1987[3]. Failure to effectively monitor aminoglycosides levels led to irreversible vestibular damage in a women who received a prolonged course of aminoglycosides. Subsequent legal costs against the hospital were $1.5 million[4]. The costs of the bizarre side effects and fatalities of the anti-arthritic drug benoxaprofen, introduced in the early 1980's are only now starting to be realised.

The costs of non-compliance with medicines are significant. In the US it has been calculated that 11.4% of all admissions to hospital has been directly associated with some form of non compliance at a cost of $2150 per patient. Two million hospital admissions a year result from medication non-compliance at a total cost of $8.5 billion and it has been estimated that lost work productivity through non- compliance in the US is more than $50 billion per year[5].

Decision analysis offers a method of pictorial representing treatment decisions. If the results from clinical trials are available probabilities can be placed within the arms of the decision tree and outcomes can be assessed in either monetary or quality units[6].

This model can be used for a number of clinical situations. For example one study examined the incidence of wound infections which occurred by giving prophylactic antibiotics too early or too late in the surgical process and compared with giving them on induction. A decision tree can be created for the costs associated with surgery, together with the wound infection rates published in the original paper. Using this model it can be shown that there is an average £51 saving for each operation if the antibiotic is given on time. Commuted to an average hospital undertaking 10,000 surgical operations a year this reflects a potential cost saving of half a million pounds. This approach is referred to as *risk management* and is a part of quality assurance in any given process[7].

An example of the cost effectiveness of the addition of GMCSF after autologous bone marrow transplantation for lymphoid cancer. A randomised controlled double blind trial was undertaken in 40 patients to ascertain the effect of GMCSF with placebo. Outcomes measured included length of stay, total charges department, departmental charges, re-hospitalisation and outpatient charges. In all cases except pharmacy costs the charges were less with the GMCSF treatment indicating an overall saving to the organisation at a better treatment outcome[8].

A fundamental element of the use of pharmacoeconomics in practice is the view point from which the analysis is conducted. Ideally this should be

from a societal perspective but frequently it is from a Government, or Department of Health viewpoint. Purchasers of healthcare may also have a different perspective to provider units as might clinicians and patients may also differ. The pharmaceutical industry will have another viewpoint which will be focused on their particular products.

Health economics which is applied to medicines might compare:

- medicines versus surgery eg H pylori elimination v HSV
- medicines versus hospitalisation eg avoidance of admission by using specific antibiotics
- the place of diagnostic test costs eg. MRI
- the costs and consequences of prevention programmes
- the setting in which patients are treated eg. hospital, outpatient or home - eg home intravenous antimicrobial therapy
- risk management in avoiding unwanted effects of medicines
- total quality management where the best outcomes are sought

A recent study of three groups of health service decision makers sought to explore the reasons for the impact, or lack of impact, of the results of economic evaluations of medicines. An anonymous postal questionnaire was sent to directors of pharmacy, health authority directors of public health and NHS prescribing advisors. The results

identified the educational need of these individuals to appreciate studies on cost effectiveness and highlighted that the biggest barrier to implementing decisions on clinical and economic grounds was the inability to move funds around within the system[9].

REFERENCES

1. Audit Commission. A Prescription for Improvement - Towards more rational prescribing in General Practice. London: HMSO, 1994:
2. House of Commons Health Committee. Priority setting in the NHS: the NHS drugs budget. Vol. ll: minutes of evidence and appendices. London: Her Majesty's Stationary Office, 1994:
3. Eisenberg JM, Koffer H, Glick HA, Connell ML, Loss LE, et al. What is the cost of nephrotoxicity associated with aminoglycosides? *Annals of Internal Medicine* 1987; **107**:900-909.
4. Brushwood DB. Government liable for failure to monitor a patient's serum gentamicin concentration in an Army hospital. *American Journal of Hospital Pharmacy* 1992; **49**: 1748-50.
5. Task Force for Compliance. Non-compliance with medicines: An economic tragedy with important implications for health care reforms. Baltimore: 1993:
6. Cooke J, Doreau C, Eandi M. Pharmacoeconomic aspects of antibacterial treatment with cefotaxime. *Journal of Chemotherapy* 1997; **9** (supp 2):32-44.
7. Cooke J. Pharmacoeconomic aspects of antibacterial treatment with cefotaxime. *Research and Clinical Forums*. 1997; **19**:23-33.
8. Luce B, Singer J, Weschler J, et al. Recombinant human granulocyte - macrophage colony - stimulating factor after autologous bone marrow transplantation for lymphoid cancer. *Pharmaceconomics* 1994; **6**:42-48.
9. Cooke J, Walley T, Drummond M. The use of health economics by hospital pharmacist decision makers. - a survey of UK chief pharmacists. *Pharmaceutical Journal*. 1997; **259**:779-781.

Lies, damn lies and cost-effectiveness

James A McGuigan MB, BCh, FRCS

Consultant Thoracic Surgeon
Royal Victoria Hospital

The rationing of health care is not new. If we are interested in the origins of health economics we should remember 1699 (not quite a tercentennial). This was the year that William Petty published his discourse that evaluated many things including human beings in "Political Arithmetick". Since then the investment in health has depended on the wealth of the individual or state and the emphasis on health provision. In 1978 the World Health Organisation met at Alma Ata and defined the factors that led to the allocation of primary care resources; economic conditions, socio-cultural attitudes and political characteristics.

One of the greatest problems with publicly funded health care is a high rate of inflation. As the population becomes relatively more elderly greater demands ensue. Improvements in imaging and treatment technologies result in cost increases which are additional to underlying inflation. New drug therapies are expensive to develop and therefore newer drugs cost more. Politicians and the media have artificially raised expectations that have financial implications. The failure to keep up with "medical hyperinflation" was most dramatically seen in Britain in the 1980's. Inability to finance real cost increases led to cuts in services, although many politicians, in "Marie Antoinette" fashion, insisted that things were getting better.

Professor Ham has calculated that the real annual increase in hospital funding during the 1980's was 1.6% above general inflation. This was insufficient to match medical inflation and produced a cumulative deficit in hospital funding. The public were misled by statistics that seemed to indicate that the finances of hospitals were improving in relation to baseline inflation but this was of little relevance.

This kind of dealing in fiscal semantics brings to mind Mark Twain's biographical remarks, attributed originally to Benjamin Disraeli, "There are three kinds of lies, lies, damned lies and statistics". Hansard also attributes this phrase to Harold Wilson.

Statistics were often quoted which were at variance with popular perceptions. New units for monitoring activity in treatment episodes were introduced which were viewed with suspicion by health professionals. Civil service surrealism was in full sway, to a degree that the Jonathon Lynn and Antony Jay's fictional characters Sir Humphrey Appleby or Bernard Wooley would have endorsed.

Health care depends on taxation and the performance of the general economy. The United Kingdom rate of growth fell in the 1980's. There was a dogma that almost any cut in public spending was desirable, ,regardless of the consequences. The attempt to try to replace a mixed economy with a service dominated system was not entirely successful. The visible trade balance that had been within two thousand million pounds of breakeven since the 1950's, deteriorated. There was a year on year deterioration from 1980 as the manufacturing base was reduced. By 1990 the visible trade balance bottomed out at minus twenty thousand million pounds annually. Between 1970 and 1995 the percentage of the workforce in manufacturing had declined from 33.7% to 15.4%.

Adherence to the simplistic monetarist policies consistent with "sound economic management" saw the British economy decline relative to our trading partners. In 1995, the group of G7 nations recorded Britian firmly in last place behind Italy and France, ranked according to gross domestic product [GDP] per head of population.

By 1988, the fraction of GDP spent on health was only 5.9% which was below all of our major economic competitors. There was a repetitive underspend each year in the British health system. The King's Fund Institute published a national cumulative underfunding between 1981 and 1988 of £1,800 million for hospital and community services. Only five countries, in the greater European Area, spend less on health than the UK (expressed as a fraction of GDP). These countries include Turkey and Portugal. Not only do our major competitors spend a higher fraction of GDP but the higher GDP per head in those countries produces a multiplier effect. Proportionately greater amounts are spent on patients by countries such as Germany and France.

The oft vented assertion that we waste less in our system, is not borne out by comparative data, that indicate higher standards of health care in other countries. Examples are found in perinatal mortality,

survival following myocardial infarction and in certain cancers. Significant financial efficiencies have been made and further reduction in spending creates pressure to reduce existing services. By 1990 we had already seen a reduction in the numbers of hospital nurses and the closure of no less than 4,000 beds. [National Association of Health Authorities and Trusts]

Health spending has been described as a bottomless pit. Enoch Powell described an "infinity of demand" in 'A New look at Medicine and Politics'. Such facile but fallacious logic is often used to defend decisions where improvements in healthcare have been prevented because of significant cost implications. This is seen in the underprovision of intensive care beds.

In the early 1980's a working group under Norman Fowler looked at alternative funding for health. While private financing was attractive this would lead to higher spending with some improvements in health, as evidenced by the USA. The cheapest system was to use taxes to pay for health while central control could restrict growth in provision. No official report from this working party was ever published.

Improvements were obviously needed in NHS management and the "grocer" Roy Griffiths produced a report of how the system could be changed to more closely resemble "Sainsbury's" efficiency. Many good quality managers were appointed and major changes were foreseen. However, when political interference became rife, many of these managers resigned.

The Department of Health and Social Services realised that cuts would have to be made by health authorities. No guidance was given to where these cuts should be made. No official recognition of the inevitable cuts was politically palatable and a new term was coined, Cost Improvement Programmes [CIP's]. These programmes were introduced and were frequently euphemisms for many service cuts. Propaganda was more important than actual improvement in treatment.

In the 1980's there was steadfast opposition to public acceptance of rationing or honestly, admitting that certain services could no longer be provided by the NHS. The Government determinedly ensured that the finance debate should not be raised. Instead of recognising the effects of serious underfunding, the emphasis was put on blaming the existing system of delivery for the majority of the problems. This is a recurring theme.

Originally described by Enthoven in 1985, the idea of a market where hospitals would compete for resources was given the full backing of some politicians. The idea was developed by organisations not universally acclaimed for their concerns for the sick or disadvantaged members of society. It was actually the Adam Smith Institute and the Centre for Policy Studies that developed the ideas of 'The Internal Market'.

Kenneth Clarke drew up the white paper, "Working for Patients", published in 1989. This had major implications for acute hospital services. With great political wisdom, it was stated that the real aims of the changes were to raise standards of care, to place a greater emphasis on health promotion and to offer a wider choice. It was suggested [perhaps a little cynically] that the changes might detach politicians from criticism for inevitable future cuts by blaming health authorities and acute hospitals instead. The major problem of underlying cumulative underfunding was not to be corrected. The government and DHSS would not openly admit that certain areas of health care might need to be removed from the NHS if stretched health authorities and acute hospital units were to handle difficult situations.

Stresses became clear between health authorities and hospital trusts as a result of government underfunding. Since those in power in these organisations were often regarded by the public as "bungling bureaucrats", blame could be very effectively removed from "the centre". Many people believed that the mythical administrator's paradise of St Edward's Hospital [in "Yes Minister"] was close to real life. This was a very efficient hospital with many offices and administrators where "there would probably be some patients when the financial situation has eased up".

It would be wrong not to recognise the improvements in many aspects of the National Health Service since the White paper of 1989. Management is vastly improved at hospital level. Financial control is better and the importance of strategic planning is realised. From the patients' point of view the service is better focused and more accountable. Despite popular assumptions, the fraction of costs attributed to trust hospitals' management is low, considering the complexity and relative size of the budgets. This area is likely to become a target for "efficiencies" as cumulative underfunding, the real problem, persists and other scape-goats are sought.

Resources have been appropriated in the past, based on selective medical assumptions and compounded by management consultants' teams who were 'feeling their way' in the new seller-buyer scheme for health. In surgical services the assertion that procedures would become overwhelmingly laparoscopic and associated with short-term admissions was embraced by government departments despite lack of evidence. The belief that fewer elderly patients would require admission to medical units was wishful thinking. Self delusion about future demands seemed to be the order

of the day because it fitted fiscal restrictions.

The role of management consultants in all of this would be amusing if the resources spent on them were not so large. One executive described management consultants as "experts" who borrowed your watch and then charge to tell you the time.

Health economics has come of age in the 1990's NHS. Terms such as value for money and cost-benefit ratios are glibly used by people who know little of their precise meaning. Lord Kelvin correctly stated that when one can numerically quantify a problem one is half-way to solving it. However the units of cost comparison against health gain are not as simple as the units of temperature change. It is important that we use the measurements of health care versus costs in a scientific attempt to assess priorities not an "AppletonWooley" theatrical exercise in mathematical semantics to justify short-term savings.

We do not have a credible science of health economics. The simplistic concepts presently used in this area are limited in their usefulness. Policy decisions always have been the result of making value judgements, setting priorities and calculating how we can best achieve them. In the general economy, growth and efficiency are firmly bound. All macroeconomic changes have distributive results and inevitable implications for equity. Against this background, public health economics has not yet begun to grapple with the major problems of determining how much should be spent.

The most basic economic assessment of treatments requires a step analysis consisting of the selection of alternatives, costing and comparison of outcomes. Unfortunately we place an emphasis on the short term costings. There is a lack of understanding of what cost means in a limited overall budget. In these situations costs need to be defined in terms of the opportunity that has been denied if the investments were diverted to their best alternative use. There is no useful strategy or model that allows a mechanism for determining 'best alternative use'.

Best alternative use in trust terms may be that which improves the hospital's image. This is seen when technologically advanced high profile specialties which are relatively overresourced expand, to the detriment of less glamorous areas. For the community the best possible use might be to replace cheap psychiatric drugs with more expensive versions that ensure better patient compliance.

Cost-effectiveness is a crude measure that must not be used as a stand-alone factor to determine policy. It simply produces a ratio of a measured effect, such as the cost of a treatment for one patient for one month divided by the percentage of patients successfully responding to the treatment. Equal importance is given to increments of cost and effect, even when the effect is saving lives! It is only of guaranteed ethical value when used in its special variant of cost-minimisation where the clinical outcome is the same for different treatments at different costs. Cost-effectiveness measurement is useful in a factory making washers regardless of how many are damaged and thrown out as a result of the process. This may not be a good model for assessing health-care funding. In healthcare individual outcome is of enormous importance. When the most cost-effective drug is not the most effective drug, because of disproportionately high costs, ethical problems arise. Is it right to use the most cost-effective treatment when a number of patients are thus deprived of a cure? Cure may have been achieved by the use of a less cost-effective but more effective treatment in the first place.

TABLE 1.

Ethics versus economics

	Cost per unit	Effectiveness	Cost-effective ratio
Vaccine A [VA]	**£100**	**100%**	**£100/100% = £1 per 1%**
Vaccine B [VB]	**£20**	**50%**	**£20/50% = £0.4 per 1%**

VA is 2.5 times more expensive than VB per 1% effect [£1 versus £ 0.4]

VA should still be used as it would be unethical to leave 50% of the population unprotected

In a theoretical example two vaccines are available to prevent a severely maiming or fatal disease. [Table] Vaccine A [VA] costs £100 per person and is 100% successful. Its cost- effective ratio (CER) is one pound per one per cent treated successfully. Vaccine B [VB] costs £20 per person and is 50% successful with a CER of only £0.4 per one per cent. If we allow cost-effectiveness alone to make our decision we should use VB, but that would leave 50% unprotected. VA is the ethical choice. So why do the cost-effectiveness calculation? One cynical view may be that this ratio is useful to justify limiting investment.

While many policy makers and budget holders use cost-effectiveness as a defence for decision making one suspects they are like the drunk leaning against a lamp-post. They are using the structure more in support a weak position than as a means of illumination.

Other problems exist with cost-effectiveness ratios. In pharmacutical studies the effect measured may be selected to suit the drug produced by the organiser of the study. Patient selection criteria may enlist those who will show the greatest effect with a particular

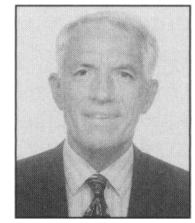
drug. The side-effects of a drug are not measured in cost-effectiveness studies. Most importantly, in controlled studies compliance is high in well motivated patients who have side-effects carefully explained to them, and who are more likely to complete courses of treatment. Drugs that must be taken with an empty stomach and have high levels of side-effects may have very different cost-effectiveness outside controlled studies. When patients do not fully comply with the optimum conditions drugs may not act properly.

More sophisticated indices of the relative 'worth' of drugs exist. Cost-benefit analysis is frequently quoted but rarely measured since it is almost impossible to calculate accurately. Cost is related to all the benefits and disadvantages that result from treatment. If a patient's arthritis is improved one should take into consideration the cost of the quicker wearing out of shoes.

The most promising prospect is the use of cost-utility analysis. Here a value is put on the clinical improvement often using QALY's [Quality Adjusted Life Years]. By having a monetary value on both sides of the equation, costs and improvements can be related in direct terms. This may be unattractive to budget controllers. It is hard to opt for a drug that saves a few pence per day when the advantages to the patient can be measured in several pounds per day. Alas, the interest in health economics is frequently anti-intellectual and used to justify cuts rather than to investigate the value of treatments.

Rather than an emphasis on simplistic economics in the NHS we need to research the value of good health. We must evaluate health education more fully and investigate methods of improving this with long-term analysis of cost implications. The debate about the inefficiency or efficiency of a purchaser-provider split remote from central budget holders will persist. The real debate as to what should be expected of a health service seriously underfunded over many years has been unpalatable to politicians in the past.

Microbiology & Risk Management



A Mike Emmerson FRCPath, FRCP(G), FRCP
Professor of Microbiology
University of Nottingham

In this presentation I will focus my comments on patients in the intensive care unit (ICU) primarily because the greatest challenges to risk management occur on a daily basis and also because microbiological decisions come under the microscope with daily scrutiny.

Analyzing infection rates in the intensive care unit is largely meaningless unless patients are stratified according to underlying risk factors. Infection rates in ICUs caring for post coronary, or post cardiac, surgery are very low, whilst those units coping with major gut trauma or burns are plagued with infection and cross infection. Richard Brown and colleague in 1985 compared infection rates among five different ICUs in the same hospital in Boston and found infection rates varied from 1.0% in cardiac surgery to 23.5% in the medical/surgical ICU, half of the latter being acquired in the unit from both exogenous and endogenous sources.[1] Survival rates of infected patients was over 87% in the paediatric and neonatal ICUs, compared with only 55.4% in the medical/surgical ICU.

These differences in types and rates of infection have an important bearing on infection-control activities in the ICU, thus making inter-unit comparisons difficult. In order to evaluate ICU performance, risk-adjusted in-hospital mortality rates and length of ICU stay should be used. Should there be wide variations in infection rates and mortality then a detailed evaluation of medical practice would be called for.

Nosocomial infections in the ICU cost money. Conservative estimates suggest that they lead to an extra stay in hospital of at least four days, but this can mean anything up to 13 days. The main risk factors for ICU acquiring nosocomial infection are:

- severity of underlying illness
- exposure to invasive life-saving procedures
- cross infection
- widespread use of antibiotics

Sepsis scoring in the ICU

Scoring systems which take organ failure into account are the most appropriate for sepsis in the ICU.[2] The best systems are those which are easy to perform, have been verified and which are applicable to all ICUs, or at least to comparable ICU. They are often used to predict mortality for which they are not always appropriate. They should not be used to predict the outcome of individual patients as this may influence the amount of treatment provided. A number of different scoring systems are available and in common use, eg:

APACHE II and III
SAPS (simplified acute physiological scoring)
TISS (therapeutic intervention scoring system)
ISS (injury severity score)

The burns scoring system seems to be good at predicting outcome, although all scoring systems have their limitations and there is no universally applicable scoring system. Scoring systems can be used as an audit tool.

Clinical audit has been described as 'systematic, critical analysis of the quality of medical care, including the procedures used for diagnosis and treatment and the resulting outcome for the patient'.

Human resources

An ICU needs medical, nursing, technical, clerical, administrative and domestic staff of the highest order of training and commitment. Intensive care units are also expensive care units as by definition they provide intensive life support around the clock. The current recommendation from the Intensive Care Society is for a minimum of one nurse to each patient, which is equivalent to 6.5 whole-time nurses per bed. Various nursing dependency scores do exit, but the daily requirement should be left in the hands of the unit administrator. Suffice it to say that sufficient unit-trained nurses should be available to carry out the detailed policies and procedures necessary to provide a high class service. Whenever staff-patient levels fall, then infection control practices are less than optimal and cross-infection occurs largely due to lack of compliance with hand washing practices.

Isolation procedures

It is common place to admit infected patients from other parts of the hospital, or from other hospitals. One

possible solution is to admit patients into isolation rooms, screen them and then, if free from known 'alert organisms', admit them to the open unit. This policy has enormous staff implications and often a risk assessment is made on the admission of each patient and the patient managed accordingly. For airborne infections, eg tuberculosis, patients should be isolated to lessen the risk of cross-infection to staff and other patients. All other infected patients can be managed using source isolation, although universal precautions are frequently not necessary. Care of equipment, attention to policies and procedures and frequent appropriate hand washing are essential. On rare occasions, when cross-infection is out of control, or patients safety is threatened, then the possibility of closing the unit should be considered. This decision should be taken only after wide consultation and only after a full assessment of risk has been made.

Setting Standards

Certain aspects of the clinical management of critically ill patients lend themselves to written protocols. Policies and procedures are useful guidelines for the management of patients and are useful for new staff and a good aide de memoir for more experienced staff. Written policies need to be updated regularly taking into account new interventions and outdated therapies. Some units find value in producing standing operating procedures (SOPs) which can be audited in a more formal way. Trained and well-motivated staff carry out their duties with quiet confidence and react well to unforeseen emergencies.

Mechanical Ventilation

Patients in the ICU are usually the most ill in the hospital and almost all require ventilator support. According to surveillance data from the National Nosocomial Infection Surveillance (NNIS) System, pneumonia is the second most common nosocomial infection overall, and the most common nosocomial infection in ICU, accounting for 18% of all nosocomial infections and 31% of those in ICU.[3] Pneumonia is associated with the greatest mortality among nosocomial infections and with substantial increased costs of care. Mechanical ventilation and tracheal intubation have been linked to a 3-fold to 21-fold increased risk for nosocomial pneumonia. Mechanical devices bypass the normal defence mechanisms and aerobic gram negative bacilli readily colonize the oropharynx from a number of sources. I will discuss the likely pathogenesis of ventilator-associated pneumonia, but the ways to prevent or lessen the incidence is more problematic.

Ventilator design

Ventilators are now available which have few infection problems. Inspiratory and expiratory circuits are kept separated and filters can be used to prevent contamination of the machine, the patient and the environment. Single-use filters are expensive, as are most disposables, and a risk assessment should be made before these are used. Ventilator circuits do not need to be changed at 48 hour intervals since evidence shows that, with care of the humidifier and condensate traps, circuits can be left in place for a week.[4] Great attention to the maintenance and care of the circuits is necessary to ensure that they function correctly. Machines that have detachable circuits are preferable since these can be replaced easily with a decontaminated one. Circuits and humidifiers should be sent to a central decontamination unit where they can be processed safely and their function checked. Decontamination procedures should not be carried out on the ICU in a small side room; too many problems have resulted by doing this. Likewise, flexible endoscopes, e.g., bronchoscopes should be returned for processing to a purpose designed endoscopy unit. The risks associated with 'in house' decontamination will be illustrated.

Ventilator-associated pneumonia

The epidemiology of VAP is fraught with diagnostic problems. Tracheal intubation predisposes to aspiration by breaching natural barriers, but unless endotracheal intubation is feasible, it is a necessary evil. Risk factors include chronic lung disease, large volume gastric aspiration (with a raised pH), re-intubation, repeated circuit changes and duration of mechanical ventilation.

Diagnosis of VAP - Clinical, radiological and microbiological features are often misleading in diagnosing VAP. The relative predictive value of positive surveillance culture of upper airways in high risk patients is poor. Quantitative cultures of endotracheal aspirates using bronchoalveolar lavage (BAL) or protected brush sample (PBS), both have high sensitivities and specificity's, but their accuracy remains unproved. Microbiological lung surveillance using non-directed bronchial lavage and quantitative culture is an alternative technique which may predict the clinical onset of pneumonia. Because of the vagaries of diagnosis of VAP, it is essential that there is close collaboration between the ICU staff and the clinical microbiologists; without close liaison there is ample opportunity for the excess use of empirical broad-spectrum antibiotics with their attendant problems.

Indwelling devices

In addition to mechanical ventilation, most patients in the ICU will have a central venous line and an indwelling urethral catheter. Both of these indwelling devices breach the natural defences and allow ready access to the blood stream. As with the respiratory tract, aerobic gram-negative bacilli are the commonest causes of urinary tract infection and septicaemia. Many are multiply resistant to most broad spectrum antibiotics and risks are taken in starting empirical therapy. Good surveillance and pre-treatment samples, offer the best way forward to manage this risk. Coagulase negative staphylococci are the commonest causes of central venous catheter infections and these are often methicillin and gentamicin resistant. The diagnosis of these infections and the salvage of these CVC is a major undertaking.

Surveillance in the ICU

The major advantages of surveillance is that it helps to direct therapy without having to resort to using broad-spectrum antibiotics unless indicated. Routine cultures provide little useful information and at best are misleading. Samples taken when patients are infected are more relevant and reflect the infecting organisms in the patient at that time in that unit. Studies like the European Prevalence of Infection in ICU do not help in the treatment of individual patients.[5] Local treatment policies should be based on local surveillance information.

Treatment of infections in ICU

Every ICU should have its own antibiotic policy or guidelines for the use, or not, of antibiotics. This should include guidance on the use of prophylactic, empirical and the therapeutic use of all antibiotics. Antibiotics should be controlled and their use based on local patterns of sensitivity and on the predominant micro-organisms in the unit. We have yet to come to grips with the excessive use of antibiotics in the ICU. Often, up to 60-70% of patients are on antibiotics at any one time. It requires a tough policy that includes the following guidelines:

- Stop antibiotics when patient admitted and re-assess
- Attempt a working clinical diagnosis
- Take appropriate pre-treatment samples
- Try physiotherapy, drain pus, remove lines
- If unavoidable, use 'directed' spectrum

Assess after each dose and monitor potentially toxic drugs like vancomycin and gentamicin. Try to restrict the use of third and fourth generations, unless there are good indications for use.

Costs

What are the costs attributable to nosocomial infection? Urinary tract infections are very common, but are relatively cheap to diagnose and treat. In a cost-conscious world we should really be focusing on the management of pneumonia and septicaemia since these are most costly. Using the valuable tool of clinical audit it should be possible to cost each stage of a procedure and to calculate additional costs due to protocol violations Most disposables (single use items) are costly and are used in large numbers. Ventilator circuits do not have to be changed frequently, filters do not need to be changed daily, CVCs do not need to be removed at the slightest hint of infection. The costs of diagnosis are high, but not as high as the excessive use of inappropriate antibiotics. Additional length of stay attributable to an ICU acquired infection has a considerable economic impact and every effort should be made to wean the patient off the ventilator and to return him/her to a recovery ward.

Prevention and control of infection

Infection control resources should be devoted to education and monitoring compliance with established policies and procedures. The microbiology laboratory should provide a rapid and accurate diagnosis of infection and the clinical microbiologist should liaise closely with ICU staff and thus share the burden of diagnostic uncertainty in a very complex unit.

REFERENCES

1. Brown R B, Hosmer D, Chen H C, Teres D, Sands M, Bradley S, Opitz E, Szwedzinski D, Opalenik D. A comparison of infections in different ICU's within the same hospital. Crit. *Care Med.* 1985; **(6)**: 472-476.

2. Palazzo M. The use and interpretation of scoring systems in the ICU. Part I. *Brit. J. of Intensive Care.* 1993; July, p.255-260 and August, p.286-289.

3. Weinstein RA. Epidemiology and control of nosocomial infections in adult ICU. *Amer. J. Med.* 1990; **91**(suppl.): 179-184.

4. Kollef MH, Shapiro SD, Fraser VS, et al. Mechanical ventilation with or without 7- day circuit changes. *Ann. Intern. Med.* 1995; **123**: 1618-174.

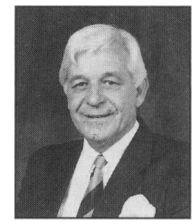
5. Vincent JL, Bihari DJ, Suter DM, et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European prevalence of infection in intensive care (EPIC) study. *JAMA*, 1995; **274**: 639-644.

JP Howard Fee MD, PhD, FFARCSI
Introduction of The WFK Morrow Lecture

Keith Morrow was appointed to the consultant staff of the Royal Victoria Hospital in 1968 and served it devotedly until his premature death in 1982. He studied Medicine at Queen's having crossed the road from Methodist College, and qualified in 1948. He then trained in anaesthetics in the Royal but his first consultant appointment was in Banbridge and then Lurgan hospitals. He was a fellow of the Faculty of Anaesthetists of the Royal College of Surgeons in Ireland and a Fellow of the Royal College of Physicians of Edinburgh. Specialization was not for him. Although his main area of interest was in the, then young but rapidly, developing area of intensive care, he was comfortable providing anaesthesia for eye, ent, dental, thoracic, abdominal and orthopaedic surgery. As far as his juniors were concerned, he was always approachable, always supportive and always knew exactly what to do. He was immensely courageous in the face of relentless disease, he managed to retain his puckish sense of humour through it all. A lovable person and a generous host he had great personal charm and warmth. By recognition of his unique qualities the medical staff of the Royal Victoria Hospital asked that this lecture be given each year to perpetuate his memory.

From Wards 5 and 6 to Sainsburys

(The history of out-of-hospital cardiac arrest.)



Peter J F Baskett FRCA, MRCP
Consulant Anaesthetist
Frenchay Hospital, Bristol

When history is written, one J Frank Pantridge will appear high on the list of original thinkers who changed the face of medical practice and who has been responsible for saving countless lives across the length and breadth of the globe. (Fig1)

Appalled at the high mortality from ischaemic heart disease in the province, his studies showed that there was a substantial delay between the onset of symptoms and the call for professional help. Moreover, there was little being done to treat these patients in the pre-hospital phase, apart from reassurance, and perhaps some analgesia and basic life support should cardiac arrest occur. The results were poor.

In the early 1960's, it was beginning to be realised that many patients with cardiac arrest due to ischaemic heart disease were suffering, not from terminal asystole but from ventricular fibrillation. External defibrillators had recently been introduced into clinical hospital practice and were producing survivors if used early. Frank Pantridge, together with his colleague John Geddes, after experience in defibrillation in hospital at the "Royal" in Wards 5 and 6, set about bringing defibrillation and advanced cardiac care provided by physicians into the community.

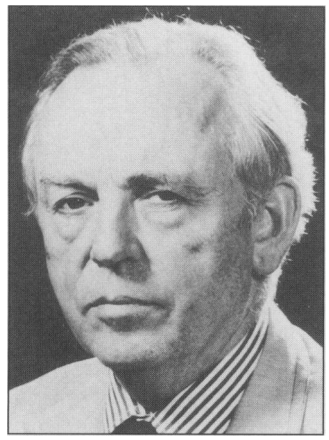


Figure 1 J. F. Pantridge

By hook or by crook, as was his wont, he acquired a "coronary ambulance" based at the "Royal", staffed by one or more of his own trainees and equipped with a huge defibrillator and a wide variety of drugs.

In landmark papers, Pantridge and Geddes reported their results in the Lancet[1,2]. The concept of Mobile Coronary Care was very soon picked up in the United States[3,4] and continental Europe but, except in a few isolated instances, was not supported in the UK.

In the US, pre-hospital care was provided by non-physician paramedics and in continental Europe by physicians - mostly anaesthetists. In the UK, family doctors provided diagnostic skills but, by and large, they were ill equipped for cardiac emergencies. The majority of the UK was provided for by an ambulance service who had only very basic training. Only in Brighton, and in Bristol, where Douglas Chamberlain and I struggled against the establishment, and in Hampshire was any effort made to train paramedics who could provide defibrillation, intravenous access, drug therapy and sophisticated management of the airway and ventilation.[5,6]

Despite published exhortations[7], this dismal situation continued until the 1980's when common sense at last began to prevail under the leadership of an enlightened Chief Medical Officer at the Department of Health - Sir Donald Acheson, who gave the go ahead for paramedic training and the provision of defibrillators on all front line ambulances.

THE EARLY DEFIBRILLATORS

In the 1960s and 70s, the defibrillator was a massive piece of apparatus - barely liftable by one man and powered by mains electricity. (Fig 2) Pantridge, who was now working with John Geddes, Jennifer Adgey and Sam Webb, set about designing a portable model

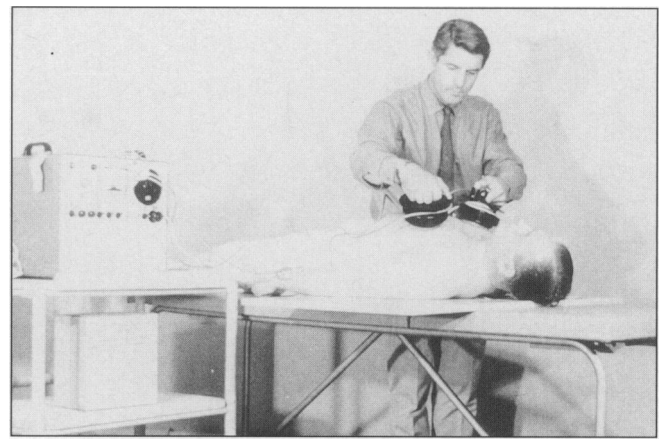


Figure 2 Demonstration of early difibrillator by author

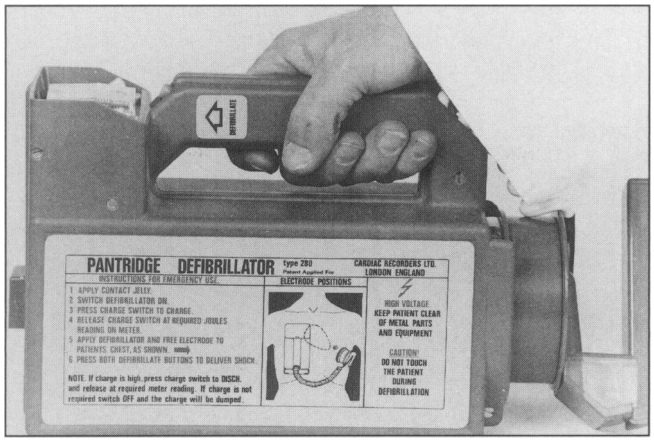


Figure 3 The Pantridge defribulator

to be battery powered which would be much more suitable for use in the community and for an in-hospital cardiac arrest service. The Pantridge Defibrillator developed with Cardiac Recorders Ltd, was a milestone[8](Fig 3). It was small, portable and simple. It was unencumbered by an ECG recorder for that would have increased the cost and the size and weight. Pantridge believed that the survival rates from asystole were so poor that the only potential for a good outcome was to treat the patient blindly as if they had ventricular fibrillation. The patient with asystole had nothing to lose and the patient with ventricular fibrillation had everything to gain.

In the United States leading defibrillator manufacturers such as PhysioControl improved the technology on a steady basis and the portable defibrillator because quite sophisticated and incorporated a ECG trace, a paper recording and a synchronised facility for cardioversion of ventricular tachycardia and atrial fibrillation.

All defibrillators at that time were manually operated with hand-held paddles and required the operator either to defibrillate blindly based on a clinical diagnosis of cardiac arrest or interpret the ECG rhythm as being ventricular fibrillation and defibrillate accordingly. The potential for artefact with hand-held paddles, particularly in the prehospital arena, was high.

THE AUTOMATED EXTERNAL DEFIBRILLATOR

In the early 1980s space and computer technology were applied to defibrillators and the automated device was produced by Laerdal; PhysioControl and some other leading manufacturers. (Fig 4) The ECG signal was detected through large adhesive pads applied to the chest, and the signal was reliably interpreted within the apparatus so removing the diagnostic onus from the operator.

A shock was either delivered automatically if the rhythm was one remediable by defibrillation (the completely automatic defibrillator) or audible and/or visual signals indicated that the operator should deliver a shock by pressing a button (the semi automatic or shock advisory defibrillator).

This major advance revolutionised the practice of defibrillation, particularly in the prehospital arena. Now defibrillation was no longer the sole province of the physician or the paramedic.

Defibrillation became a relatively simple affair that could be used by basic ambulance technicians, firemen and policemen. Substantial clinical experience began to be acquired on a world wide basis.

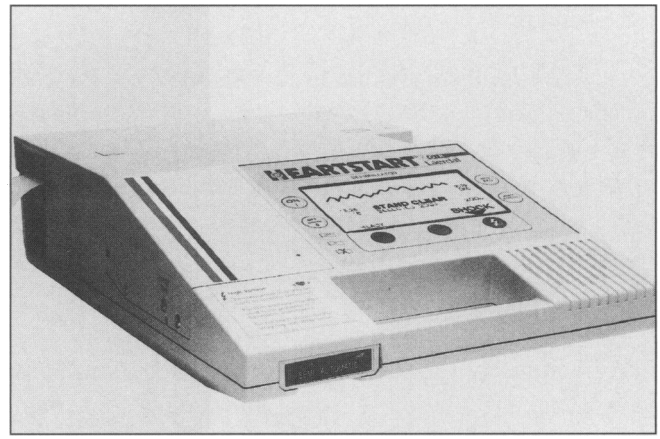


Figure 4 The HEARTSTART semi-automatic defribrillator by Laerdal

RECENT CLINICAL EXPERIENCE WITH DEFIBRILLATION

Cummins has surveyed the reports of early defibrillation from a number of centres in the US which give the survival rates before and after the introduction of the programme[9]. In King County, Washington survival rates rose from 7% to 29%, in Iowa from 3% to 19%, in SE Minnesota from 4% to 17%, and in Wisconsin from 4% to 11%. Weaver reported an improvement from 21% to 30%[10]. In Scotland, Cobbe reported the experience of the ambulance service using technicians and paramedics who defibrillated 602 patients with a 29% survival to arrival at hospital and 12.5% survival to hospital discharge[11]. In Berlin, Arntz reported on a series of 209 cases of ventricular fibrillation occurring out of hospital with survival to hospital admission in 51% and survival to discharge in 22%[12]. In West Yorkshire,

ambulance staff achieved an 11% survival to discharge in a series of 910 patients with ventricular fibrillation. In Gothenburg 11% were admitted alive to hospital and 7% were discharged in series of 949 patients[13].

In Scotland and Northern Ireland, some family doctors equipped themselves with defibrillators and more than matched the ambulance service figures with survival rates to hospital discharge and beyond of 34% and 41% respectively in patients who were defibrillated.

Very high survival rates can be achieved in patients with ventricular fibrillation if defibrillation is achieved within 3 minutes. Weaver reported survival rates of 70% within this time frame. It is estimated that survival rates fall by about 7% per minute of delay to defibrillation.

Cardiopulmonary resuscitation (CPR) may provide a circulation which will stave off neurological damage but probably buys only limited time.

Clearly for high survival rates to be achieved CPR and defibrillation must be applied within 5 minutes. These response times are plainly outside the ability of the ambulance services capability, particularly in rural areas. What then is to be done to realise the full potential of defibrillation?

THE FUTURE

Two features bring hope for the future for victims of ventricular fibrillation. Firstly, international medical opinion has realised and admitted that early CPR and defibrillation is the way forward. Secondly, the defibrillator technology has taken a further step forward with the introduction of the biphasic waveform which allows defibrillators such as the *FORERUNNER* by Heartstream to be just as effective with lower energy and therefore to be smaller, lighter, cheaper and even simpler to operate. (Fig 5) Battery technology has improved to produce greater reliability and regular self testing.

As a consequence, august bodies such as the American Heart Association and the European and Australian Resuscitation Councils have issued statements encouraging the introduction of early access to defibrillation programmes and acknowledging that defibrillation can be performed in the community by trained individuals who are not necessarily health care professionals.

In the future, defibrillation will be provided by the police, fire brigade, St John, the Red Cross, sports event marshals, transport stewards (rail and air) and by

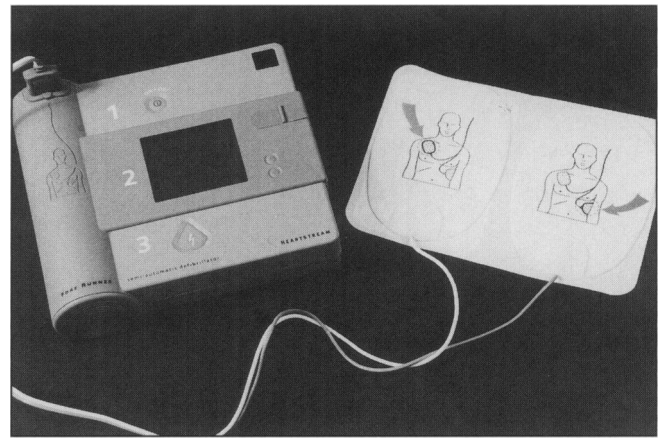


Figure 5 The FORERUNNER Semi-automatic defribrillator

designated trained individuals in public places including shopping malls and large department stores. It will be essential that such community activities must be operated through the ambulance service who will be able to give advice, and perhaps more importantly, moral support. As such it will be necessary to have a communication system between the rescuer and the ambulance service. The answer may be a mobile telephone although at present there is evidence that these devices interfere with defibrillator function.

In the first decade of the new millennium, defibrillators will be as common as fire extinguishers but smaller, cheaper and used more frequently.

To enhance the benefits of defibrillation, the other factor in resuscitation that needs to be sorted out is the airway. I suspect that the laryngeal mask will have a major role to play[14]. But that's another story.....

REFERENCES

1. Pantridge JF and Geddes JS. Cardiac arrest after myocardial infarction. *Lancet* 1966; 807 - 808.

2. Pantridge JF and Geddes JS. A mobile intensive care unit in the management of myocardial infarction. *Lancet* 1967; 271 - 273.

3. Cobb LA, Conn RD, Samson WE, Philibin JE. Early experiences in the management of sudden death with a mobile intensive/coronary care unit. *Circulation.* 1970; **42:** Suppl 3. 144.

4. Grace WJ, Chaubourn J . The Mobile Coronary Care Unit. *Dis Chest.* 1969; **55:** 452 - 455.

5. Chamberlain DA, White NM, Binning RA, Parker WS and Kimber ER. Mobile coronary care provided by ambulance personnel. *British Heart Journal* 1973. **35:** 550 (abstract).

6. Baskett PJF, Diamond AW, Cochrane DF. Urban mobile resuscitation - training and service. *British Journal of Anaesthesia.* 1976. **48**: 377 - 385.

7. Baskett PJF, Boulton TB. Editorial. *Anaesthesia.* 1979; **94**: 989 - 990.

8. Pantridge JF, Adgey AAJ, Geddes JS and Webb SW. The Acute Coronary Attack. (1975). Grune and Stratton, New York.

9. Cummins RO. Firm concept to standard of care. Review of the clinical experience with automated external debbrillators. *Annals of Emergency Medicine* 1980; **18:** 1269- 1276.

10. Weaver MD, Hill D, Fahrenbusch CE et al. Use of the automatic external defibrillator in the management of out of hospital cardiac arrest. *New England Journal of Medicine.* 1988; **319**: 661 - 666.

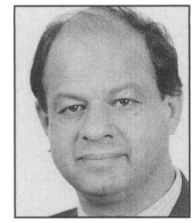
11. Cobbe S, Redmond M, Watson J, Hollingworth J, Carrington D. Heartstart, Scotland - initial experience of a national scheme for out of hospital defibrillation. *Brit Med Journal.* 1991; **302:** 1517 - 1520.

12. Arntz H - R, Oeff M, Willich S N, Storch W H, Schroder R. Establishment and results of an EMT-D program in a two tiered physician escorted rescue system. The experience in Berlin, Germany. *Resuscitation* 1993; **26:** 139-146.

13. Ekstrom J, Herlitz J, Wennerblom B, Axelsson A, Bang A, Holmberg S. Survival after cardiac arrest outside hospital over a 12 year period in Gothenberg. *Resuscitation* 1994; **27**; 3: 181 - 188.

14. The use of the laryngeal mask airway by nurses during cardiopulmonary resuscitation. Results of a multicentre trial (co-ordinator Baskett P J F). *Anaesthesia* 1994; **49**: 3-7.

Vasa Vitae - Keeping The Channels Open



Aires AB Barros D'Sa MD, FRCS, FRCSEd
Consultant Vascular Surgeon
Royal Victoria Hospital

Surgical attitudes to blood vessels through the millennia and leading up to the middle of the twentieth century were, with anecdotal exceptions, limited to life-saving cautery or ligation. The practice of vascular surgery was initiated only in the fifties when arteries and veins - these vasa vitae or vessels of life - were deliberately sought out and reconstructed. Keeping the channels open in order to preserve life, to revitalise an organ or to salvage a limb has been the raison d'être of the vascular surgeon. The objectives of surgical intervention are also its rewards.

The fun and the reward of vascular surgical practice lies in the challenge of dealing with patients with major cardiovascular and other risk factors, in the precision of operative technique and in the generally gratifying outcomes, tempered on occasion by the experience of failure. It is a specialty which has grown enormously in the range and complexity of procedures undertaken. Over a third of the large numbers treated require emergency attention. The ubiquitous presence of diseased blood vessels makes for refreshing changes of clinical and operative scene and also accounts for the close links between vascular surgeons and other doctors. These fortuitous associations generate varied interdisciplinary research programmes which not only straddle the neat boundaries of prescribed research groupings but also extend outwards to the sciences, engineering and so on. It is exactly such collaborative vascular research which has enriched our knowledge of the microcirculation, led to advances in haemodynamic monitoring, introduced the concept of the non-invasive ultrasound investigation, stimulated prosthetic graft development and brought about innovations in surgical instrumentation.

During the seventies, the broadening repertoire of exciting operative procedures in this relatively young specialty, in personal terms, proved both captivating and timely. My objective on being appointed to the very firm where the distinguished surgeons Mr Sinclair Irwin and the late Mr Reginald Livingston had once been my mentors, was the conversion of a general surgery unit with 11% vascular throughput into a dedicated, regional vascular centre and to set up a clinical vascular laboratory. This process of engineered metamorphosis was entirely in keeping with the best progressive traditions of the Royal Victoria Hospital wherein interlinking specialties have evolved to create a favourable milieu for clinical care and research.

This Vascular Surgery Unit at the Royal, one of the first of three or four such centres in the British Isles, has contributed to vascular research and specialist development at international level for two decades. The vascular service at the Royal relies on the combined expertise of vascular surgeons, radiologists, anaesthetists, nursing staff and laboratory personnel. This team provides a tertiary regional service covering the entire spectrum of vascular disease.

In a very busy clinical vascular laboratory, over 4,000 studies are undertaken annually. The Vascular Surgery Unit is licensed to provide specialist vascular training over the final two-year span. In research it is represented on national bodies and is also involved in international projects. A regional Northern Ireland Vascular Registry (NIVASC), in which other vascular surgeons in the province participate, is in its second year of operation and joins half-a-dozen other such national registries extant in Europe. The Royal Victoria Hospital, with its clinical profile and facilities is well placed to meet the challenges at the threshold of the new millennium.

If these vivid lines from Shakespeare

> *'...but when we have stuffed*
> *These pipes and these conveyances of our blood*
> *With wine and feeding, we have suppler souls*
> *Than in our priest-like fasts...'*
>
> Menenius
> Coriolanus V.1.

seem to extol the spiritual dividends of gluttony, then they also appear a trifle prescient about recent knowledge of the health-giving properties of red wine. On the other hand, they do not, by any stretch of the imagination, demonstrate an understanding of the best

way of escaping the onset of atherosclerosis. That knowledge, relatively recently acquired, is being accelerated by crucially important observations which will undoubtedly shape therapeusis in the early years of the next millennium.

New information is constantly expanding our knowledge of the pathophysiology of injury to the arterial flow surface. We now know that fluid shear stresses promote the release of platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF)[1] and regulate the expression of adhesion molecules,[2] all of which have pathophysiological relevance to the process of development of intimal hyperplasia. Equally, the epidemiology and pathogenesis of atherosclerosis is being unravelled by the addition of new pieces to a complex jigsaw. In studies at the Karolinska, autoantibodies against oxidised LDL,[3] endothelial cells and cardiolipin[4] were found to be associated with early onset of peripheral arterial disease. An Australian group has shown that raised serum lipoprotein(a) in association with elevated LDL cholesterol is a significant determinant of the extent of carotid atheroma.[5] The spotlight on elevated homocysteine as a risk factor in the progression, not only of premature and widespread arterial disease but, interestingly, also of venous thrombosis,[6] may in future merit its inclusion in the routine thrombophilia screen. The observed dose-dependent atherogenic effects of alcohol consumption on carotid arteries[7] may give pause to the current enthusiasm for a prophylactic glass of wine.

The complex morphogenesis of the fibrous cap on an atherosclerotic plaque eventually leading to erosion and the dangerous consequences of plaque haemorrhage, rupture and thromboembolism has caught the imagination of investigators on both sides of the Atlantic. The accumulation of activated mast cells around the fibrous cap[8] and the production of matrix-degrading metalloproteinases (MMPs) which induce collagen breakdown destabilise the fibrous cap,[9] the thinness of which determines its vulnerability. A fibrous cap at such risk, can now be detected by 'attenuation-slope mapping'. of plaque using a sophisticated intravascular ultrasound probe.[10] The discovery of Chlamydia pneumoniae in atherosclerotic plaque[11] and a possible causal relationship is a fascinating mystery which awaits clarification.

The landmark Scandinavian Simvastatin Survival Study (4S) convincingly proved that the lowering of cholesterol prolongs life in patients with established coronary artery disease.[12] Clinical research reports of the value of pravastatin, lovastatin, and other statins leave one with the impression that a specific statin attuned to each permutation of lipid abnormalities will probably come on line. The exciting observation of carotid plaque regression in women receiving oestrogen replacement therapy[13] offers a seductive avenue for a large-scale controlled study, the practicalities of which are already under consideration. Vast quantities of research data in this area are accumulating which will catalyse the development of new modalities of treatment aimed at arresting and reversing the march of atherosclerosis.

In the years ahead, molecular genetic and gene therapy will be mobilised in the task of vitiating major risk factors such as hyperlipidaemic disorders and diabetes, both of which accelerate the advance of arterial disease. Recombinant DNA technology has already been used experimentally to modify endothelial and vascular smooth muscle cell expression.[14] In this way, intimal hyperplasia developing at prosthetic graft anastomoses with the host artery, might be suppressed sufficiently to prevent occlusion of the lumen and graft failure. In time, miniaturised endovascular delivery techniques might well be employed to treat a particular diseased segment of artery but before that goal is realised several hurdles of technique, safety and efficacy in using gene therapy will have to be faced.

New operative techniques will undoubtedly herald the new millennium but their implementation should be dependent on objective appraisal. In the past, vascular operations originated in three main ways: through argument based on knowledge of the pathophysiology, empirically through successful experiment or on the strength of results of a controlled trial, and thirdly, on the pragmatic basis that it works.[15] Thus *a priori* knowledge that emboli from carotid plaque and thrombus produced acute neurological and ocular events, persuaded surgeons to proceed with carotid endarterectomy. Around the world, excessive zeal by a few to operate even when the case for surgery was not convincing, has been matched by the therapeutic nihilism of some neurologists grounded on the Descartian assertion that carotid artery disease as such did not exist. The North American Symptomatic Carotid Endarterectomy Trial (NASCET)[16] and the European Carotid Surgery Trial (ECST)[17] simultaneously concluded that surgery for symptomatic carotid stenosis of 70% or more was preferable to best medical treatment in reducing the rate of stroke and mortality. That position is founded

on the presumption that selection of patients follows careful assessment and that surgical technique is meticulous. The advantage of patch angioplasty in reducing the incidence of recurrent stenosis has been increasingly appreciated.[18] Transcranial Doppler monitoring of middle cerebral artery flow perioperatively provides objective assurance of the safety of surgery. Surgeons should continue to perform this operation only if their audited morbidity and mortality figures remain within the bounds of best reported practice.

It is predicted that two major international trials into which I have entered cases, namely the Asymptomatic Carotid Surgery Trial (ACST) and the Asymptomatic Carotid Stenosis Risk of Stroke (ACSRS) Study will provide important answers. The former is likely to confirm that surgery, in good hands, is preferable to best medical treatment, while the latter is likely to show that certain plaque characteristics are associated with a higher incidence of stroke. Certainly, accumulating evidence of the natural history of carotid atheroma would lead one to anticipate the recommendation that surgery is worthwhile even in the asymptomatic carotid patient.

Diagnostic imaging of the cerebrovascular tree has evolved over the years. Carotid angiography which carries a small but finite risk has been displaced to some extent by colour flow Duplex scans. It must be admitted, however, that during the occasional carotid operation one would have given anything for a set of clear cerebrovascular angiography films in place of the necessarily limited ultrasound image. Nevertheless, it is not just the image or the flow data but the capacity of the Duplex scan to characterise plaque, in terms of echodensity or more unstable echolucency, which has enhanced its popularity. Precise computer-assisted plaque characterisation will eventually be the norm in evaluating the degree of plaque instability.

Evidence-based treatment supported by sustained audit of outcome should be the touchstone of ideal vascular practice. Acute carotid ischaemic stroke represents a scenario which challenges the clinician to act quickly to prevent disaster. The American trial of intravenous tissue plasminogen activator (pt-PA) aimed at arterial clot lysis within three hours of onset of stroke resulted in 30% of patients having minimal disability or none at three months, but the dilemma lies in the knowledge that this benefit was bought at the cost of a 6.4% incidence of symptomatic intracranial haemorrhage.[19] The results of the European Co-operative Acute Stroke Study (ECAS) and that of an Italian trial have been comparatively discouraging, but further study in this area is bound to continue.

In the United States the activities of many cardiologists have been attenuated in the wake of constraints placed by the flourishing HMO systems. Not to be outdone by such reversals, some of them have mobilized their costly, but otherwise redundant equipment, to perform angioplasties and stenting procedures on patients with carotid artery disease. The assessment and selection of these patients for treatment and the outcomes, however, ought to be submitted to the detailed scrutiny generally accorded to carotid endarterectomy by vascular surgeons. If carotid angioplasty is to gain acceptance, data based on standardised protocols must first be produced and, if deemed appropriate, a randomised double-blind controlled trial comparing it with carotid endarterectomy should follow.

Severe vertebrobasilar insufficiency (VBI) has hitherto received scant surgical attention but operations to improve vertebral artery flow are being undertaken more often. A detached distal vertebral artery may be transposed directly into the common carotid artery or, alternatively, a skeletonised external carotid artery may be mobilised and anastomosed to the distal vertebral artery.

The quality of surface ultrasound in revealing plaque on the walls of the arch of the aorta and great vessels has been superseded by transoesophageal echocardiography(TOE) which, being safe, portable and accurate, may become the investigation of choice in acute traumatic aortic disruption. Data reconstruction from spiral CT scans already provides 3-D images of aortic dissection and of thoraco-abdominal aneurysms. Both (TOE) and the more invasive technique of intravascular ultrasound will continue to compete with CT in the diagnosis of thoracic aortic dissection.

Operative reconstruction of the great vessels for atheroma or Takayasu's disease, aimed at preventing stroke, blindness, and upper limb ischaemia, will still be necessary. The occasional practice of balloon angioplasty of stenotic lesions at the origin of the great vessels is not risk-free. The safety margins in surgery for thoraco-abdominal aneurysms have slowly improved: a mortality rate of 5% and a paraplegia rate of 1.5% reported from Houston by Joseph Coselli can hardly be excelled.[20] Epidural spinal cord protection, increasing preference for a 'clamp-and-repair' approach and the selective use of partial bypass may

have contributed to a better outcome.

Endovascular repair of infrarenal aortic aneurysms was perceived as an exciting development in that it offered an alternative form of treatment for the high risk patient with the added bonus of a shorter stay. 3-D multiplane reformats from spiral CT scans and virtual reality software can be used to plan the procedure. James May of Sydney, a key exponent, acknowledges that the technique creates its own problems.[21] Two major operative risks are micro-embolisation of clot from within the aneurysm and failure of the procedure itself requiring conversion to conventional surgery. Late dangers include delayed rupture, leaks into the aneurysm sac and even dislodgement of the proximal end of the stent graft as the aorta dilates. Clearly, this procedure requires to be monitored, but as entry into available registries is voluntary, failures may go unrecorded. One clear and recognised indication for endoluminal stenting is aortic dissection for which it is safer than conventional surgery. Premature conclusions regarding endoluminal aneurysm repair places vascular surgeons under pressure from potential consumers, and it has also spawned a proliferation of competing and sometimes unreliable products. These influences may induce some surgeons to join the bandwagon simply to 'enhance' their centres regardless of the phenomenal expense involved. The timeless axiom of 'primium non nocere', ie 'first do no harm', ought to be kept in mind before initiating any change. That can only come after disciplined evaluation through well controlled studies using standardized protocols based on an intention to treat. Progress in technological support is also required and therefore the precise indications for endovascular aneurysm repair will become clearer well after the year 2000.

One apparently simple but elusive question on surgery for abdominal aortic aneurysms is the optimal diameter at which operation should be undertaken to preempt rupture. A recent Canadian study has confirmed prejudices that aneurysms exceeding 5 cm diameter require surgery and that intervention in those of lesser size should depend on their rate of enlargement. Recent papers have highlighted the appearances of the 'crescent sign', a high-attenuating peripheral crescent observed on an unenhanced CT scan, which signals impending rupture and therefore demands urgent intervention.[22] An increased turnover of Type III collagen in the aneurysm wall[23] may reflect the rate of degradation and may turn out to be a useful marker of the rate of enlargement. Research into elastin cross-linking, collagen, and the importance of elastase and collagenase in aneurysm wall activity will probably continue in desultory fashion well into the next century. A few surgeons have attempted laparoscopic aorto-iliac surgery: this expensive and potentially disastrous procedure which requires up to seven ports and lasts approximately 7-8 hours has little hope of being accepted in the forseeable future. Surgery for renal artery stenosis, for both ostial and non-ostial atherosclerotic lesions as well as for fibromuscular hyperplasia, has been replaced almost completely by balloon angioplasty and stent insertion but we must keep our eye open for recurrent stenosis in the longer term. An interventional approach also bodes well for the management of symptomatic mesenteric arterial lesions.

Hypercoagulability is observed in up to 40% of vascular patients although the nature of the underlying problem is not always identified with ease. Factor V resistance to activated protein C, attributable to a single point mutation is now recognised as the most frequent offender.[24] Undoubtedly other such abnormalities will come to light. Catheter-guided intra-arterial thrombolysis has secured its place in the management of some patients presenting with an acutely ischaemic limb. In acute occlusion of bypass grafts, lytic therapy, sometimes as a prelude to balloon or operative angioplasty, is also well established. Nonetheless, in either instance, if the vascular surgeon believes that the time taken for effective lysis will compromise viability, he should proceed immediately to surgery.

Angioscopically-directed thrombo-embolectomy is an attractive technique in ensuring more complete clearance of clot but its application may wane as intraoperative adjuvant thrombolytic techniques become more refined and less frequently complicated by bleeding, stroke, ischaemia-reperfusion injury, limb loss and even mortality.[25] Using the isolated thrombolysis perfusion technique pioneered by Tony Comerota of Philadelphia,[26] effectively high local levels can be attained while the risks of systemic problems remain negligible. In resolving doubt as to the viability of ischaemic muscle, positron emission tomography (PET) scans using [18F] fluoro-2-deoxyglucose (FDG) uptake have shown high accuracy[27] but this innovative approach is very cumbersome and for the present has to remain no more than a research tool.

The severely disabled claudicant deserves bypass surgery but in the ordinary case doctors are drifting to promising exercise rehabilitation programmes.

Carnitine (propionyl-L-carnitine), a naturally occurring compound, which removes excess acetyl co-enzyme A and improves oxidative metabolism, is especially effective in claudication and may become a valuable adjuvant.[28] Even more intriguing has been the experimental demonstration of the biological response to ischaemia of angiogenesis or neovascularisation in which the mitogenic potential of acidic fibroblast growth factor (aFGF) can be enhanced by heparin which is a cofactor for aFGF.[29] The possible clinical impact of accelerating the development of collateral flow using this concept of 'therapeutic' angiogenesis in patients with limb ischaemia ought to become clearer during the next decade.

The large calibre Dacron graft used in aorto-femoral bypass operations represents an unparalleled success story for lengthy occlusions. Balloon angioplasty, possibly along with stenting, works well in a good proportion of short-segment iliac occlusive lesions. In the femoro-popliteal region the success rate of angioplasty is modest and it often has to be repeated; whereas vein bypass grafts of short length have the best patency rates on record and ought to be the first line of treatment. At infrageniculate level angioplasty tends to be no more than a temporising measure. In general, however, the vascular radiologist is proving to be an increasingly valuable ally in the battle to keep the channels open. Stent grafts of polytetrafluoroethylene to replace lengthy femoro-popliteal occlusions is a new but rather clumsy solution to a problem eminently dealt with by the vascular surgeon. Fortunately, as in the past, many such innovations become fashionable but fail to displace well tried operations and are consigned swiftly to the waste-bin of obsolescence.

Femoro-distal bypass surgery in patients with critical lower limb ischaemia, many of them with diabetes and some with Buerger's disease, have been rewarded by improving rates of limb salvage. After over two decades of disillusionment with a variety of small-calibre prosthetic grafts surgeons are turning increasingly to the original gold standard of autogenous vein, harvesting it from the upper limb if necessary. In-situ vein grafts or unreversed vein grafts, the valves of which require to be disrupted by a valvulotome, allow a better match of calibre of vein to host vessel at each end and therefore became popular in long bypasses. This technique of vein grafting led to the introduction of myriad techniques for disabling vein valves, including angioscopically-guided valvulotomy. After mature reflection and having noted the incidence of failure, especially of small-diameter in-situ bypass grafts, vascular surgeons are showing a renewed faith in the well-tried and tested reversed vein graft. In the anastomotic field, fine clips may in time replace polypropylene suture while fibrin glues and sealants which reduce suture line bleeding are now available. Spinal cord stimulation is being used in an attempt to relieve pain in extreme cases of lower limb ischaemia but this expensive device should not be used indiscriminately until it is first subjected to the rigours of a randomised trial.

Surveillance of limb bypass grafts using colour flow Duplex scans to pick up early signs of stenosis in vein grafts or of intimal hyperplasia at prosthetic graft anastomoses has been one of the many functions of the clinical vascular laboratory. These changes, usually discovered in a modest proportion of cases within a year of implantation, allow the opportunity for corrective surgery to preempt graft failure. There is much debate on the value of ultrasound surveillance but the view is held, not surprisingly from the cold-blooded perspective of cost-effectiveness, that it is not worth while. It should be appreciated that prompt intervention to prolong graft patency can save a limb, and also that early postoperative evidence of normality of a graft does not bestow perpetual patency on it.

Much more desirable, of course, is an effective deterrent against intimal hyperplasia. Vascular literature is replete with reports on restenosis of arterial grafts and the complex pathophysiological mechanisms involved in smooth muscle cell proliferation and matrix deposition observed in intimal hyperplasia. Various drugs such as heparin, calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitors have been employed to discourage this process. Less appealing strategies include the interposition of vein cuffs and collars between prosthesis and host artery, and the more disturbing measure of intravascular low-dose irradiation. Encouraging research work using matrix metalloproteinase activity inhibitors,[30] photodynamic therapy[31] and others await the test of time.

Low molecular weight heparin (LMWH) is safe, effective and convenient and has almost completely displaced the use of unfractioned heparin in deep vein thrombosis prophylaxis. The peroperative physical measures of intermittent pneumatic compression of the calf used by some surgeons is being superseded by the surprisingly effective impulse foot-pump. In acute deep vein thrombosis, colour flow Duplex scans of the major channels are accurate and informative but venography will still remain important in the detailed

imaging of calf vein tributaries. Advances in MRA technology will in due course offer a fresh alternative to current diagnostic imaging of the venous system. Thrombolysis in instances of ilio-femoral vein thrombosis perhaps protected by a caval filter has the attractive potential for clearing clot early enough to preserve valve function while also expediting discharge from hospital. When contraindications to lysis exist, surgical thrombectomy and construction of a temporary arteriovenous fistula is the best available alternative.[32]

In the management of post-thrombotic lower limb venous hypertension, valve reconstruction and valve transposition techniques have been refined and will be increasingly applied. The durability of the much-vaunted technique of endoscopic subfascial ligation of incompetent perforators in promoting ulcer healing, so far unproven, can only be established by a proper controlled trial. In vein trunk compression syndromes, usually a feature of advanced cancer, stents carefully placed by the skilled interventional radiologist have brought profound relief.

Management of the non-operative aspects of vascular disease, which in this country is largely the responsibility of the vascular surgeon, falls within the discipline of angiology, a specialty which has been successfully nurtured in several European countries. Some angiologists even undertake interventional vascular procedures, a technical role which in most British centres is exercised by our radiology colleagues. This collaborative relationship between vascular surgeons and radiologists is set fair for the next millennium as long as it is rooted on the immutable premise that optimal care of the vascular patient as a whole remains the pre-eminent consideration. A case should be made for the enlargement of this team to include a physician with a specific interest in vascular disease.

Looking ahead to the future of vascular surgery one could concievably become preoccupied rather fruitlessly by the inequities and the underfunding of health care in general. These concerns however, seem, ephemeral, particularly when viewed against the ethos of service, immeasurable devotion, compassion, sacrifice and, not least, the optimism, which have steered this great hospital through two long centuries, and which will doubtless sustain it in the years to come.

REFERENCES

1. Sterpetti AV, Cucina A, Fragale A, et al. Shear stress influences the release of platelet-derived growth factor and basic fibroblast growth factor by arterial smooth muscle cells. *Eur J Vasc Surg* 1994; **8**: 138- 42.

2. Nagel T, Resnick N, Atkinson WJ, et al. Shear stress selectively upregulates intercellular adhesion molecule-1 expression in cultured human vascular endothelial cells. *J Clin Invest* 1994; **94**: 885-91.

3. Bergmark C, Wu R, de Faire U, et al. Patients with early-onset peripheral vascular disease have increased levels of antibodies against oxidised LDL. *Arterioscler Thromb Vasc Biol* 1995; **15**: 441-5.

4. Nityanand S, Bergmark C, de Faire U, et al. Antibodies against endothelial cells and cardiolipin in young patients with peripheral atherosclerotic disease. *J Intern Med* 1995; **238**: 437-43.

5. Watts GF, Mazurkiewicz JC, Tonge K, et al. Lipoprotein(a) as a determinant of the severity of angiographically defined carotid atherosclerosis. *Quart J Med* 1995; **88**: 321-6.

6. Fermo I, Vigano S, Parone R, et al. Prevalence of moderate hyperhomocysteinemia in patients with early onset venous and arterial occlusive disease. *Ann Intern Med* 1995; **123**: 747-53.

7. Kiechl S, Willeit J, Egger G. Alcohol consumption and carotid atherosclerosis: evidence of dose dependent atherogenic and antiatherogenic effects - results from the Bruneck Study. *Stroke* 1994; **25**: 1593-8.

8. Kaartinen M, Penttila A, Kovanen PT. Accumulation of activated mast cells in the shoulder region of human coronary atheroma, the predilection site of atheromatous rupture. *Circulation* 1994; **90**: 1669- 78.

9. Shah PK, Faik E, Badimon JJ, et al. Human monocyte-derived macrophages induce collagen breakdown in fibrous caps of atherosclerotic plaque: potential role of matrix-degrading metalloproteinases and implications for plaque rupture. *Circulation* 1995; **92**: 1565-9.

10. Wilson CS, Neale ML, Talham I, Appleberg M. Preliminary results from attenuation slope mapping of plaque using intravascular ultrasound. *Ultrasound Med Biol* 1994; **20**: 529-42.

11. Kuo C-C, Coulson AS, Campbell LA, et al. Detection of Chlamydia pneumoniae in atherosclerotic plaques in the walls of arteries of lower extremities from patients undergoing bypass operation for arterial obstruction. *J*

Vasc Surg. 1997; **26**: 29-31.

12. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; **344**: 1383-9.

13. Akkad A, Hartshorne T, Bell PRF, et al. Carotid plaque regression on oestrogen replacement: a pilot study. *Eur J Vasc Endovasc Surg* 1996; **11**: 347-8.

14. Clowes MM, Lynch CM, Miller AD, et al. Long term biological response of injured rat carotid artery seeded with smooth muscle cells expressing retrovirally induced human genes. *J Clin Invest* 1994; **93**: 644-51.

15. Chant ADB. Carotid endarterectomy - a pragmatic viewpoint. in Barros D'Sa AAB, Bell PRF, Darke SG, Harris PL eds. Vascular Surgery: Current Questions. London: Butterworth Heinemann 1991, p 21.

16. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991; **325**: 445-53.

17. European Carotid Surgery Trialists' Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. *Lancet* 1991; **337**: 1235-43.

18. Ranoboldo CJ, Barros D'Sa AAB, Bell PRF, Chant ADB, Perry PM. Randomized controlled trial of patch angioplasty for carotid endarterectomy. *Br J Surg* 1993; **80**: 1528-30.

19. Marler JR (National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, Bethesda, Md). Tissue plasminogen activators for acute ischaemic stroke. *N Engl J Med* 1995; **333**: 1584-7.

20. Coselli JS, Plestis KA, la Francesca S, et al. Results of contemporary surgical treatment of descending thoracic aortic aneurysms: experience in 198 patients. *Ann Vasc Surg* 1996; **10**: 131-7.

21. May J, White CH, Yu W, et al. Surgical management of complications following endoluminal grafting of abdominal aortic aneurysms. *Eur J Vasc Surg* 1995; **10**: 51-9.

22. Mehard WB, Heiken JP, Sicard GA. High-attenuating crescent in abdominal aortic aneurysm wall at CT: a sign of acute or impending rupture. *Radiology* 1994; **192**: 359-62.

23. Satta J, Juvonen H, Aukipuro K, et al. Increased turnover of collagen in abdominal aortic aneurysms, demonstrated by measuring the concentration of the aminoterminal propeptide of type III procollagen in peripheral and aortic blood samples. *J Vasc Surg* 1995; **22**: 155-60.

24. Ridker PM, Hennekens CH, Lindpaintner K, et al. Mutation in the gene coding for coagulation Factor V and the risk of myocardial infarction, stroke and venous thrombosis in apparently healthy men. *N Engl J Med* 1995; **332**: 912-7.

25. Yassin MMI, Barros D'Sa AAB, Parks TG, Abdulkadir AS, Halliday MI, Rowlands BJ. Mortality following lower limb ischaemia-reperfusion: a systemic response to lipopolysaccharide? *World J Surg* 1996; **20**: 961-7.

26. Comerota AJ. Intraoperative intra-arterial thrombolytic therapy. in Yao JST, Pearce wH eds. Progress in Vascular Surgery. Stamford, Connecticut: Appleton Lange 1996, p 341.

27. Smith GT, Wilson TS, Hunter K, et al. Assessment of skeletal muscle viability by PET. *J Nuclear Med* 1995; **36**: 1408-14.

28. Brevetti G, Perna S, Sabba C, et al. Propionyl-L-carnitine in intermittent claudication: double-blind placebo-controlled, dose titration, multicenter study. *J Am Coll Cardiol* 1995; **26**: 1411-6.

29. Rosengart TK, Budenbender KT, Duenas M, et al. Therapeutic angiogenesis: a comparative study of the angiogenic potential of acidic fibroblast growth factor and heparin. *J Vasc Surg* 1997; **26**: 302- 12.

30. Benedeck MP, Irvin C, Reidy MA. Inhibition of matrix metalloproteinase activity inhibits smooth muscle cell migration but not neointimal thickening after arterial injury. *Circ Res* 1996; **78**: 38-43.

31. Nyamekye I, Buonaccorsi G, McElvan J, et al. Inhibition of intimal hyperplasia in balloon injured arteries with adjunctive phthalocyanine sensitised photodynamic therapy. *Eur J Vasc Endovasc Surg* 1996; **11**: 19- 28.

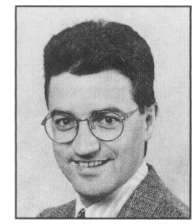
32. Eklof BGH. Deep venous thrombosis and pulmonary embolism. In Chant ADB, Barros D'Sa AAB eds. Emergency Vascular Practice. London: Arnold 1997, p 135.

Brian J Rowlands MD, FRCS, FACS
Introduction of the Purce Lecture

George Ralph Hewitt Purce, known to his friends and colleagues as Barney, graduated with honours in 1914 and then went straight off to the first world war with the Royal Irish Rifles and won the Military Cross. He returned in 1920 to the Royal Victoria Hospital and, for the next 30 years, served as a general surgeon, a thoracic surgeon and a neurosurgeon and along with Calvert, (the other research lecture), he established many of the techniques that were used in the early days of neurosurgery. In addition to his professional pursuits, he was a great sportsman, played hockey for Ireland in his youth and then took up fishing, shooting and sailing which he did with great passion and great skill. He died at the relatively young age of 59 in 1950 and was truly one of the great sons of Ulster and his contribution to surgery and surgical history of the Royal is immense.

Gut Barrier Dysfunction in Obstructive Jaundice

THE PURCE LECTURE 1997



Rowan Parks MD, FRCS
Department of Surgery
The Queen's University of Belfast

INTRODUCTION

Invasive diagnostic and therapeutic procedures in patients with obstructive jaundice are associated with high morbidity and mortality, due to the development of complications, such as renal failure, sepsis, coagulation disorders and impaired wound healing.[1,2] The high incidence of these complications has prompted much research into the underlying pathophysiological mechanisms responsible for their development and also into various potential therapeutic strategies aimed at reducing their incidence. Proposed aetiological factors include the presence of potential toxic substances in the circulation, such as bilirubin and bile salts, overt or latent hypovolaemia, hypotension, and impaired nutritional status[3-5]. However, since Wardle and Wright demonstrated an association between the presence of endotoxaemia and renal failure in obstructive jaundice[6], endotoxin has been increasingly implicated in the pathophysiology of the complications seen in jaundiced patients.

It is currently postulated that there are two major contributing factors in the development of endotoxaemia in obstructive jaundice. One is impaired gastrointestinal barrier function allowing permeation of bacteria and endotoxins into the portal circulation and the lymphatic drainage system of the gut.[7,8] The other is impaired reticuloendothelial cell phagocytic function resulting in reduced clearance of bacteria and endotoxin[9,10], thereby allowing "spillover" of endotoxin into the systemic circulation with the subsequent development of systemic complications (Figure 1).

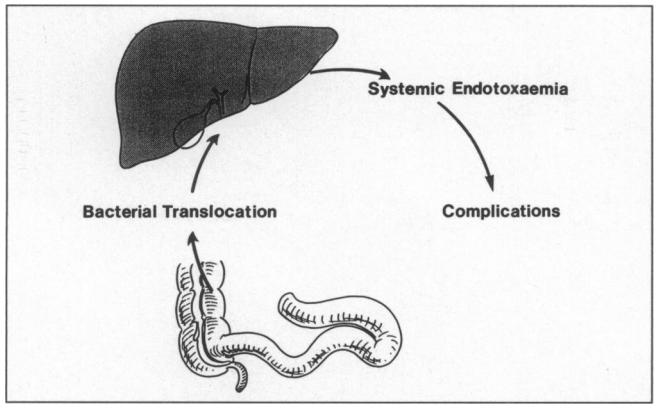


Figure 1

The intestine performs many functions, including the complex processes of digestion, selective absorption, secretion and immune modulation. In addition, it normally prevents bacteria contained within the lumen of the gut from escaping and invading systemic organs and tissues. When indigenous bacteria or endotoxin pass from the gut lumen to normally sterile extraintestinal sites, such as the mesenteric lymph nodes, liver, spleen, peritoneal cavity and blood-stream, the process is known as bacterial translocation and its occurrence implies gut barrier failure[11]. A significantly higher incidence of septic complications has been shown in patients who have evidence of bacterial translocation at the time of laparotomy (28%) compared to those who do not (11%).[12] The integrity of the mucosal barrier can also be assessed by measuring intestinal permeability. Increased permeability implies functional impairment of the intestinal mucosal barrier and has been shown in burn patients to be a significant risk factor for the development of sepsis.[13,14]

The aim of these studies was to investigate gut barrier function in an experimental model of biliary obstruction and in jaundiced patients. The incidence of bacterial translocation was examined following bile duct ligation in rats, and factors known to promote this phenomenon were studied. Changes in intestinal permeability were also determined in this animal model and in patients with obstructive jaundice. In addition, the effect of internal biliary drainage on intestinal permeability was assessed in the clinical setting.

ANIMAL STUDIES

Adult female Wistar rats (250 - 300g) were used in the following series of studies. Experimental extrahepatic obstructive jaundice was produced using the method described by Lee[15]. Significantly raised bilirubin concentrations were recorded in all animals following bile duct ligation.

(1) Bacteriological Study

Rats were randomised to having no operation (n=14),

bile duct ligation (BDL) (n=16) or sham operation (n=16). After a period of one week, the animals were anaesthetised and laparotomy was performed under sterile conditions. Portal blood was collected, and segments of the intra-abdominal solid organs and caecum were harvested. Samples were cultured aerobically and anaerobically at 37°C. After appropriate incubation periods, individual colonies were identified by standard bacteriological techniques.[16] Bile duct ligation resulted in a significantly increased incidence of bacterial translocation compared with animals having no operation or sham operation (68.5% BDL vs 6.3% Sham vs 0% No operation, $P < 0.01$, Fisher's Exact test). Translocation was predominantly to the mesenteric lymph nodes and the organism most commonly cultured was Escherichia coli.

A broader spectrum of gram negative organisms was cultured from the caecum of jaundiced rats compared with the control groups, with an increased prevalence of pseudomonas, pasteurella, shigella and proteus. In addition to this qualitative disturbance, a quantitative disturbance of the indigenous caecal microflora was also demonstrated following bile duct ligation. A significant increase in the caecal gram negative aerobic population was shown as evidence of bacterial overgrowth.

(2) Morphological Study

Rats were assigned to one of three groups: no operation (n=8), bile duct ligation (n=11) or sham operation (n=10). One week following intervention, the animals were anaesthetised and laparotomy was performed. Segments of bowel were harvested from the following sites: 5 cm distal to the gastric outlet (jejunum), 5 cm proximal to the caecum (ileum), the caecum itself and the transverse colon. The bowel was opened along its length and immediately fixed in formalin. After fixation, segments were embedded in paraffin wax and 5μm sections were then cut and stained with haematoxylin and eosin. Histological evaluation was performed by an independent pathologist. Well-orientated sections showing good preservation of structure and cytological detail were selected for morphometric assessment using a computerised image analysis system.

There was no obvious breach or gross ulceration of the mucosa in any of the animals studied. Morphometric assessment showed no difference in mucosal measurements in the jejunum, caecum or colon. However, significant morphological changes were demonstrated in the terminal ileum of jaundiced rats compared with the control groups of animals (Table 1). The reduction of total mucosal thickness observed in this study largely reflected a significant decrease in villus height.

TABLE 1

	Ideal measurements (pm)		
	Mucosal thickness	Villus height	Crypt depth
Control	744 (95)	559 (79)	183 (19)
Sham	731(27)	515 (18)	193 (11)
BDL	650 (23) *	451 (20) *	180 (8)

Morphometric measurements of ideal mucosa. Results are expressed as mean (SEM). * $P < 0.02$, Mann-Whitney U test.

(3) Intestinal Permeability Study.

Rats were randomised to undergo bile duct ligation (n=12) or sham operation (n=12). Intestinal permeability was measured by calculating the percentage change in the 24 hour urinary recovery of orally administered radiolabelled polyethylene glycol 4000 (^{14}C PEG 4000) given 1 week prior to operation and 1 week following operation with each animal acting as its own control[17]. PEG 4000 was used as it is a macromolecule whose size mimics that of antigenic substances, such as endotoxin.

There was a significant increase in intestinal permeability in bile duct ligated animals compared with sham operated controls (+66.2% BDL vs -11.6% Sham, $P<0.01$, Mann Whitney U test) (Figure 2).

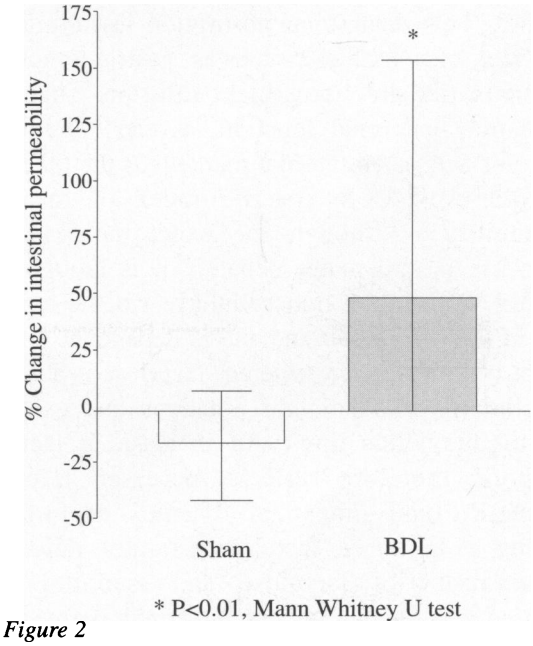


Figure 2

CLINICAL STUDY

A prospective study was performed on 45 consecutive patients with obstructive jaundice (bilirubin > 100 μmol/1) undergoing internal biliary drainage as a definitive therapeutic procedure by surgical (n=11), endoscopic (n=16) or percutaneous (n=18) means. Of those patients who had surgical intervention, five patients had choledocholithiasis and underwent open cholecystectomy with exploration of the common bile duct, and six had malignant biliary obstruction. Of the later group, two had a Whipple procedure, one had a localised resection of a periampullary tumour and three had biliary bypass procedures performed without resection.

Ten nonjaundiced patients undergoing laparotomy (n=9) or diagnostic endoscopic retrograde cholangiopancreatography (ERCP)(n=l) were also studied to act as control patients. All patients received 1.5g cefuroxime immediately prior to intervention. Systemic or oral antibiotics were not administered routinely following intervention, but were administered if clinically indicated. Each patient was studied on the day prior to therapeutic intervention and on days 1, 7 and 28 following their procedure. Routine liver function tests were performed and intestinal permeability was measured. In addition, intestinal permeability was assessed in 11 healthy volunteers to obtain a reference value for our test of intestinal permeability which would reflect normal gut barrier function.

Intestinal Permeability

Intestinal permeability was assessed by measuring the urinary excretion of orally administered lactulose and mannitol. This dual sugar absorption test eliminates the effect of variables, such as gastric emptying, intestinal transit, intestinal dilution, bacterial degradation and renal function, as each of the test molecules acts as an internal marker for the other and therefore provides a specific index of intestinal permeability.[18] Although the exact pathways the probes use is still under debate,[19] it is thought that mannitol is absorbed transcellularly via the aqueous pores in the cell membrane and is dependant on total absorptive surface area, whereas lactulose is absorbed paracellularly, via the tight junctions and extrusion zones at the villus tips.[20] An increase in lactulose absorption therefore reflects increased intestinal "leakiness" and intestinal barrier dysfunction, resulting in a raised lactulose/mannitol ratio. The concentrations of lactulose and mannitol were measured enzymatically and intestinal permeability was expressed as the lactulose / mannitol ratio [17]

The mean serum bilirubin in the jaundiced group prior to therapeutic intervention was significantly higher than in the control group of patients (235 μmol/l vs 7.5 μmol/1, P<0.0001, Mann Whitney U test). Following therapeutic intervention, the mean serum bilirubin in the jaundiced group of patients was progressively lower at each of the time points studied (182 ,μmol/1 Day +1 vs 73 μmol/1 Day +7 vs 21 μmol/l Day +28).

The median [interquartile range (i.q.r.)] lactulose / mannitol permeability index in 11 normal healthy volunteers [0.019 (0.012 - 0.030)] was not significantly different from the control group of nonjaundiced patients [0.015 (0.011 - 0.021)] (P = 0.377, Mann Whitney U test). However, the median (i.q.r.) lactulose / mannitol ratio for patients with unrelieved obstructive jaundice [0.033 (0.021 - 0.046)] was significantly higher than that of the control group of patients studied preoperatively (P<0.0001, Mann Whitney U test). Twenty eight days following intervention, the lactulose / mannitol ratio in patients who had presented with obstructive jaundice had returned to normal and was significantly less than on the day before internal biliary drainage (P < 0.05, Wilcoxon's Signed Rank test) (Figure 3).

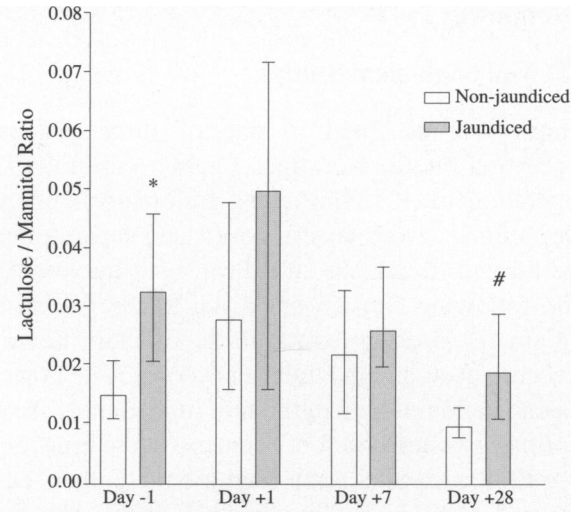


Figure 3 * P < 0.0001, vs Non-jaundiced, Mann Whitney U test
# P < 0.05, vs Day -1, Wilcoxon's Signed Rank test

DISCUSSION

These studies have demonstrated evidence of impaired intestinal barrier function in obstructive jaundice. Significant bacterial translocation and significantly increased intestinal permeability were shown following bile duct ligation in an animal model. In addition, significantly increased intestinal permeability was demonstrated in jaundiced patients and this impairment of gut barrier function was shown

to be reversed by returning bile to the gastrointestinal tract.

Bacterial translocation following bile duct ligation has been reported by others[21-24], However, the mechanisms by which bacteria escape from the intestinal lumen remain to be clearly defined. Deitch, has proposed three factors which may promote this process, namely, disruption of the indigenous gut microecology, physical injury of the gut mucosa and impairment of host immunity.[25] Previously, our group has demonstrated impaired reticuloendothelial cell function in jaundiced rats.[10] In these present studies, we have demonstrated a qualitative and quantitative alteration of the indigenous caecal microflora following bile duct ligation. Bacterial overgrowth of the gram negative aerobes was associated with significant bacterial translocation, predominantly to the mesenteric lymph nodes. In addition, we have demonstrated morphometric evidence of intestinal mucosal injury in jaundiced rats.

Absence of intraluminal bile may be responsible for these findings. Bile salts are known to inhibit the growth of intestinal bacteria both in vitro and in vivo[26,27] and, therefore, their absence may allow overgrowth of certain species of bacteria and thus promote the likelihood of that species translocating from the gastrointestinal tract. In addition, Iwasaki and Tanikawa reported that bile salts had anti-endotoxin effects by breaking down the endotoxin molecule into subunits and forming unabsorbable micellar aggregates.[28] Therefore, loss of the emulsifying properties of intraluminal bile salts could result in a larger pool of endotoxin available for translocation into the portal circulation. Bile is also known to promote cell proliferation and has a trophic effect upon intestinal mucosa.[29,31] Hence, absence of intraluminal bile may also contribute to the morphological changes demonstrated following bile duct ligation.

To date, there has been no evaluation of intestinal permeability in obstructive jaundice. The finding of significantly increased intestinal permeability in the experimental study was confirmed in the clinical study and this provides the first reported evidence of gut barrier dysfunction in jaundiced patients.

In the clinical study, intestinal permeability was increased on the first postoperative day in both jaundiced and nonjaundiced patients. This increase was more marked in patients who underwent surgical intervention than in those who had non-operative biliary decompression, and this may reflect a further endotoxin challenge to intestinal barrier function through exposure of the peritoneal cavity to endotoxin in the air at laparotomy[40]. By the seventh postoperative day the lactulose / mannitol ratio had returned to preoperative levels. More importantly, in patients with jaundice, the intestinal permeability index continued to fall and after 28 days of internal biliary drainage had returned to normal.

In conclusion, these studies demonstrate evidence of impaired intestinal barrier function following experimental biliary obstruction with significant bacterial translocation and increased intestinal permeability. There was also significantly increased intestinal permeability in jaundiced patients which returned to normal after 28 days of internal biliary drainage. This suggests that return of bile to the gastrointestinal tract may improve intestinal barrier function and reduce the incidence of gut-derived sepsis or other complications associated with endotoxaemia in obstructive jaundice.

ACKNOWLEDGEMENT

This work was supported by a research fellowship from Charitable Funds of the Royal Victoria Hospital, Belfast, Northern Ireland.

REFERENCES

1. Pain JA, Cahill CJ, Bailey ME. Perioperative complications in obstructive jaundice: therapeutic considerations. *Br J Surg* 1985; **72**: 942-5.

2. Greig JD, Krukowski ZH, Matheson NA. Surgical morbidity and mortality in one hundred and twenty-nine patients with obstructive jaundice. *Br J Surg* 1988; **75**: 216-9.

3. Aoyagi T, Lowenstein LM. The effect of bile acids and renal ischaemia on renal function. *J Lab Clin Med* 1968; **71**: 686-92.

4 Armstrong CP, Dixon JM, Taylor TV, Davies GC. Surgical experience of deeply jaundiced patientswith bile duct obstruction. *Br J Surg* 1984; **71**: 234-8.

5 Bomzon A, Finberg JPM, Tovbin D, Naidu SG, Better OS. Bile salts, hypotension and obstructive jaundice. *Clin Sci* 1984; **67**: 177-83.

6. Wardle EN, Wright NA. Endotoxin and acute renal failure associated with obstructive jaundice. *Br Med J* 1970; **4**: 472-4.

7. Bailey ME. Endotoxin, bile salts and renal function in obstructive jaundice. *Br J Surg*, 1976; **63**: 774-778.

8. Reynolds JV, Murchan P, Leonard N, Clarke P, Keane FB, Tanner WA. Gut barrier failure in experimental obstructive jaundice. *J Surg Res* 1996; **62**: 11-16.

9. Pain JA. Reticuloendothelial function in obstructive jaundice. *Br J Surg* 1987; **74**:1091-4.

10. Clements WDB, Halliday Ml, McCaigue M, Barclay RG, Rowlands BJ. Effect of extrahepatic obstructive jaundice on Kupffer cell clearance capacity. *Arch Surg* 1993; **128**: 200-5.

11. Berg RD, Garlington AW. Translocation of certain indigenous bacteria from the gastrointestinal tract to the mesenteric lymph nodes and other organs in a gnotobiotic mouse model. *Infect Immun* 1979; **23**: 403-11.

12. Sedman PC, Macfie J, Sagar P, Mitchell CJ, May J, Mancey-Jones B, Johnstone D. The prevalence of gut translocation in humans. *Gastroenterology* 1994; **107**: 643-9.

13. LeVoyer T, Cioffi WG, Pratt L, et al. Alterations in intestinal permeability after thermal injury. Arch Surg 1992; **127**: 26-30.

14. Ziegler TR, Smith RJ, O'Dwyer ST, Demling RH Wilmore DW. Increased intestinal permeability associated with infection in burn patients. *Arch Surg* 1988; **123**: 1313-9.

15. Lee E. The effect of obstructive jaundice on the migration of reticuloendothelial cells and fibroblasts into early experimental granulomata. *Br J Surg* 1972; **59**:875-7.

16. Parks RW, Clements WDB, Pope C, Halliday MI, Rowlands BJ, Diamond T. Bacterial translocation and gut microflora in obstructive jaundice. *J Anat* 1996; **189**: 561-5.

17. Parks RW, Clements WDB, Smye MG, Pope C, Rowlands BJ, Diamond T. Intestinal barrier dysfunction in clinical and experimental obstructive jaundice and its reversal by internal biliary drainage. *Br J Surg* 1996; **83**: 1345-9.

18. Menzies IS, Pounder R, Heyer S, Laker MF, Bull J, Wheeler PG, Creamer B. Abnormal intestinal permeability to sugars in villus atrophy. *Lancet* 1979; **2**: 1107-1109.

19. Bjarnason I, MacPherson A, Hollander D. Intestinal permeability: An overview. *Gastroenterology* 1995; **108**: 1566-81.

20. Deitch EA. Intestinal permeability is increased in burn patients shortly after injury. Surgery 1990; **102**: 411-6.

21. Deitch EA, Sittig K, Ma L, Berg R, Specian RD. Obstructive jaundice promotes bacterial translocation from the gut. *Am J Surg* 1990; **159**: 79-84.

22. Slocum MM, Sittig KM, Specian RD, Deitch EA. Absence of intestinal bile promotes bacterial translocation. *Am Surgeon* 1992; **58**: 305-10.

23. Ding JW, Andersson R, Soltesz V, Willen R, Bengmark S. Obstructive jaundice impairs reticuloendothelial function and promotes bacterial translocation in the rat. *J Surg Res* 1994; **57**: 238-45.

24. Reynolds JV, Murchan P, Redmond HP, Watson RWG, Leonard N, Hill A, Clarke P, Marks P, Keane FBV, Tanner WA. Failure of macrophage activation in experimental obstructive jaundice: association with bacterial translocation. *Br J Surg* 1995; **82**: 534-8.

25. Deitch EA. Bacterial translocation of the gut flora. *J Trauma* 1990; **30**: S 184-9.

26. Floch MH, Gershengoren W, Elliott S, Spiro HM. Bile acid inhibition of the intestinal microflora. A function for simple bile acids ? *Gastroenterology* 1971; **61**: 228-33.

27. Williams RC, Showalter R, Kern F. In vivo effect of bile salts and cholestyramine on intestinal anaerobic bacteria. *Gastroenterology* 1975; **69**: 483-91.

28. Iwasaki M, Tanikawa K. Liver disease and endotoxin. Effect of bile acid on endotoxin. *Nippon Shokakibyo Gakki Zasshi* 1981; **78**: 1232-40.

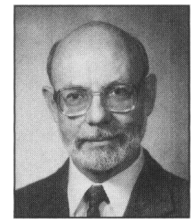
29. Altmann GG. Influence of bile and pancreatic secretions on the size of the intestinal villi in the rat. *Am J Anat* 1971; **132**: 167-77.

30. Williamson RCN, Bauer FLR, Ross JS, Malt RA. Contributions of bile and pancreatic juice to cell proliferation in ileal mucosa. *Surgery* 1978; **83**: 570-6.

31. Levi AC, Borghi F, Petrino R, Bargoni A, Fronticelli CM, Gentilli S. Modifications of the trophism of intestinal mucosa after intestinal and biliopancreatic diversion in the rat. *Ital J Gastroenterol* 1991; **23**: 202-7.

32. Watson RWG, Redmond HP, McCarthy J, Burke PE, Bouchier-Hayes D. Exposure of the peritoneal cavity to air regulates early inflammatory responses to surgery in a murine model. *Br J Surg* 1995; **82**: 1060-5.

Electronic medical records- promises, promises!



Colum A Gorman MB, BCh, PhD
Endocrinologist & Internal Medicine
Mayo Clinic, Rochester, USA

Introduction

There is little doubt that when we seek the defining characteristics of this century, and indeed of this millennium, we will number among them the advent of electronic computing. The potential of computers to favorably affect the human condition is undoubted and is far from being fully realized. Computers have already revolutionized banking and business, tax collection and warfare, automobiles and science. Combined with the communications revolution, especially the Internet, the power of computing now reaches into almost every school in the developed world and permits the greatest teachers, previously restricted to those within the sound of their voices, now to reach an audience of millions.

In medicine, too, these joint revolutions in communication and computing have changed us more in the last thirty years than in the previous three hundred. Our laboratories are connected by telephone lines to our clinical work stations and our tomographic and nuclear medicine scanners could not exist without powerful computers. Our insurance and social agencies would be inoperative without the host of computers that help us with cost accounting and billing.

So where are the unfulfilled promises? They are in the direct application of computers to clinical patient care. At present your credit history is accessible in an instant at your petrol pump. Your banking business is electronically recorded at a terminal. But most clinical interactions take place face to face and are still recorded on paper. With few and partial exceptions, the direct involvement of computers into clinical care delivery remains a promise rather than an achievement.

Why is this so? Everyone says they want an electronic medical record. Some of them actually mean it! And everyone has his or her concept of what it should achieve. Physicians dream of a time when the patient's chart is always available. When those aging, tattering, yellowing, bulky, illegible, time-eating monsters will be replaced by neat computer summaries with trend lines displayed, reminders offered and guidelines in place. Pharmacists hope to have the electronically placed order instantly arrive, legible, at their desktops. Patients hope to hear no more apologies for lost charts and anticipate a time when the data they have provided in one clinical setting is consistently available in another. They hope for transferability of medical records and protection of their privacy. They yearn for an end to medication errors in the hospital and outpatient department. Administrators seek trouble free and timely analysis of practice trends and of physician performance. They hope for reduced costs of paper handling and implementation of practice guidelines embedded in the electronic patient record. They envisage Monday morning data analyses that tell them how the enterprise is functioning. Currently not many have this luxury available.

In face of such potential why are we so short of achievement? In my view, complex human and technical factors are responsible. To begin with a metaphor. Physicians are fighter pilots in a commercial airline age! Consider the fighter pilot. He—almost all are male—is chosen for his rapid decision making, his ad hoc reaction to any circumstance in a dogfight, his technological skills in handling powerful and expensive machinery, his single minded pursuit of the target. Independence of thought and action! Exciting, high risk stuff! Glamorous!

Consider the commercial airline pilot! He or she is chosen for sober responsible behavior. There are sensors on the landing gear and his or her performance rating is lowered if the passengers are bumped on landing. The take off and landing instructions are given by executives. The course is determined by the meteorologist and bumpy air is avoided by lengthy detours if necessary. The amount of fuel is defined precisely to provide an adequate safety margin, and the comfort and safety of the passengers collectively is the goal. Fighter pilots find such work boring. They probably do not do it well. Yet airline travel is remarkably safe.

Medicine today is moving away from the independent

thinking "I like to do it my way" physician fighter pilot mode toward a model where precise guidelines toward optimized outcomes can be defined. When followed carefully, application of these guidelines will improve the public health. Physicians recognize with their heads that this is the way they must go—but they hate it. They are fighter pilots at heart-and the computer that is the messenger of those who would control their behavior-takes it on the chin! The blank sheet is the symbol of totally independent judgment. One can write or omit exactly what one wants. The structured data entry modes loved by electronic medical record designers symbolize constraint. "I am not a form filler nor a secretary—Take it away!" is the cry.

There is some merit to their plaint. There are some things computers should not do and there are some clinical judgments that we should not have to document because the faculties that led us to those decisions are at such a high level of cerebration that their documentation would be inordinately burdensome. I will use a trivial example. Let us write a program for a computer to pick out a tie!

What does the programmer need to know? Certainly the parameters of type-bow or pendant, colors, surface design, texture and the hierarchical rules that establish which of these takes precedence. What is the occasion—wedding or funeral? What will be worn with it? Program in all the colors and the textures of the accompanying garments. Program in all the socially and culturally undesirable images that the designer should exclude—no naked ladies or political symbols. How old is the person? At this point we are ready to program in the attributes of the available tie selection. Depending on how many to choose from this may be a long job. Now we will be ready to go. It will require about a year of programming time or your wife could do it in ten seconds!

Seriously, the knowing glance of an experienced clinician can reveal in seconds what systematic computer programs may never be able to accomplish. The symphonic interaction of clinical faculties can be learned and is amazingly efficient but is very difficult to take into account in computer systems. Clinicians know this intuitively but rarely articulate the concept. Computer scientists seek to disaggregate the elements of the clinical interaction, and physicians chafe at the slowness of the disassembled process. They perceive, correctly, that the computer is slowing them down and they resist it.

Another frequent objection to the use of computers among physicians is the aphorism that medicine is an art not a science. While partly true, this is a diminishing truth. Good diagnoses and good clinical judgment are founded on data, information, knowledge, and wisdom. These are largely science. The communication of the prognosis to the patient or the gentle evocation of long held secrets is an art. We need to apply computers to the science and retain our loyalty to the art and to the ethic. Most of all we need to recognize when art has been supplanted by technology. I will exchange all the clinical judgment in the world, applied to the diagnosis of primary hypothyroidism, for a good TSH assay!

The fundamentals of a physician patient relationship have not changed substantially for thousands of years. Patients still seek an explanation of phenomena they do not understand, relief of pain and an altered prognosis. Whether accomplished by throwing bones, reading the stars or by computerized tomography, these fundamentals will remain. Our electronic patient records have the potential to provide and display better data. They can be programmed as to how to process those data by the consensus wisdom of experts in the field. They will always require an interpreter with a human face and human values.

Technical Factors

I will allude only briefly to the technical factors that have attenuated the introduction of electronic medical records. Information about a specific patient comes from diverse sources-laboratories, history, physical findings, registration desk, nurses, physicians, and physiotherapists to quote a few examples. This information must be recorded, stored, retrieved, displayed, edited, analyzed and printed. At each step there are problems. We have already alluded to some of the resistance to recording the information in a structured format. Storage of electronic information is becoming cheaper annually but images are especially demanding of storage space. My home computer is three years old. It has 160 megabytes of hard disc space. A single 4x8 photographic image occupies 28 megabytes of that space. The content of a hospital X ray department represents a formidable storage challenge. Optical discs are helping but the problem has not been fully solved.

Retrieval of information is quick and easy when the information is actually stored on the client computer. Problems multiply when the information is stored on a distant computer and has to be retrieved over an institutional network. Physicians accustomed to instant availability of some kind of paper on which

they can record their diagnostic impressions are highly impatient when the network is down or even when it is slow. Furthermore, only very recently have standards become adopted that define the way in which the information is to be transferred. To use a different metaphor, if one computer is speaking the machine equivalent of French and the other is using English, the meaning may be the same but the communication will be problematic. Recent widespread acceptance of the HL7 format for data communication will help.

Display of information is also a challenge. How many observations? Over what period of time? In histogram or line diagram or table? What is the definition of the variable to be displayed? For example, patients record blood glucose on home glucose meters. Hospital technicians make the same measurements on slightly different machines at the bedside and on still different equipment in the laboratory. Which of these data points represents the "true" blood glucose and are values of different reliability all to be recorded and displayed similarly?

How are the data to be entered and edited? Typing is not a strong suit for physicians. Typically they can dictate at 120 words per minute. Does it make sense to slow them down to their typing speed? If someone else enters the data how will the physician edit it in accordance with their medical judgment. More typing? More dictation?

Of the technical problems, analysis of data is the easiest to solve. If the information is in the system in a structured format it can be retrieved and analyzed. Free text can only be analyzed at present, with difficulty, using specialized search and analysis engines. This means that we again encounter the tension between structure, freedom and clinical efficiency.

How may computers be effectively applied in direct patient care ?

Computers are very effective in certain activities. They record and display numerical data in tabular or graphic format. They track dates and times and can trigger time-dependent actions. They can apply specific rules to data to detect inconsistencies, trigger alerts, warnings, or reminders. They can analyze practice patterns to permit remedial actions and they can provide concise summary reports of medical encounters. One area in which we are making some progress in applying these favorable characteristics is in the field of diabetes.

For those (in the audience) who are not aware of the ravages of diabetes in the population, I will offer a few facts. In the USA one health care dollar in seven is spent on diabetes and its complications. Diabetes is the leading cause of kidney failure and dialysis, of amputations and blindness. It is a major underlying problem for patients with heart attack and stroke. These complications of diabetes are largely preventable, and their avoidance requires only the consistent application of tried and true therapies involving the use of insulin and oral hypoglycemic agents. Yet, in every survey with which I am familiar, institutions have failed to comply with the standards of good care for people with diabetes. In part the problem is an unduly relaxed attitude to patients who have "a touch of diabetes". These patients are exactly those in whom early intervention and rigorous control has the greatest potential to avoid later complications. Partly it is our medical record system that leaves it to the memory of individual physicians and their patients to recall when to intervene with what measures. Partly it is the perception of many physicians that diabetes is a dull disease that requires little diagnostic or therapeutic skill. Partly it is in the way we have structured our care patterns and have failed to delegate our tasks to appropriately trained assistants. Our procedures and our attitudes are at fault and can be aided by computers.

We have worked to address these problems through an electronic medical record for patients with diabetes and have some evidence that it can modify patient and physician behavior and improve patient care. The underlying principles are that trends in patient care should be readily visible and graphically displayed and that on each visit the caregiver should be prompted to take the actions that the patientís status requires at that time.

Together with my colleagues at the Mayo Clinic including Bruce Zimmerman, Sean Dinneen, Steven Smith and with the support of Novo Nordisk and Dr. Jens Knudsen, we have worked with software engineers to develop an electronic medical record intended to facilitate the care of people with diabetes. With this system we remind care givers about the tests and procedures required for good diabetes care. These alerts warnings and reminders are patient and provider specific. They are keyed to the designated responsibility of the person logged on to the computer. Appropriate delegation of care processes that do not require the involvement of physicians is facilitated. We graphically display trend lines and structure encounters electronically to meet the needs of the various team members who care for patients with

diabetes. Throughout the system we aggregate only those data on screen that are needed for a particular provider and a specific encounter. For example, a follow-up visit requires a different data set than a new consultation. A dietitian needs different information than a nurse educator. We permit easy printing of medically relevant screens. To facilitate care of patients who are new to the care provider, we show a continuously updated summary of the status of the patient's diabetes. Our goal has been to permit a physician, diabetes nurse or dietitian, within one minute, to fully comprehend the status of the patient and to permit them to proceed immediately with patient care.

Because we foresee networked medical facilities in the future, the system is designed to permit centralized supervision of dispersed care sites. We can audit the quality of care offered by individuals or the office as a whole and we can analyze the business aspects of the practice. We are currently testing the system in four regional practices and intend to extend it to others in the near future.

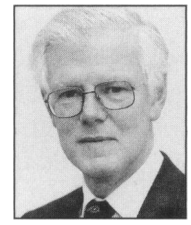
Will computers modify traditional physician roles? Undoubtedly! In addition to the guideline-determined clinical pathways physicians are expected to follow, there will be an increasing awareness that if the pathway is predetermined perhaps one does not need a physician to do it. The role of physicians may evolve into one of understanding the field sufficiently to formulate the guidelines and to outline the clinical pathways. Implementation is increasingly likely to be a responsibility of those with lesser training and whose employment is less costly. For a time this may be fought as endangering physician jobs. In my judgment, it will eventually be accepted as industry presses inexorably for progressively lower costs of care.

What lies ahead?

In the future, computers are unlikely to do worse than we have done in the past by relying on human intuition and the experience of single individuals. In my professional lifetime, I have seen us change from feeding heart attack victims for a week with a spoon lest they exert themselves, to exercising them on a treadmill on the second post infarction day. We have gone from enjoining diverticulosis patients to abjure all seeds and roughage, to increasing their dietary fiber content. Hepatitis patients were formerly advised to rest in bed for six weeks. Now they exercise at will.

As a profession, in the past, we have had more prejudice than data to guide our decisions and the systematic accumulation of data from computers will only improve our practice. Magic and mystery are gradually giving way to data and science. Rather than resist the process we need to lead it so that the essentials of our profession and of our ethic are preserved. That is a noble goal and one to which we all aspire. There will be challenges, but it can be done and in the process medicine will be transformed.

Hospital Management in the 21st Century



Robert J Maxwell CBE, PhD
Chief Executive, Kings Fund,
London

In forecasting the future, one thing we can be certain about is that we will be wrong. With hindsight, everything will be much clearer. Nevertheless, even if we are wrong in many particulars we may be right about the nature of some of the issues. For example, few of us would have forecast the implosion of the Soviet Union and the Eastern Bloc, but it was obvious enough that competition between capitalism and communism was a theme of fundamental importance: the competition simply was more one-sided than most (any?) of us recognised.

Influences

So, looking with a degree of diffidence unto my crystal ball, I predict 5 formative influences:

- Continuing changes in medicine that will shape clinical practice both within hospitals and outside them. On the whole, the advances will be towards more sophisticated diagnosis and care, expanding what can be treated and helping us better to understand what can be prevented.
- Acute hospital care will continue to be very expensive, being people intensive and requiring care around the clock. The constraints will be not only financial, but also in terms of human resources, case-loads and training requirements. Not every local acute hospital that now exists will be able safely to sustain every service that its local population wants.
- There will be a continuing tension between arguments for concentration of services on grounds of quality and safety, and dispersion on grounds of access.
- The revolution in information technology will continue, affecting diagnosis, treatment and administration. It will be more possible than ever before, for clinicians and patients to have at their finger-tips, all the information relevant to a particular decision. Provided the data are linked, epidemiological information will also be richer.
- Boundary issues between social and medical care are likely to pose problems, particularly for frail, elderly patients with chronic conditions. For elderly people there is often little distinction between medical need and social need. Unfortunately, however, the coordination between the two sets of services (or even between primary medical care and secondary) is far from perfect. As acute hospital stays shorten, frail, elderly patients will depend more and more on what one might call "intermediate care" and strong support at home. Will they receive it?

Continuing truths

Against such a background, what can one say about hospital management? First, let me suggest that continuities will, in their own way, be as important as discontinuities. Some things will not change For example:

- Successful hospital management will continue to require a partnership with the clinicians. Just as you cannot run a successful legal practice without the commitment of the lawyers, you cannot run a successful hospital without the commitment of the doctors. the nurses and the other givers of care. This is not just a matter of giving them some delegated responsibility for the resources that they directly control, but also of involving them in the strategic management of the institution.
- Team-work is crucial to patient care. Brilliant individuals are, of course, of enormous value, provided that they are not impossible to work with. But the care of every patient and the provision of every service require a team effort. In general we take the workings and the leadership of teams too much for granted.
- Morale is also a strong factor in patient care and institutional performance. It is a truism for a service industry that people who take a pride in what they do, who value those they serve and are proud of the institution of which they are a part, are the lifeblood of the organisation. Equally, those who feel exploited, miserable and alienated

are unlikely to give a good service. Currently both types of organisations are to be found within the NHS, without most of us recognising how great the contrasts can be, nor how precious is the sense of individual and institutional worth where it exists.

- For many patients, however, hospitals are almost by definition frightening places. Staff, to whom the hospital is simply somewhere that they work, need unusual empathy and imagination to understand this fear. But there is nothing irrational about it. Apart from anything else, hospitals are dangerous places.

- Small units are easier to manage than big ones. Conventional wisdom currently suggests that hospital economies of scale peak at about 200 beds and that efficiency then declines. Because of the possible confounding effects of case-mix, I am not sure about that. But I am sure that monster institutions of anything approaching 1,000 beds are extremely hard to run - at least on a centralised basis.

Some issues of rising importance

While observations such as these are, it seems to me, likely to hold as true for the future as they are now, other issues are likely to be of rising importance. Among these are:-

- An increasing importance of staffing constraints. Technical considerations and changes in training patterns mean that hospitals will be able to rely less on a serfdom of young nurses and doctors to maintain their services around the clock. There will also be fewer fully-trained specialists working in the senior registrar and registrar grades, so the Service is likely to have to be more consultant-led, around the clock. It simply will not be possible to maintain a fully safe service in all sub-specialities in all hospitals.

- A greater need for interhospital collaboration. The Calman/Hine proposals for cancer care are one example of "hub-and-spoke" arrangements directed at linking the expertise of specialists with the work of less specialised units. In fields like the main cancers, the volume of cases may be such that it would be unrealistic to try to draw them all into the specialist centre. It may make better sense, through close relationships and linked appointments, to make sure that the specialist expertise is available in all the hospitals that comprise the hub-and-spoke network. Moreover, I would suggest that the network will be more stable over time, and of better quality, if the hub is not always the regional hospital, but can also be one of the specialist or district general hospitals included in the network.

- An imperative not only for interhospital collaboration, but also for intersystem collaboration. Hospital stays continue to shorten. Day-cases rise. Technological developments make self-monitoring and home care more feasible for chronic diseases like diabetes, renal impairment, psychotic conditions, and many others. But only if the health system can function effectively as a whole, so that when support is needed, it is provided promptly.

- Non-medical aspects of care will also be essential. As I said earlier, boundary issues between the NHS and Social Services pose severe problems, particularly for frail, elderly patients. Ministers (of all parties) sometimes talk about seamless patterns of care. I have doubts about the reality of that; partly because, as a seamstress pointed out to me, the strength of a garment lies in the seams, and partly because seamlessness is so far from everyday realities of care. We simply have to have good cooperation across boundaries - geographic, professional, organisational, public/private, paid/voluntary/family - to stand any chance of a Service adequate for people in the 21st century.

Finally, a paradox. The quality of care that an individual receives - now and in the 21st century - depends upon a complex set of interactions: among people, and across institutional and service boundaries. To a large extent these interactions happen spontaneously, or do not happen. Management can facilitate or hinder, but (in the main) management is of the institutions, not of the interactions.

I conclude that hospital management in the 21st century will need to be more outward-looking, less institutionally bounded, than it has sometimes been, more concerned with clinical networks and with the overall effectiveness, continuity and quality of care received by patients, as they move across service boundaries.

Deirdre O'Brien RGN, RM, MBA, DMCert
Introduction of the Florence Elliott Lecture.

Florence Eileen Elliott was born on 6 October 1905 in Randalstown. She qualified as a registered nurse in 1930 from the Royal, she undertook midwifery training in Edinburgh and worked there as midwifery Sister for a number of years. In 1943 she was invited to apply for a post as Matron of Whiteabbey Sanatorium. There, with her innovative approach, she introduced affiliated nurse training, in association with Belfast City Hospital. In 1946, Florence Elliott became Matron of the Royal Victoria Hospital. She was the first Royal trained nurse to do so and the first Ulsterwoman to hold the post. In 1948, she guided the hospital nursing service into the complex and rapidly changing world of the NHS. She would feel very at home today in the fast changing NHS of current times.

Florence Elliott held a number of posts in her time. From 1948 to 1951 she held the chair of the Executive of Northern Ireland Committee of the Royal College of Nursing (RCN) and was vice-president of the RCN of Great Britain and Northern Ireland. In 1951, she was awarded an OBE; the first Northern Ireland nurse to receive such an award. In 1967, she was awarded an Honorary Masters Degree at Queens University, again, the first nurse from Northern Ireland and that Masters was awarded in regard to her contribution to nursing here in Northern Ireland. She retired in 1966 and was made a life Governor of the Royal Victoria Hospital. She spent some years in Australia where she became a focal point for visiting Royal nurses, medical students and doctors, returning to Northern Ireland in 1990. In 1996, she died, having attained her 91st year.

The Elements of Nursing ... all but unknown

Sue Norman RGN, RNT, BEd (Hons)

Chief Executive/Registrar

United Kingdom Central Council for Nursing, Midwifery and Health Visiting

Introduction

Nursing at the Royal Victoria Hospital has consistently been in the vanguard of professional excellence and innovation. From within its ranks came the first nurse practitioner in Northern Ireland, the first tissue viability nurse, the first nutrition and specialist nutrition nurses and the first Macmillan paediatric nurse. There are an increasing number of specialist nurses working in areas such as stoma care, epilepsy, fractures, diabetes, glaucoma and pain management. The commitment to enhancing roles and improving clinical outcomes has been supported through a thriving commitment to nursing research.

I am particularly delighted to see how you have embraced the liberating principles of the UKCC's document *The scope of professional practice* and have accepted the challenge of expanding your roles to enhance further the quality of the care you provide to your patients and clients. This has given rise to nurse-led clinics for people with asthma, bone fractures and skin complaints which have been recognised through a host of national awards. The Royal Hospital Trust is the first acute trust in Northern Ireland to gain full King's Fund accreditation.

Florence Elliott

This address is given in honour of Florence Elliott, one of the most outstanding nurses that Northern Ireland has produced. After a distinguished career as a staff nurse and midwife, she was appointed to the post of Matron at the Royal Victoria Hospital in 1946. Florence was the first Royal-trained nurse and the first Ulster woman to hold this prestigious position.

She was a great believer in innovation in nurse training and practice, provided that it was of benefit to patients and clients. She never wavered from her firm belief that the prime and over-riding concern of the nurse is the welfare of the patient. Florence also contributed actively within the wider world of nursing. She was a Vice-President of the Royal College of Nursing from 1964 to 1965 and a member of the Joint Nursing and Midwives Council for Northern Ireland from 1946 to 1966. She served as Chairman of the Council for the three years before her retirement in 1966. Her considerable achievements were recognised through the award of the OBE in 1951 and, latterly, by being made a Life Governor of the Royal Victoria Hospital.

On her retirement, Peggy Nuttall, the then editor of *Nursing Times*, described Florence as:

"the greatest nursing leader Northern Ireland has ever known and one whose contribution to the nursing affairs of the United Kingdom was as valued 'over the water' as at home."

Role, Characteristics and Elements of Nursing

The Bicentenary provides an opportunity not only to celebrate past and current achievements but also to look towards the future. Today, as in Florence Nightingale's time, the role of the nurse is to provide skilled nursing care to those who require it and in accordance with the needs and circumstances of those who require it. In exploring some notions on the elements of nursing I would like to use the theme of *partnership* - nursing's partnership with the public and nursing's partnership with others who contribute to that broad canvass that we call health care.

Nursing, perhaps above and beyond all other health care professional groups, is closest to the people it serves. This closeness and sustained contact demands a set of unique personal characteristics on the part of the nurse - sympathy, understanding, tolerance and compassion. These qualities are required not only at the individual patient-practitioner level but also, through collective responsibility, at the community and societal level. The aim of nursing remains the same as in 1859. What has changed beyond recognition is the means by which nursing can achieve that aim.

But, what is nursing care? What are the elements that

differentiate it from medical care or the care given by therapists, support workers, technicians and many others? Several definitions have been attempted not least by the four Chief Nursing Officers of the United Kingdom in their report 'The Challenges for Nursing and Midwifery in the 21st Century', better known as the Heathrow Debate. Their definition, drawn from a tradition of caring based on skills and values, was immediately recognisable in its description of what nurses and midwives do and the concerns and special responsibilities they should have. However, debates on the elements of nursing, medicine or any other group involved in health care are, to my mind, incomplete unless they start with what the patient and the public needs from their perspective, rather than what it is that those in health care currently do. The difficulties of genuinely involving the public in such debates cannot be under estimated. Nevertheless, it cannot be denied that the health professions' partnership with the public is, in general, an unequal one and we should strive to redress that.

A particular problem with defining nursing is that it has been and is very flexible in responding to different needs over the decades. For example, shortages of domestic staff in the two World Wars led to nurses taking on such work in hospitals - much against Miss Nightingales' principles. More recently, changes in the hours worked by junior doctors and difficulties in recruiting and retaining general practitioners have provided opportunities for nurses to develop their roles in closer support of their medical colleagues. This flexibility is both a strength and potential weakness - the latter because in today's climate, if you cannot define it and justify it how do you calculate its added value and therefore financial worth?

Nursing and the Public

The elements of nursing with which I am concerned are those which serve patients and clients and which the patient or client helps to determine. Nursing as a profession should, in my view, be a little less concerned with debates about its status as an art or science and rather more with its role within a partnership, not only with patients and clients but also with the wider public.

We are all familiar with the terminology and buzz phrases - user participation, patient empowerment, client-focused care. But how does nursing, as a body, engage directly with patients and clients in a genuine and meaningful partnership, as well as indirectly through health care consumer organisations? One of the UKCC's key objectives is to increase direct public access to, and involvement in, all our public protection work.

First and foremost, the UKCC's *Code of professional conduct* sets out the standards of education, practice and conduct required of all registered nurses, midwives and health visitors at all times. The code is, therefore, an instrument of public protection and a contract with the public, defining the expectations that the public can have of our practitioners. It also defines that which distinguishes registered nurses, midwives and health visitors from unregulated health care assistants.

Secondly, some of our Council members and many of our committee members represent the voice of the health care consumer. All of our professional conduct committees, which consider allegations of professional misconduct by registered nurses, midwives and health visitors, now include at least one consumer representative. We hold an annual conference with representatives of consumer organisations so that we can listen to their views and explain our public protection work to them. Our Council meetings and all of our Professional Conduct Committee meetings are open to the public.

And thirdly, we have recently published an information leaflet, *Protecting the public*, which is the first ever UKCC publication to be written specifically for the information of patients and clients, rather than registered nurses, midwives and health visitors. The leaflet explains the public protection work of the UKCC, how the public is involved in our work and sets out contact details.

Sadly, what gets into the media and therefore what the public hears most about, is when that partnership is violated in some way. Abuse of any kind is indefensible and at the UKCC we are working on how we can help registrants and employers recognise, deal with and most importantly, prevent abuse happening at all. At both an individual and organisational level, we need to strive to ensure that every person's health care experience is a good one and that, at the very least, people's vulnerability is not exploited.

Nursing, Teams and Multi-disciplinary Working

Providing quality nursing care is undoubtedly a team exercise - not only with the patient but with all those involved, be they a qualified professional or

unqualified carer, relative or friend. Good nurses are good co-ordinators not just in the administrative sense but also in the 'whole person' sense. Professor Celia Davies of the Open University has termed this " ... the skills of 'creating community', drawing out and enhancing the contribution of others whatever their formal roles and titles." I would venture to suggest that this is a fundamental element of nursing. Nevertheless, the 'team exercise' that is mentioned the most is multi-disciplinary working. This term has many interpretations and manifestations but whichever one is used, multi-disciplinary working has increased markedly over the last few years and most commentators expect that this trend will continue and deepen. Rarely can it be said that within a health care team one practitioner possesses all the requisite experience, attributes and skills to deal alone with the individual needs of a patient. However, there are genuine difficulties in achieving *effective* multi-disciplinary working - not least the different levels of initial preparation for practice between disciplines not to mention defence of dearly held 'territories' and the expectations of patients and employers. These difficulties will have to be tackled openly and honestly if the perceived benefits of disciplines working more closely together are to materialise.

At the Royal Victoria Hospital, Nursing Development Units have recently become Care Development Units to promote and support a multi-disciplinary initiative. Care Pathways also embody the multidisciplinary approach, reinforced by the commitment from senior management within the trust to drive forward multi-disciplinary working. I am sure the energetic research programme will, if it has not already, start to evidence the benefits to patients.

Education - Preparing for Future Practice

But, how will professional education and training provide the appropriate preparation for a more flexible and multi-disciplinary workforce? 'The Future Health care Workforce' report published last year from the University of Manchester's Health Service Management Unit threw some fairly large pebbles into the pond of professional education and training. For example, common core training including medical students and management trainees; preparation of 'generic carers' - admittedly, a term the report disliked - and those 'generic carers' forming the pool from which therapists, or specialists would be drawn; more flexible entry levels to training through Accreditation of Prior Learning or Achievement; an occupational standards base to education and training and a greater influence by employers in the education of the current and future health care workforce. The resulting ripples from these 'pebbles' have varied in size and intensity. But - whatever the reaction - the report has made people think. It cannot be denied that patients should be able to expect a consistent level of competency from all health care professionals and therefore some commonality in how that competence is expressed in education would make sense; neither can it be denied that there are inflexibilities - for organisations and trainees - in the current single discipline approach to professional education. However, any moves towards greater commonality of education and increased flexibility of working need to be firmly driven by the needs of patients and clients - not economic or administrative imperatives although, these will play their part.

Increasingly, reflective practice is replacing the more traditional interpretation of professional knowledge as something to be acquired or possessed. This, of course, is nothing new. As Florence Nightingale observed as long ago as 1859,

"The everyday management of a large ward, let alone of a hospital, - the knowing what are the laws of life and death for men, and what are the laws of health for wards ... - are not these matters of sufficient importance and difficulty to require learning by experience and careful inquiry ...?"

Reflective practice works towards an alternative concept of knowledge - seeing knowledge as not something to be obtained once and for all but as something which, in Celia Davies' terms, " ... grows and develops from the fusion of expertise and experience and of the formal and the intuitive." Increasingly that fusion will come from and need to support multi-disciplinary and multi-agency health care.

The UKCC has presaged this development both through what in 1991 was a relatively new preparation for nursing and midwifery practice - Project 2000, and more recently through the introduction of its standards for maintaining registration and continuing professional development, more widely known as PREP. The current Project 2000 model of pre-registration education encourages nurses and midwives to think widely, to study alongside other professional and non-professional health care groups and to develop a firm base of skill and competence. However, as the report of the four UK Chief Nursing

Officers' Heathrow Debate makes clear, it is important that the Project 2000 model and its successors do not limit opportunities for nurses to cross frontiers - a point that was picked up in the 'The Future Health Care Workforce' report I mentioned previously.

The UKCC's Post Registration Education Project requirements will, from April 1998, affect every single registered nurse, midwife and health visitor - all 650,000 of them. By linking evidence of continuing professional education and development with continuing registration, the UKCC has taken a significant step towards ensuring that practice more closely meets the needs of patients and clients.

The initiative is about linking professional development with quality practice. The process, particularly through the use of the personal professional profile, demands a lifelong commitment to personal development but, more importantly, the ability to reflect upon and to analyse the beneficial impact upon professional practice of study activity undertaken by registered nurses, midwives and health visitors. It is this impact which the UKCC will be most concerned with monitoring when its audit system for PREP is in place from 2001. Continuing professional development should lead to better patient and client care otherwise it is a waste of time. However, proving the exclusivity of its influence in challenging to say the least.

Patterns of Health Care and Professional Boundaries

Looking more widely, it is clear that existing patterns of health and social care are being remoulded as pressures for health care increase, not just in the United Kingdom but across the world.

Public resources are increasingly being focused on providing services that address the basic questions of:

- what do people need?
- how can those needs be met? and
- will it lead to an improved outcome for the patient or client?

Inevitably this raises questions about how skills and expertise are used to best effect.

Developing broader-based and more flexible roles is at the centre of the patient-focused care initiative, still in its infancy in the United Kingdom but already providing examples of effective and innovative health care. The challenge for us all - the UKCC included - is to embrace flexibility without diluting the value to the public of employing registered nurses, midwives and health visitors. The blurring and crossing of traditional role boundaries is already happening. In the past, relationships between different groups of health care professionals has led to a tacit acceptance of each other's responsibility and authority. Sometimes the law, but more often custom and practice, have defined who does what and how. Some of these accepted demarcations are coming under pressure and dissipating. This is challenging enough for the professions to deal with but probably even more of a challenge for the public to comprehend. It is incumbent upon us all to ensure that the public know what to expect of those who are caring for them and that they are competent.

Nurses' roles have changed and often the person who a patient believes to be a registered nurse may be an unregulated health care assistant. This raises the question of whether the public's perceptions of nurses are clear and realistic. Expectations are driven not just by changing needs but also by what people want and what they believe they are entitled to. Nursing, however it is defined, exists to serve the public and the public have generally had confidence in them. They have been accessible to and active on behalf of those who depend on the care they provide. Although, the public's view of nurses and nursing has probably always been a compound of myth and reality, what has not changed is the public's recognition of nurses' duty of care for patients and clients.

Summary

In summing up, I have explored briefly some notions on the elements of nursing through the theme of partnership with the public and with others involved in health care. These notions, which are by no means exclusive, have centred around five main areas;

Firstly, the unique personal characteristics demanded by the closeness of sustained contact with patients and clients;

Secondly, the primacy of the patient's and the public's needs in defining nursing or any other health care profession;

Thirdly, the need for nursing both individually and organisationally to look outwards and engage with the wider public and their changing attitudes towards the professions;

Fourthly, the unique skill of 'creating community', *working with, co-ordinating* and *leading* teams across disciplines in the interests of the patient and the challenge that true effectiveness of multi-disciplinary working presents for both education and practice; and

Fifthly, the importance of reflective practice throughout the working life of nurses as a means of better meeting patients' needs.

How nursing retains this focus whilst adapting to a constantly and rapidly shifting health and social care environment, will largely determine how nursing endures as a profession. If the example set by Florence Elliott and the many innovations and developments at the Royal Victoria Hospital are anything to go by, the people of Northern Ireland, nurses in Northern Ireland and health care generally in Northern Ireland, can look forward to another 200 years of healthy partnership.

FURTHER READING:

Celia Davies
The Cloak of Professionalism: - A case of Yesterday's Fashion? Unpublished speech to UKCC Council members, June 1996.

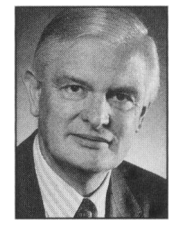
Department of Health
The Heathrow Debate: The Challenges for Nursing and Midwifery in the 21st Century London, HMSO,1993.

Health Services Management Unit
The Future Healthcare Workforce University of Manchester, 1996.

Florence Nightingale
Notes on Nursing Churchhill Livingstone, London, 1980.

Muriel Skeet
Notes on Nursing: The Science and the Art Churchhill Livingstone, London, 1980.

Medicine beyond 2000 - Trust me I am (still) a doctor



Sir Donald Irvine CBE

President of the General Medical Council
London

Change and its impact

Our professionalism is shaped and influenced by the context in which we work. First and foremost, medical knowledge and skill continue to expand in a geometric progression. So, in truth, we can only guess at what new discoveries lie ahead within the professional lifespan of young doctors starting their careers now. Equally challenging is the revolution in information technology which will have far-reaching implications for the practice of medicine in ways we are only just beginning to see. What, for instance, will be the impact on the doctor/patient relationship when most patients have direct access through the Internet to the database of knowledge which is the foundation of our professionalism?

One effect of rapid scientific and technological advance has been to drive subspecialisation in medicine further and further. If this trend continues, will it be possible to hold medicine together as the distinctive entity it is today, or will it come apart? All of us want the benefits of the best science for our families and ourselves when we become ill. Yet, at the same time, many of us yearn to retain the humanity associated with traditional doctoring. Will it be possible for patients to have it both ways in future? Indeed, will they always want to?

As if that were not enough, patients' expectations of medicine continue to rise. Given the complexities and pressures of modern practice, doctors often see these expectations as unreasonably demanding, and at times too critical and too testing of our performance. Yet we could look at it another way. Patients' greater expectations flow from our successes; the question, therefore, is how to maintain the confidence already there.

Compounding these changes are the political issues around the rising costs of health care, in particular how society is to pay for the many good but costly things that modern medicine can do, the total bill for which seems to exceed the limit of our willingness as a society to pay.

Last, but by no means least, there are the ethical dilemmas. Scarcely a week passes now without practical ethical questions arising which flow from medical advance - in genetics, in the ability to sustain life artificially, in the more familiar areas of consent and confidentiality, and so on.

Any one of these areas of change would be a challenge to handle. Taken together, it is not surprising that doctors find professional life so stressful. So, looking ahead, can we find better ways of handling and coping with a professional life in which continuous change will be the norm rather than the exception?

There are many important consequences of change. Here are three examples

First is the fact that now, more than ever, the patient has come centre stage. The consumer, if I can describe patients that way, is king. For doctors used to being in the driving seat, that change can be difficult.

Secondly, we are likely to see more flexibility, on a scale that we have not experienced in our lifetimes, in the structure of health care, in the way we develop and use our buildings and technical plant, and especially in the way we organise the work. For doctors this will imply a re-appraisal of what really distinguishes medicine from the many other health professions, when increasing numbers of non-medical health professionals have a role in clinical management. Is it, at its most elemental, the science and art of diagnosis? Similarly, as doctors we will surely have to look anew at how we reconcile the ethos of personal responsibility, linked with the one- to-one relationship between doctor and patient, with the future operational necessity for effective team-working. Certainly in medicine, we have still to reconcile these apparently contradictory requirements satisfactorily.

The third consequence focuses on accountability. For doctors, as with other professions, we are moving inexorably towards more emphasis in future on accountability, on the means whereby the quality of care can be steadily and incrementally improved and explicitly assured. This implies the development of

attitudes of openness and responsiveness so that more light is shed on how and why we take the decisions we do, and on the effectiveness of our care, especially of our personal and team-based clinical performance.

Public Perceptions

So how do patients see their doctors today? What does the public think about the performance of the medical profession? It is actually quite difficult to say, but what evidence there is from opinion polls, from the image of medicine on television, from analyses of complaints, from a wealth of anecdote - sometimes crystallised by the press - and from we ourselves when we listen to what patients say, seems to suggest three general messages.

First, people in this country have a high respect for the medical profession In the United Kingdom. People seem to believe that in the main they enjoy a good standard of medical care, particularly at the technical level, and that we are honest and trustworthy. That good standing is an immense asset; the medical profession in many other countries is not so well regarded.

Second, notwithstanding the good feeling people tend to have about 'their' doctor, there are nevertheless many more complaints about doctors' attitudes to patients and colleagues. The commonest cause of complaint is poor communication. A proper dialogue about the cause, direction and progress of illness and care is an expectation too often unrealised. More generally, we are often seen as paternalistic - in some cases to the point of arrogance - and can all too easily convey a lack of respect for patients and other colleagues. Nevertheless, more and more patients in a better educated society expect the courtesies and good manners that have always been associated with the best of practice.

The third perception is about our willingness and ability to protect patients from poor practice when it occurs. There is still a suspicion, fuelled by some very public failures, that things can go wrong and patients can be harmed in situations where problems of performance were known about, and where energetic and active prevention could have avoided tragedy. Hence the public, which believes that by and large we get the basic training of doctors right, now wants to know - with increasing insistence - how we are going to assure them systematically and explicitly that senior doctors, notably consultants or principals in general practice, are really up-to-date, know what they are doing, and are maintaining an optimal level of performance.

So, against a background of general confidence and respect for the professionalism of doctors, there are problem areas which have got to be addressed by the whole profession if we are to continue to enjoy public trust.

Assuring Doctors' Performance: The GMC's Approach

Not surprisingly, the GMC sees effective professional self-regulation as critical to maintaining public trust and at the same time to ensuring that doctors retain that independence of thought and action essential, at the clinical decision-making level, to optimal care for individual patients. To be successful the Council believes that professional self- regulation must become an active process in which every practising doctor is involved; patients depend, ultimately, on the sense of commitment and the conscientiousness of individual clinicians to do their best in all the countless unsupervised clinical decisions that are still at the heart of medical practice.

There are three elements to the GMC's approach[1]:

- to guide doctors on the principles of good medical practice;
- to help doctors maintain good practice through effective local professional self-regulation;
- to protect patients by dealing firmly and fairly with seriously dysfunctional doctors.

Professional standards

The starting point must be our values and standards. Values and standards have always been important in medicine, but until recently much has been implicit. We are now moving into an era where explicitness is the name of the game wherever that is possible.

The GMC took this route for the first time in 1995 with the publication of Duties of a Doctor and Good Medical Practice[2]. There, the GMC sets out, in explicit and positive terms, what the essential attributes of good medical practice are. We expect this guidance to inform everyday practice, and to be reflected in basic medical education, specialist training and the continuing further professional development of all established doctors. Explicit standards make it clear what doctors have signed up to and what is expected, and are the visible baseline against which their performance can be subsequently assessed.

The GMC guidelines, which have been well received by the public as well as the profession, deal with the generic attributes of medical practice. In addition, explicit clinical guidelines and protocols are becoming part of the litany and armamentarium of practice. As we search for more clinical effectiveness in medicine, clinical guidelines can provide an excellent yardstick of what should be expected. But I believe they should never be allowed to usurp the responsibility of the doctor in making the ultimate judgement in individual cases, and that that judgement should be respected provided always that the doctor can provide proper justification.

The move towards greater explicitness will, in the long term, prove to have been healthy, for it will ensure greater common understanding between doctors and patients. Equally, it will help the medical profession to indicate to the outside world what is, and just as important what is not, possible in medicine at any point.

Maintaining good medical practice

By far the biggest challenge we face is in the arrangements we will need to make in future to assure our patients of good practice in an open and systematic way. Each of us has individual responsibilities: to be competent

- to perform consistently well
- to practice ethically
- to protect patients
- to be an effective team-player.

But as a profession we need to go further than that. We now need to think in terms of assuming some local collective responsibility for standards of practice and performance at the level of the partnership in general practice, or the clinical team, department or directorate in hospital[3]. At one level this would remain a medical responsibility. But, since most of us now practice in multi-disciplinary teams, the notion of multi-professional collective responsibility is beginning to take shape and be explored. The concept of local professional self-regulation is beginning to take shape as a distinct entity.

So what are the characteristics of effective self-regulating teams? Fortunately there are already many examples across the country in every specialty and in general practice. Such teams have common attributes (Table 1) and tend to use a constellation of methods (Table 2). Significantly, such clinical teams are willing and able regularly to test themselves against others, so that they can see how their performance relates to others doing similar work; and they are open about their standards and their clinical results - their performance.

TABLE 1

Maintaining Good Practice

Effective clinical teams:

- Show leadership
- Have clear values/standards
- Care for each member
- Are keen to learn
- Communicate well
- Are committed to quality
- Are competently managed
- Are determined to protect patients

TABLE 2

Maintaining Good Practice

Effective clinical teams use:

- Clinical guidelines/operational protocols
- Good systems
- Good data
- Systematic audit of performance
- Feedback/appraisal/professional development
- Risk avoidance methods

I cannot overstate the importance of this local collective approach, and all that it implies. At the GMC we tend to see the failures in medical practice. In these cases, especially where there is a pattern of persistent dysfunction, local collective responsibility is invariably missing.

So, the question now is how the profession can take local self-regulation forwards, based on clinical teams.

One of the keys will lie with the nature of the leadership given by clinical teachers in our hospitals and teaching general practices. In medicine modelling is a very powerful influence. What we do is, for good or ill, often more powerful than what we say. Students and doctors in training acquire habits from the behaviour of their clinical teachers which will often remain with them, or colour their own behaviour, for the rest of their practising lives. I suggest that those of us who are clinicians and teachers need to give much more thought to the picture we present as doctors to

the outside world. We need to talk more about the kind of doctors we really are, or should be. By addressing such questions of attitude, behaviour and accountability, which are at the top of the public's agenda, we make them part of ours too. The messages are unlikely to be lost on students and young doctors.

Protecting patients from harm, the third limb in the GMC's approach, is about protecting patients from dysfunctional practice. The key elements of the strategy are already clear. In Good Medical Practice the GMC made it an explicit obligation on doctors to identify poor practice where, if it were to continue, patients could be put at serious risk. For practising doctors the action point is in the clinical teams described above. Clinicians and clinical teams, which regularly use internal clinical audit and appraisal, are probably best placed to tackle dysfunctional practice in a colleague when it first arises, before damage is done to patients or the doctor irretrievably. In future, if satisfactory progress towards resolution cannot be achieved at that level, then clinical teams must seek help from someone in appropriate authority who will be in a position to act further. In hospitals this may well be the clinical or medical director; in general practice the director of public health or the secretary of the local medical committee. If local help can then be brought to bear and achieve proper results, well and good. If not, then the dysfunctional doctor should be referred to the GMC.

The GMC, for its part, has recently had its fitness to practise procedures strengthened by the passing of the Medical (Professional Performance) Act 1995. Essentially this gives the Council the power to assess the performance of a doctor at work using a team of three assessors, two medically qualified from the doctor's own speciality and one lay person.

The object of the GMC performance procedures is, firstly, to make sure that patients are protected and, secondly, to help the doctor to be rehabilitated wherever possible and appropriate.

TOWARDS A NEW AGREEMENT

The kind of proactive, team-based self-regulation that I have described needs proper resources. Carried out systematically and thoroughly across the country, it would represent a new element to medical practice. It takes time and effort to do well. NHS Trusts, Health Authorities and Health Boards will need to find the ways and means of valuing and resourcing it as a tangible expression of their commitment to supporting their medical staff providing care at the sharp end. The achievement of management's aims is critically dependent on the sense of professionalism, and commitment among doctors and other health professionals.

Against this background, I believe that the time is now right for a new agreement between medicine, the state and the public generally. It is the medical profession's responsibility to see that professional practice is at one with people's expectations and that self-regulation really is effective. For its part, the state must give doctors the time needed to do a professional job for patients and to maintain standards of practice using modern methods. The proper resourcing of good medical practice - including medical education - must become an agreed given of good quality health care. With such an approach, we can be confident that our strengthened professionalism will keep the public's respect and trust.

REFERENCES

1. Irvine D. The performance of doctors. I: Professionalism and self-regulation in a changing world. London: *BMJ* 1997; **314**, 1540-42.

2. General Medical Council. Duties of a doctor: good medical practice. London: GMC, 1995.

3. Irvine D. The performance of doctors. II: Maintaining good practice, protecting patients from poor performance. London: *BMJ* 1997; **314**, 1613-15.

Final Address.

Elizabeth E Mayne MD, FRCPath, FRCP

Chairman of the Medical Staff Committee.

Royal Victoria Hospital

Two very special days in the life and history of the Royal Victoria Hospital, Belfast, are nearing conclusion. At the end of such a Bicentenary Scientific Meeting, it may seem that "all has been said". Indeed the best of modern medicine has been presented by past and present members of staff and by our distinguished guests. The audience has been informed, educated and entertained by the excellence of the presentations.

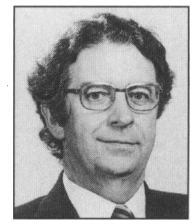
Looking forward to the Millennium, perhaps it is now appropriate to reflect on the future of medicine in general and the National Health Service in particular. The latter will celebrate 50 years of existence next year. The main areas of concern are finance, education, research and development. The present funding is woefully inadequate. The U.K. spends less per capita on its Health Service than many countries worldwide. The introduction of PFI has only partially solved old problems and may have merely created new ones. It is to be hoped that the Government will soon seek more substantial methods for funding our National Health Service.

Educational issues are of paramount importance. Today, graduate doctors and nurses emerge from training as more technologically competent and scientifically aware than ever before. It is to be hoped that this achievement does not endanger the best practice in medicine and nursing and that individuals do not lose the qualities of compassion and caring. Clearly it is the duty of all engaged in teaching to prevent "the art" being subsumed by "the science".

The explosion of technology and the ever-changing advances in therapeutics presents the problem of allocation. Who should receive 'fivestar' treatment? It has been said that we should maintain clear ethical views regarding such decisions. This is difficult. Within my own specialty, namely caring for patients with haemophilia, the cost of the treatment can be exorbitant. If such a patient is bleeding and an expensive remedy exists, who is to decide whether to give or withhold that treatment? It is relatively easy to take the decision sitting in an office at a desk but not easy when one is at the patient's bedside and he is overtly bleeding. Whilst wrestling with such problems, it should be borne in mind that many countries do not have, as Kipling would say, even the bare necessities of a Health Service to which we have become accustomed. Recognition of such problems could induce despondency and/or depression. However, looking back more than 200 years, when one recalls the achievements of our forebearers, I feel that our future is secure and we should remain optimistic.

In conclusion, I wish to refer to a letter received from our most senior retired surgeon, namely Sir Ian Fraser. Last evening he sent his congratulations on the success of the Waterfront Hall meeting. In his hospital practice, he was an individual who always knew what exactly was going on. He has not changed. I believe his diagnosis to be accurate. This meeting has been a success and it is due to teamwork under the direction of Professor J M Bridges, Chairman of the Bicentenary Committee and of Dr Julian R Johnston and his Scientific Committee. I would like to extend my thanks to them, to all the staff in the Waterfront Hall and to you all for coming.

The 'Connexion' between the Royal and Queen's 1849-1949. Alliance or Special Relationship?



Sir Peter Froggatt MA, MD, LLD (Hon), DSc (Hon), PhD, DPH, FRCP, FFCM, FRCPI, FFCMI, FFOMI, FRCSI (Hon), MRIA

Former Vice-Chancellor, The Queen's University of Belfast, 1976-1986

Introduction

In April 1797 faced with epidemics of those hoary Belfast familiars, typhus fever and seditious activity, the five-year old 'Belfast General Dispensary' decided to take action against the typhus; the sedition was beyond their remit! On the 14th it resolved to provide some in-patient fever beds and rented, for one year at £20, a small terrace house in Factory Row (later Berry Street; now the side entrance to Castlecourt) and squeezed into it: six bedsteads and bedclothes, sanitary accoutrements, cooking utensils, medicines, a resident nurse, visiting doctors' facilities, 60 patients in the first five months (with only one death) and also space for the General Dispensary's apothecary on his visits from the Dispensary's rooms at the Belfast Charitable Society at North Queen Street[1] On 4th May, Dr James MacDonnell, the senior Dispensary physician, and four colleagues[2] took up their duties at Factory Row and the impressively named 'Belfast General Dispensary and Fever Hospital' was born. These humble premises were the ancestor of to-day's Royal Victoria Hospital in a line unbroken except for a year or so during the 'troubles' surrounding the '98' when Belfast's charitable classes had other things on their mind and other calls on their pocket.

On 4th November 1849, 52 years later, during epidemics this time of cholera rather than typhus, and political controversy rather than overt rebellion, and with the sombre increments produced by the great famine and its accompanying diseases, the Queen's College Belfast opened with 195 students (including 55 medical ones) and with the Royal's ancestor - then the Belfast General Hospital in Frederick Street - as its clinical partner, the whole called somewhat optimistically 'the Belfast medical school'. The 'partners' however were far from equal, the 'partnership' was far from integrated, and the 'medical school' was not strictly a school at all! In this it evoked the Holy Roman Empire, neither holy, Roman, nor an empire, although more faithfully descriptive in that the 'Belfast medical school' was unquestionably in Belfast![3]

Exactly 100 years later, on 11th May 1949, Queen's and the new Northern Ireland Hospitals Authority reached a formal agreement following the radical changes in the health services and in clinical medical education in the post-World War II period and which paved the way for the high degree of integration which we know to-day.[4] The Royal's close association with Queen's was by then firmly cemented since the Grosvenor Road site had earlier been proposed to house the first new major full-time clinical academic units, viz. medicine, surgery, child health, obstetrics and gynaecology, ophthalmology, and therapeutics and pharmacology (later to be joined by anaesthetics), with associated 'professorial' beds in the Royal group, though not exclusively. The hundred years, 1849 to 1949, is therefore a distinct and distinctive period in the Royal/Queen's association.

This paper deals with this association, or 'connexion' as it was usually called. Others have told the stories of each partner separately notably Sydney Allison[5] and Richard Clarke[6] for the Royal, and Moody and Beckett for Queen's[3]; and your humble servant has dealt with some conjoint aspects[7,8]. Nevertheless, even on this constricted historical canvas, a century is a long time, longer even than a week in politics, and I have had to be in places somewhat sketchy though not I hope more superficial or opaque than usual! There are inevitable casualties - dentistry for one, 'professions allied to medicine' for another - but in fact their stories are mainly those of the post-1949 period.

A point on nomenclature. Over the period Queen's had two names and one site - Queen's College Belfast until 1908; and The Queen's University of Belfast thereafter. The Royal had three names and two sites: in 1849 it was the Belfast General Hospital, from 1875 the Belfast Royal Hospital, and from 1899 the Royal

Victoria Hospital. All were in Frederick Street until the move in 1903 to Grosvenor Road. Both had several constitutions and many physical additions. I will refer to them conveniently as 'Queen's' and 'the Royal' throughout. I will omit detailing the politics of Irish higher education and the Irish medical charities, which provide the backdrop to the stage on which this story is played out, because these are labyrinthine. I will refer to them only where necessary. For details the resolute reader is referred elsewhere. Finally, acknowledgments (or apologies!) to John Milton for the idea for the section headings.

Paradise Perceived

The pre-Queen's situation: the first Belfast medical school (1835-1849)

The Queen's medical school was Belfast's second; the first was at the Royal Belfast Academical Institution (Belfast 'Inst') from 1835 to 1849. At the time Inst combined a boys' school with a 'college' mainly for aspiring Presbyterian ordinands but also offering vocational classes for the burgeoning infra-structure of Ulster's prosperous agriculture, industry, and commerce. Its name, 'The Belfast Academical Institution' ('Royal' from 1831), was unwieldy but apt. It had originally planned to include a medical school but this was delayed until 1835, a story which I have told elsewhere.[9-13]. Preceding Queen's, as it did, Inst conveniently identified, defined, and indeed tackled, most of the issues facing an embryo comprehensive medical school, and this experience enabled it to act as prototype and pathfinder for Queen's so successfully that in 1849 the new Queen's school was able to hit the ground running. This athletic feat also owed something to the skills of the great chemist and gifted administrator, Thomas Andrews,[14] who was already a member of both the Inst and Royal medical staffs when he was appointed in December 1845 to be the key planner of the new medical school as the first vice-president of Queen's (and incidentally the last until Michael Grant's vice-chancellorship) and he was critically placed to act as catalyst and fulcrum as was another key figure, Sir John Henry Biggart, a century later. When the Inst medical school closed in 1849 it gave to Queen's most of its medical students, three of its seven medical professors (plus Andrews), morbid specimens and books, the lease of its dissecting room at £25 p.a. until 1863, a coherent and viable curriculum, an enlightened educational philosophy and above all a ready-made 'connexion' with the Royal which was to prove remarkably robust.

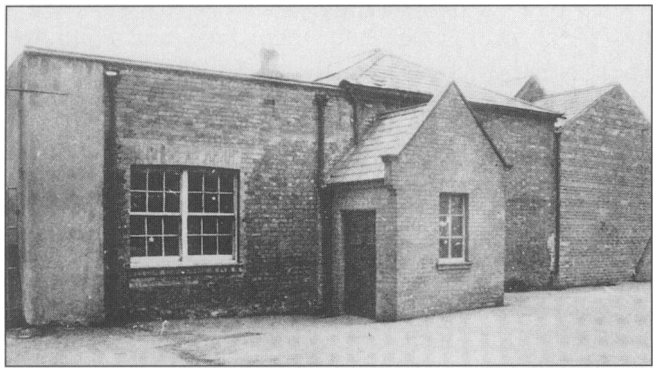


Figure 1 The former theatre workshop at Belfast 'Inst' demolished in 1983 to make way for the sixth form centre. The central and nearest block with some building out of sight comprise the original medical school (1835-1849) and leased to Queen's (1849-1863). Some of the wings and the porch were added later. (Courtesy of the Board of Governors, RBAI).

Figure 2 James Lawson Drummond (1783-1853). Professor of anatomy and medical physiology at Inst, 1818-1849, attending physician at the Fever Hospital, 1814-1818, and foundation dean of the Inst medical faculty, 1835-1837. The principal architect of the first Belfast medical school. (Courtesy of the Governors, Linenhall Library).

The key issues emerged in November 1826 when James Lawson Drummond, professor of anatomy at Inst and a former attending physician at the Royal, called publicly for a comprehensive 'preparatory' Belfast medical school, viz. a school which would be recognised by the various chartered medical bodies (Colleges of Surgeons, Societies of Apothecaries, Army and Navy Medical Boards, some universities, etc) for the 'preparation' of students to sit their examinations rather than be a licensing body itself, though Drummond had hopes that Inst would ultimately achieve 'licensing' or even degree status. Drummond wrote:

> '[After anatomy, chemistry and materia medica] ... it is of early importance to the student to have an opportunity of observing disease in its various aspects ... a ward in the hospital should be appropriated to the reception of a certain number of patients to be placed under the care of one or two physicians and that clinical lectures be delivered twice a week on said patients ... A weekly lecture or two on the surgical cases ... would be of great importance ... and students

> [should also be] entrusted under proper relations ... with cases in the Lying-in Hospital ...'[15]

This was in addition to students 'walking the wards' and serving as clerks and dressers to the hospital staff which was then the usual means of clinical instruction and which had been introduced to the Royal in 1821. What was Drummond actually advocating? Though his letter (above) does not spell it out, it is clear from subsequent Inst/Royal discussions that he was advocating nothing less than professorial teaching wards with associated clinical lectures and systematic bedside teaching conducted by the *professors* who would be appointed by Inst but admitted to the use of the Royal facilities and responsibilities for patient care purely on that basis. This would be the core of the clinical curriculum; attendance by students on, and teaching by, Royal staff acting in that capacity would be additional and complementary and, hopefully, co-ordinated.

The Royal accepted the ends of a comprehensive 'preparatory' school but balked at the means. Why? There were two major problems which like the dreary steeples of Fermanagh and Tyrone, in Churchill's deathless phrase, remained for many years to threaten the health of Royal/Queen's relationships, the second in fact endured throughout the entire period. The first was to do with money. Under an act of parliament of 1807 (47 Geo. III, c.44) initially about a quarter, later up to a half, of the Royal's income came from the rates (to use a later term) and was earmarked exclusively for 'fever' cases but actually was used as a useful subsidy for general expenditure: the Royal understandably does not want to jeopardise this lucrative arrangement by associating as closely as Drummond had suggested with an independent incorporated college itself in receipt of a government grant and accountable only to its proprietors. The second was to do with accountability and power. Put simply: the Royal staff wouldn't countenance teaching in the hospital under the auspices of any outside body, still less tolerate any of their patients (especially 'non-fever' ones) being congregated in special wards under the care of an 'outsider' with ultimate clinical responsibility, least of all appoint the outsider *ex officio* to be a member of staff especially since Inst professors were long-term appointees while Royal staff were elected annually and mainly on the basis of a seniority established though prior service in the General Dispensary. In 1949, when introducing the joint appointment system between the Northern Ireland Hospitals Authority and Queen's, the Authority's secretary (Mr E H Jones) put the kernel of this enduring problem nicely: '... the [Hospitals] Authority take the view that it is unsatisfactory for a public body ... to require and use the services of persons who are not [selected and] remunerated by them and with whom they have not specific contracted arrangements'.[4] Instead, the Royal decided to run the clinical teaching and the clinical lectures themselves and on 3 June 1827, exactly 170 years ago, the 65-year-old James MacDonnell, doyen of the Royal staff and the man who had taken charge of the six beds in Factory Row 30 years before, gave the first in a series of hospital-organised clinical lectures.[16,17] The event is symbolised in the Oration each October at the start of the Royal teaching year and given by a member of the Royal staff without any undue (or even due!) attention to Queen's, perhaps symbolically!

Despite lofty principles getting in the way both Inst and the Royal were keen to reach a permanent 'connexion'. Inst sought a deal just short of sacrificing open eligibility to their professoriate and their prerogative of seeking and appointing their own professors from the widest possible pool of talent. The Royal were more locally focused and, after suggesting grandiose unacceptable ways of subordinating Inst's prerogative, they sought damage-limitation by seeking to persuade Inst to appoint only professors from the Belfast medical fraternity; they shrank from the increasing medical competition which able medical imports to Belfast would provide which they considered would be 'an act of unkindness if not injustice'.[9] The negotiations were tough and protracted; the manoeuvring by the Royal (and Inst) skillful and ingenious. Both sides were confident of an ultimate accommodation - after all it was in their common interests to reach one, and surely this could be brokered given the compactness and cohesion of the local profession and their frequent common membership of staffs and governing bodies of both institutions.

However, for reasons I have examined elsewhere[9,10] it was not to be, or rather not *completely* to be; 'Plans' were agreed in 1831 and 1835, but a small minority of dissidents remained. Inst now divided into two camps - those (mainly among the 'Plans' supporters) who favoured expediency and those (mainly among the dissidents) who favoured principle; but the two were certainly not mutually exclusive. Though the recruitment fields were admittedly sorely limited as was nearly always the case at the time, the former group had a hand in ensuring that *all* of the first nine medical professors appointed through 'open

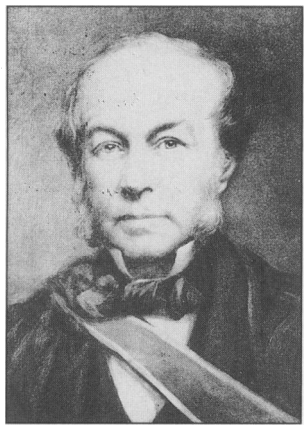


Figure 3 Thomas Andrews, FRS (1813-1885). Professor of chemistry at Inst, 1835-1847, attending physician to the Belfast Dispensary and Fever Hospital, 1838-1846, professor of chemistry, 1849-1879, and vice- president, of Queen's, 1845-1879. He ensured the success of the Queen's medical school. (Courtesy, The Queen's University, Belfast).

eligibility' just happened to be Belfast doctors and *all but two* were either already members of the Royal staff or soon would be.[9,10] The exceptions were John MacDonnell, a son of the doyen, James, but who conveniently moved to the Richmond Hospital in Dublin before seeking a bed or giving a lecture;[17] and Thomas Ferrar, professor of surgery for a few months in 1836, but who sportingly failed to report for duty and was discharged *in absentia*.[18] (Ferrer was not in practice in Belfast but was the son of a prominent Belfast citizen and had been schooled at the Belfast Academy ('Bruce's Academy')). Queen's did not forget this lesson: between opening in 1849 and appointing the Englishman from Barts, Harold Rodgers, to the chair of surgery in 1947, a period of 98 years, all but one of the *clinical* professors (the exception was John Creery Ferguson) were drawn from the Belfast medical fraternity, and all but three (Ferguson, Alexander Gordon and RF Dill) were already on the staff of the Royal and Dill and Gordon recently had been and Ferguson soon would be. In contrast, in the same 98-year period, 14 of the 16 professors in *non-clinical* medical subjects were exotic, some figuratively as well as literally; only William James Wilson and John Henry Biggart were from Ulster. This yawning gulf, 18 out of 19 local clinical as against only two out of 16 local non-clinical, neither statistically nor indeed intentionally arose by chance. Professors were appointed by the crown (by warrant under the sign manual, except for the foundation creations who were made by the lord-lieutenant) on the advice of the lord-lieutenant - effectively the advice of the chief secretary for Ireland - on the basis of a priority list prepared by the College president and vice-president who had to justify the ranking. The presidents, like the Royal staff, took the robust but common contemporary view that nepotism, protegéism, oligarchism and pragmatism in clinical appointments were acceptable if they ensured symbiosis, synergy, and co-operation between Queen's and the Royal and thus were beneficial to the school, and indeed on this basis the school remained remarkably successful and cohesive even if at the price of forfeiting cosmopolitanism among the medical professoriate and - dare I say it - even some intellectual distinction through fracturing any sturdy adherence to meritocracy. As the Queen's president in 1853 tactfully remarked of Professor Ferguson's appointment that year to the Royal staff, four years after his appointment to the chair of the practice of medicine, '... his present connexion with the [Royal] adds greatly to the means of making his course more useful and interesting to students';[19] and as the Queen's Colleges commissioners in 1858 bluntly stated '... and although [Queen's] has no direct connexion with the [Royal], the arrangements of the Medical School [in Queen's] has reference to the arrangements in the [Royal]'.[20] The official historians of Queen's put it equally plainly if more delicately: 'Appointment of local men occurred mainly in the medical faculty where established connections with [local] hospitals were of great importance'; and again 'the medical school thus developed as a local institution in a way that had no parallel in the other [faculties] ... and it was therefore of special importance that [clinical] medical chairs should be held by men acceptable to the local medical community ...'.[21] Not that the likes of the esteemed James Cuming (professor of medicine, 1865-1899) first Ulsterman to be president of the BMA, and possessor of a lofty intellect and wide reputation; the much-travelled sophisticate Thomas Sinclair (professor of surgery, 1886-1923); Andrew Fullerton (professor of surgery, 1923- 1933), with his 77 research publications, presidency of the Royal College of Surgeons in Ireland and who was formerly in charge of a great base hospital in France in World War I; and the courtly and much-loved WWD Thomson (professor of medicine, 1923-1950) could be dismissed as national nonentities, still less as mere provincials, to say nothing of William Whitla. Whitla (professor of materia medica, 1890-1919), was widely travelled and an outstandingly successful medical author with such intellectually challenging interests as being a rigorous commentator on Newton's *Daniel and the Apocalypse*, such materially rewarding ones as being an enthusiastic investor in the stock market, and such spiritually uplifting ones as being married to a senior Salvationist, and being president of the BMA and a Westminster MP to boot - though who could say that the book of Daniel, the stock-market, evangelical zeal, and political adherence were not quintessentially Ulster rather than national characteristics Neither should we be too toffee-nosed about such pragmatism especially before the arrival of the Fair Employment

Commission! Clinical chairs were part-time and paid, until 1909, £100 or £120 p.a. which, with student class fees, gave an average total of only some £200 p.a. compared to, say, the full-time professor of anatomy whose annual emoluments often exceeded £1000 (£60,000 in to-day's money), was once as high as £1464, and was handsomely in excess of the £800 salary of the Queen's president![22] A clinical professor had therefore to build a successful practice and this was easier for a local man - who was more welcome to the local fraternity for obvious reasons - and most medical schools at the time were parochial in their clinical appointments. In fairness Queen's showed frequent propriety (and loyalty to the spirit of its charter!): when there was a clearly superior alternative to a local candidate they usually chose the better man. Thus, as foundation professor of medicine they appointed the Dublin- based (though Tandragee-born) luminary, John Creery Ferguson,[23] who at the time had no connection with the Royal or indeed with Belfast, in preference to the Inst incumbent the flamboyant Henry McCormac,[24] in his prime in 1848 at age 48, an impressive scholar and prolific author of admittedly indifferent and quixotic books, and a veteran member of the Royal staff, and who was so keen for a Queen's chair that he applied in 1848, 1857 and again in 1865 just after his 65th birthday And for the foundation chair of materia medica they chose the brilliant Munsterman, Thomas O'Meara, from a field of 25 passing over *inter alia* the Inst incumbent, James Drummond Marshall, despite the support of an impressive local mafia including the Queen's vice-president, Thomas Andrews, who Marshall named as his sole referee; Marshall's father, Andrew Marshall, senior consulting surgeon at the Royal; his uncle and Inst professor of anatomy, James Lawson Drummond; and his brother-in-law, W.J. Campbell Allen, who was the Queen's foundation registrar-designate[25] O'Meara actually declined the post but Queen's again passed over Marshall to pick the 29-year-old Horatio Agnew Stewart who had been earlier unsuccessful for the chair of surgery despite being a favoured member of the Royal staff, the successful applicant - Gordon - was also at the time a Royal staff member which levelled that particular playing-field. Perhaps it was partly pedigree (Stewart was the son of a redoubtable and influential Presbyterian clergyman in Broughshane), partly pragmatism (Marshall unlike Stewart was not on the Royal staff), and partly a certain repugnance with involvement in 'trade' (Marshall was a successful retail chemist in partnership with his brother in High Street) which saw Stewart through even though '[although] he was very well thought of as a surgeon [he] does not appear to have had any particular qualifications in the subject of his chair'.[26] He didn't live long to enjoy it dying of tuberculosis seven years later.

So much for the advantages of pragmatism with a lacing of expediency. Queen's, however, learned another lesson from Inst this time from those who favoured principle. Inst, as we have seen, was unable to reach full accommodation with the Royal without the sacrifice or threatened sacrifice of some cherished autonomy. Uneasy with this situation the 'constitutionalists' logically, if in hindsight scarcely believably, decided to found a 'teaching' hospital to be wholly owned, run, and staffed by Inst, and where Inst would need to bend their knee to no-one. A (reasonably) suitable building was available and in this they saw, and not for the first time, the hand of a guiding Providence and they bought the 'old cavalry barracks' in Barrack Street - now a Christian Brothers school - and refurbished it as the 'Belfast Institution Hospital' (or 'The College Hospital'), a spartan 100-bed building which they opened in 1837 during a fever epidemic which meant that the rate-payer conveniently paid for the equipment and would contribute to the running costs, and the government paid half the purchase price. Providence smiling on Inst again. But it was never a viable scheme (despite divine support), and it was soon effectively closed, leased, and later sold off[27]. Again the lesson wasn't lost on Queen's: whatever you do don't buy a hospital; work with those who will work with you! Wise words especially with the Royal committed in its Frederick Street launch to medical teaching - 'Hoc nosocomium aegrotis et arti medicae sacrum ...' ('This hospital is devoted to the sick and to the art of medicine'), and with a fine lecture theatre suite opened in 1847.

Paradise Sought

The Queen's Colleges and the Queen's University in Ireland (1849-1882)

The Inst experience had taught that a viable college/hospital 'connexion' was possible. I now turn to its pursuit by Queen's and the Royal.

Queen's had two categories of medical student - the non-matriculated and the matriculated. The *non-matriculated* student enrolled at Queen's simply to gain the necessary class credits to allow him to sit for the parchments of various professional bodies (and the occasional university) most commonly the licence of the Royal College of Surgeons (RCS) of either England or Edinburgh, less commonly that of the

TABLE

Queen's University in Ireland

"Returns of students attending the following hospitals have been received" (1852-3)

Jervis Street	**Meath**
City of Dublin	**Belfast (Royal)**
House of Industry	**Mercer's**
St. Vincent's	**Infirmary, Galway**
South Infirmary Cork	**(Westminster)**
North Infirmary Cork	**(Others)**

Facts in the annual report of the QUI vice-chancellor for the year ending 19 June 1852 (H.C. 1852-3 [1561] xliii. 477-515, App. IX) and September 1853 (H.C. 1854 [1707] xx. 83-161, App. VIII) and subsequent reports. The presence, for example, of the Westminister Hospital means that one or more students attended there possibility 'out-of-term'; it does not mean that St. Bartholomews, Guy's, St. Thomas's etc were not worthy of recognition!

Royal College of Surgeons in Ireland which (unlike the other two) required up to two years' metropolitan attendance which was inconvenient and expensive to Ulstermen. The *matriculated* student on the other hand was the true, modern undergraduate, enrolled at entry for the four-year Queen's University in Ireland (QUI) degree course though in the event he often found it too exacting or expensive and down-graded to the more vocational, shorter, Royal College course. Furthermore, the QUI primary degree was MD *à la* Edinburgh and because it was adjudged to have an inadequate surgical content it did not qualify its holder for any of the estimated 1000 posts in Ireland in the poor law dispensaries, fever hospitals and infirmaries, nor be accepted by the Army and Navy Medical Boards, the East India Company Medical Service or the Indian Medical Service, nor hold any surgical post:[28] 'in consequence the great majority of the students in the Faculty of Medicine proceed to London for their surgical diploma [either with or without the MD]'[29] The academic standard was high and the education broad: the matriculation examination included *inter alia* Latin and Greek, classical history, and English composition, and the student had also to pass examinations in a modern language and natural philosophy (physics) before sitting finals.[30] Fees were also high, and if not living at home or with a guardian or close relatives the student had to live in 'licensed premises', less ambiguously approved categories of residence 'licensed for the purpose by the [Queen's] President'.[31] And there were other differences. The proportion of *matriculated* students, 50 per cent in 1849, rose to over 80 per cent by 1870 as the course became established, as the quality of entrants improved, and under pressure from the General Medical Council (GMC). Less than one-half however sat the QUI degree: a few dropped out while others down-graded to a Royal College 'license' course, unsurprising in view of the formidable deterrents (above) to persisting with the degree.[32]

A key requirement in the Queen's curriculum from 1852 (there were transitional arrangements before that) was 24 months' attendance at a 'medico-chirurgical hospital containing at least 60 beds, together with the clinical lectures therein delivered, at least two each week', the hospital to be 'recognised' by the senate of QUI which sat in Dublin. Six of the months were required to be taken in the 'first period' of the curriculum, viz. first and second years; the remaining 18 months in the 'second period', viz. the third and fourth years. The external professional bodies had broadly similar requirements though a shorter course. The Royal had therefore to meet the 'recognition' requirements of Queen's *and* these professional bodies. The Royal therefore saw no formal distinction between their relationship with Queen's and with, say, RCS England. It cut the other way also: Queen's saw no formal distinction between a student's attendance at the Royal and at another 'recognised' hospital of which there were many (see Table). Furthermore, QUI required at least one-third of its medical course lectures to be taken in one of the three Queen's Colleges (Belfast, Cork or Galway); the other two-thirds could be taken at other 'recognised' universities, colleges or schools.[33] It could therefore be said that QUI saw no formal distinction between attendance at a Queen's College and a 'recognised' college for two-thirds of the academic course. Neither the Royal nor Queen's was exclusive to the other and so to the lofty idealists and strict logicians at Queen's a formal 'connexion' with the Royal seemed unnecessary and even inequitable to others.

This lack of a distinct formal and explicit 'connexion' between Queen's and the Royal was much deplored by the Royal and by some Queen's staff. A.G. Malcolm, the most active and innovatory teacher on the Royal staff, spoke for many of his colleagues when he said: 'The Hospital must be admitted to be the very life of a Medical School: without incorporation with which no college, however inherently distinguished, can every hope to flourish as a seat of medical instruction; and we cannot consider it as otherwise than an oversight in the establishment of the Queen's Colleges that medical

interests had not been better attended to, and especially the principle of associating clinical with theoretical instruction ...'.[34] ('Connexion' in his lexicon had now been up-graded to 'incorporation'). Meanwhile Queen's aloofly disposed such crumbs as inviting the Royal staff to the College's opening ceremony in December 1849, along with hundreds of other.[35]

The *de facto* position, however, was very different and for good reasons. *Firstly*, some 95 per cent of Queen's medical students were from Ulster; though free to attend any ('recognised') hospital, economics and geography kept them at home, and 'home' meant the Royal which was the only 'recognised' medical and surgical hospital in Ulster. Some may have attended for a few months elsewhere, possibly during vacations and/or the 'summer session' (Table) - the lecture session was November to April inclusive which kept most students at base; the 'summer session' was May-July inclusive and usually lecture-free - but there are no data on this. For similar reasons very few students from outside Ulster attended the Royal.[36] But Ulster students certainly crowded into the Royal - 27 in 1850 had grown by the 1880s to the staggering average number of well over 200 during the six-month winter session and often over 150 during the three-month summer session[36], and this in a hospital of only some 180 total beds and 2000 intern and 10,000 extern patients per year by the later century. *Secondly*, there were the curricular logistics. The course of lectures at Queen's and the requisite hospital attendance were normally concurrent or at least interdigitated. From 1852, during the teaching session (November-April inclusive) in the final two years, lectures in medicine, surgery and materia medica occupied 4.00 pm to 6.00 pm each afternoon *including Saturday*, midwifery was at 3.00 pm on Mondays, Wednesdays and Fridays, anatomy was on Mondays to Fridays ('demonstrations' at 11.15 am; lectures at 2.00 pm; dissections 'daily'), and medical jurisprudence was 3.00 pm Tuesdays and Saturdays.[33] Students had to attend each course for six months during the final two years (three months for medical jurisprudence), normally three lectures per week other than anatomy which required five, as well as the required hospital attendance (as above) and a three-month course in the practice of compounding under a qualified apothecary, and although they could logistically have arranged their courses so as to have the opportunity for attendance at hospitals other than the Royal this was little practised if at all. *Thirdly*, most clinical professors, as we have seen, were on the Royal staff and they could co-ordinate their hospital instruction with their classroom lectures into a coherent course. *Fourthly*, Queen's and the Royal staffs had a common purpose, were colleagues in the Ulster Medical Society and other societies, had the same provincial roots and a shared culture so that symbiosis and synergy could thrive.

Reliance on *de facto* arrangements, however, no matter how strong and operationally effective, is usually constitutionally unsatisfactory; hence the Royal staff's concern as voiced by Malcolm, and the concern also of some at Queen's. Nevertheless, there is no doubt as to the keenness of both institutions for success. In 1847, even before Queen's opened, a new lecture room and operating theatre had been opened in the Royal; in 1849 the hospital lectures, under Malcolm's guidance, were systematised; and the Royal's *Annual Reports* throughout the 1850s habitually eulogised the Queen's students for their attributes and even dress and comportment! The pride in the 'connexion' is tangible. Despite, or perhaps because of, the lack of formal structures the partners were at this time getting on famously! However the honeymoon was soon to end. The complete lack of, or progress towards, formal ties let alone to what Malcolm had called 'incorporation', increasingly worried many and for cogent reasons. The clinical professors had no standing in the Royal *as professors*, only as members of the Royal staff and as such subject to annual election; and the other members of the Royal staff gave clinical instruction, good or bad, to Queen's students without any accountability to Queen's and without even being chosen by Queen's. Other colleges or schools seeking 'recognition' by QUI (for not more than two-thirds of the course - see above) had to submit the names and qualifications of the 'several lecturers whose lectures are required to be recognised', but *hospitals* did not have to do so with respect to achieving 'recognition' for 'attendance' or 'the clinical lectures therein delivered'.[33] Hospitals *did* supply lists of 'clinical teachers' but 'recognition' was based on the criteria of number of beds, bed-occupancy and case-mix rather than the academic or even professional abilities of the staff.[37] Similarly, the Royal staff as staff members had no input to, or say in, the academic affairs of Queen's: not in the structure of the curriculum nor in the selection of students, still less in the process of examining, least of all in the appointment of the professors. These were matters for the faculty of medicine, which consisted exclusively of professors in the medical subjects of the faculty; for the (college) council, which had only one member from the faculty of medicine, the dean; or ultimately for the QUI senate or the crown. In fact the senate,

which sat in Dublin, and *a fortiori* the crown, were aloof from staff, students and the professoriate alike and completely remote from the Royal and its likes. True, by 1866 the QUI senate included seven members of the growing QUI convocation, viz. graduates. True also that two of these were Belfast medical men - Dr (later Sir) William McCormac, son of that Henry McCormac who had three times failed to obtain a Queen's chair, and Dr W.A. McKeown, an ophthalmologist, who with Peter Redfern, professor of anatomy (a Queen's Belfast nominee), made three local medicos; but their influence was small.[38] Senate *did* appoint examiners and the in-put by the medical senators could have been influential, but initially only one examiner in each clinical subject was appointed and the majority were from Dublin: Queen's College examiners were in a minority and moreover were rotated among the three Colleges. In any event the examinations were exclusively papers and orals until 1869 (when clinical examinations were inaugurated in the South Dublin Workhouse Hospital) and were sat in Dublin Castle until 1877. GMC visitations took place pursuant to the 1858 Medical Act but they did not lead to any formalised Royal/Queen's 'connexion' and this period closed in 1882 in a general feeling of frustration and missed opportunities with Queen's somewhat arrogantly rejecting some GMC curricular recommendations, the only licensing body to do so, and with no changes in substance to the 1852 curriculum, and this had led at one bleak period to the GMC advising the privy council not to register Queen's graduates.[39] Against this backdrop and with mounting politico-educational upheavals in the country generally, it was time for QUI to go, and in 1882 it did.

Before leaving QUI a short postscript on the Belfast Lying-in Hospital is instructive. The Queen's curriculum from 1852 required attendance at a six-month course of three lectures a week in midwifery and diseases of women and children plus three months practical midwifery at a 'recognised' hospital 'with the clinical lectures therein delivered', if of 30 beds, and six months if of 15. William Burden the professor (1849-1867), was, conveniently, from 1837 physician to the Belfast Lying-in Hospital in Clifton Street, and was even described as 'the master'.[40] His successor in 1868, Robert Foster Dill, was a substantial figure in Belfast medical and social circles but had resigned from the hospital staff in 1861 over some *contretemps* with the ladies' committee and so had to give his clinical instruction on district and in his own ample house at 3 Fisherwick Place.[41] This was inconvenient and flew in the face of normal Queen's practice. Why had Queen's abandoned the pragmatism that had served them so well? There is a simple answer. They had not abandoned it. Following their usual practice they had chosen for the chair the outstanding Dr John M Pirrie, attending physician at the Royal and effectively acting-master at the Lying-in Hospital who had frequently deputised for Burden. But Pirrie was a staunch liberal and Dill an impeccable conservative, the conservatives were then in power, the Dill clan was remarkably influential none more than Professor Dill's cousin, Dr John Dill, of Brighton, who secured the support of the Irish government for his cousin as 'the only conservative candidate',[42] and the lord-lieutenant overrode the first choice of the president of Queen's of Pirrie and instead had Dill appointed. Dill's grandson the neurologist, Robert Foster Kennedy, is only one of two Queensmen to be eponymously remembered through a disease - the Foster Kennedy syndrome;[43] the other is Ashton Morrison who shares with JV Verner, the Verner-Morrison syndrome.[44]

Paradise Lost

The Queen's Colleges and the Royal University of Ireland (1882-1909)

In 1882 the Queen's University in Ireland (QUI) was replaced by the Royal University of Ireland (RUI), a purely examining body centred at Earlsfort Terrace in Dublin, now the National Concert Hall where great music fills the auditoria where once students were examined. The three Queen's Colleges remained though now as external not constituent colleges. This was a monumental structural upheaval in response, as often in Ireland, to politically-sensitive academic imperatives, or possibly academic-sensitive political imperatives, but as regards the Queen's/Royal 'connexion' it was more a high jump than a long jump: a great flurry and prodigious leap but a return to earth close to the take-off point. Medically this period saw the mushrooming of knowledge which led, under the eye now of the GMC, to the compartmentalising of the former general umbrella disciplines into the more discrete specialties familiar to-day. The degree curriculum became even more crowded reaching five years from 1887 and even six years from 1892 including a mandatory arts year,[45] an effective deterrent which as in the case of the former (QUI) MD course, drove increasing numbers into the shorter, cheaper, and - dare I say it - less demanding course for the examinations of the newly founded conjoint boards of the various Royal Colleges while remaining in Queen's for their course instruction. Mandatory

hospital attendance was widened to include the emerging specialties: three months at a fever hospital or fever wards in a general hospital; three months at an eye and ear hospital or in an eye and ear unit of more than ten beds in a general hospital; three months at a 'lunatic asylum where clinical teaching is given'; three months at a pathology unit in a general hospital; 24 days at operative surgery; three months at practical pharmacy under a qualified apothecary; and two months as a clinical clerk and surgical dresser, all in addition to six months practical midwifery in a hospital with at least 15 midwifery beds in regular occupation, and 24 months at a general hospital of which 18 would be taken as three winter sessions of six months each and two summer sessions of three months each. This meant that specialist hospitals or specialist units within general hospitals, as well as general hospitals themselves, had now to be 'recognised' by the RUI senate, and Queen's prudently decided to arrange teaching provisions in these specialties. This increased the complexity of the logistics of the 'new' curriculum which cried out as never before for formal rather than ad hoc joint arrangements and this became a recurrent *cri de coeur*.

Initially much of the specialist teaching fell on the Royal since the requisite specialist hospitals in Belfast were either unbuilt, inadequate, or for various reasons were unsuccessful in attracting students. The Royal rose to the challenge; indeed they welcomed it and as early as 5 May 1882, before the RUI requirements were in force, the medical staff unanimously agreed 'that the Royal Hospital should endeavour to embrace within itself the power of granting certificates for clinical teaching to meet *all* the requirements [other than those for mental diseases] of the examining bodies'.[46] (My italics). This meant in practice up-grading the fever facilities, re-organising the teaching programmes, tightening the teaching obligations of the staff, and creating new departments of gynaecology and of eye and ear diseases. (It also meant reaching an arrangement with the Belfast Lying-in Hospital about joint midwifery teaching, but this fell through!). These were soon done and with an altruistic eye to Belfast's interests as well as their own, or perhaps just in a burst of the Belfast chauvinism of the time, the medical staff were writing in June 1884 direct to RUI in Dublin pointing out that the Belfast facilities constituted 'a field ... which is hardly possible to conceive could be utilised or exhausted by any University or number of students'.[47] When more stringent regulations came into force in 1887 pursuant to the 1886 Medical Act the Royal effectively had to abandon their earlier ambitions for a comprehensive clinical teaching service (other than in midwifery and mental disease) and many specialist hospitals were soon recognised: in 1888 both the Belfast Ophthalmic in Great Victoria Street, and the Ulster Eye, Ear and Throat (the Benn) Hospital in Clifton Street, both with 30 beds against only four at the Royal when a unit of ten beds was strictly required; in 1890 the Belfast Hospital for Sick Children in Queen Street on foot of new RUI requirements for attendance on diseases of children; and in 1899 the Belfast Union Hospital on Lisburn Road (now the Belfast City Hospital) but only for 'fevers' (and for 'vaccination'), increasingly uniquely appropriate with its large 250+ bed fever hospital, from 1906 at Purdysburn, as against the original 55-bed fever wards in the Royal in Frederick Street, and the reduced 24-bed facility planned for the Grosvenor Road site but ultimately whittled down to only eight.[48]

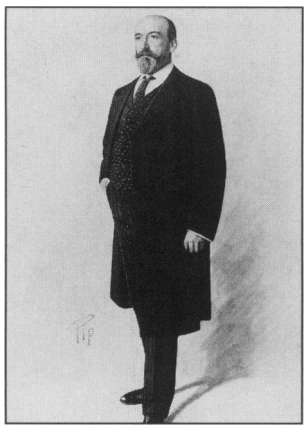


Figure 4 Sir William Whitla (1851-1933). Professor of materia medica at Queen's, 1890-1919, attending physician, 1882-1918, and consulting physician, 1918-1933, to the Royal, president BMA, 1909-1910, MP, 1918-1923. A generous benefactor to Queen's, many Belfast institutions and his profession. (Cartoon by 'Pip').

Queen's also had its academic role to play in these 'minor specialties' (to use a later term) but not so pressingly since the academic, as distinct from the clinical attachment, parts of the RUI curriculum were not operative until 1893 rather than 1887. Extension of academic posts in the 'new' minor specialties were therefore delayed, but when operative Queen's followed the successful tactic of appointing established Belfast doctors, this time not to tenured professorships, which would hardly be justified, but to (part-time) *lectureships* on annual appointment which not being professorships gave the incumbent no university standing, no university stipend other than the class fees of the students, and such little status that they were not even consulted by Queen's when preparing its crucial submission to the Royal Commission (the 'Robertson Commission') on its own future in 1902. The first such part-time lecturers were: William Barrett in 1892 in pathology (he received a small stipend since he travelled from Edinburgh for his teaching blocks); William McKeown from the Benn Hospital in 1896 in ophthalmology and otology; Henry Whittaker, medical officer of health for Belfast,

in 1896 in sanitary science; (Victor Fielden soon to be first consultant anaesthetist to the Royal, had been appointed demonstrator in practical pharmacy in 1893); while in 1903, John McLeish, superintendent of the fever hospital, was appointed *teacher* in vaccination, a post which surprisingly survived up to 1949.[49]

The centrifugal dispersion away from the Royal and its consequent logistical, administrative and operational complexities, demanded the integrated approach which the Belfast medical fraternity increasingly wanted. In 1899 they were potentially compounded when RUI, on the application of the Mater Infirmorum staff, recognised (from 1900) the recently much enlarged Mater Infirmorum Hospital for general medical and surgery teaching, the only general hospital other than the Royal to be so recognised in Ulster, indeed outside Dublin, Cork and Galway, and breaking - if you like - the Royal's monopoly in place since 1835.[50] This was a very sizeable cheque for the new Mater but in the event they did not present it for another eight years because Henry, Bishop of Down and Connor, chairman of trustees refused to sanction this 'connexion' with RUI and with Queen's because of the opposition of the catholic prelacy, now more rigorous than ever, to the Queen's College system, and in his own words 'until we can see our way to have a medical school in Belfast under Catholic auspices'.[51] Despite repeated efforts by the staff to have this decision reversed, it was not until October 1908 that Bishop Tohill, Henry's recent successor, acquiesced[52] though whether this was due more to the passing of the conciliatory Irish Universities Act in August that year or the passing of Bishop Henry in March, is a moot point! Within a few years an average of some 20-30 students were attending the Mater,[53] and until the end of our period the hospital continued to attract a loyal *cadre*[54].

No such specific *de jure* 'connexion' resulted and this deepened RUI's unpopularity with the Royal staff and many at Queen's. Some had seen a ray of hope in the creation of RUI medical fellows and a panel of examiners, but the fellows were non-teaching, attracted only some £150 pa stipend, and only four were allotted in total to the three Queen's Colleges. [13] But in truth RUI was deeply unpopular in the country generally and with the Queen's Colleges notably with their students who now voted with their feet. The reasons were basic. The examiners were mainly Dublin-based and the examinations were held in Dublin where Belfast (and Cork and Galway) students were examined in unfamiliar hospitals by unfamiliar examiners many of whom had taught the Dublin-based students who were often enrolled at colleges other than the Queen's Colleges, especially at the Catholic University Medical School (a component of the Catholic University of Ireland) which by 1900 had overtaken Queen's (Belfast) as the largest medical school in Ireland. The Queen's Colleges naturally raised the question of an uneven playing-field biased against them including allegations by staff and others at the 'Robertson Committee' in 1902. This was energetically if not completely convincingly rebutted but the hostility lingered.[13] It was of small future consequence since the days of RUI were numbered. The Royal staff anticipated this approaching demise and in a letter to RUI as early as 1903 they noted: 'While the Royal ... is an integral part of the Belfast Medical School there is at present no definite official connection between the Hospital and Queen's ... In any re-organisation of the Queen's Colleges this might be accompanied by the formation of a joint board ... to supervise education'.[55] Such a 'joint board', long sought by the Royal, was now crucial in a thriving, thrusting city of 350,000 people, bereft of the compactness, cosy oligarchies, and curricular simplicity of the past, and with mushrooming hospitals the existing *de facto* relationships were patently inadequate and the Royal was right to press for something more formal. Had Queen's had a faculty of medicine during the RUI years some form of improved liaison machinery would likely have emerged, but deans and faculties had been swept away in the second Queen's charter in 1863, the title 'faculty' being preserved in the records only as a taxonomic convenience. In its place was a cosily informal non-statutary 'committee of medical professors' which was rarely convened and in fact only once met with the Royal staff in joint conclave (on 6 January 1902), but the business was not to do with collaboration, only pernickety detail of RAMC examinations and the proposed holding of the (Irish) conjoint board examinations in Belfast.[56] It was the darkest before the dawn, with paradise nowhere in sight.

Paradise (Re-)Gained

The Queen's University of Belfast (1908-1949)

In 1908 the pressures which were later to lead to the partition of Ireland led to the partition of its higher education bodies. Queen's Belfast was cut off from the other Queen's Colleges - or if you prefer the other

Queen's Colleges were cut off from Queen's Belfast - and on 2nd December Queen's Belfast was given independence and up-graded to a university in its own right as from the following year. The results for institutional medical collaboration in Belfast were little short of electric.

The Queen's governing body, the senate, was for the first time situated in Belfast and now represented exclusively Ulster (later, Northern Ireland) interests. One of its 44 members was to be 'a person elected by the board of management of the Royal Victoria Hospital', and the first nominee was Sir William Crawford, chairman of the Royal board and who was also honorary treasurer of Queen's and chairman of its finance committee, a powerful and pivotal position. Never before had one person held such influential administrative offices in both Queen's and the Royal. Six professors from academic council, eight members of convocation, four crown nominees, and up to four co-optees were also members of senate and each category either invariably (in the case of the council members) or usually included several medical men (including Royal staff members) though appointed or elected in their own right unlike Crawford who was appointed to senate as the Royal's nominee. Faculties were re-created now as powerful bodies, the medical faculty being far wider in membership than the exclusively professorial bodies of 1849-1863, and 1863-1908. As well as the 'professors in the subject of the faculty', the lecturers in these subjects were now also members and that included the part-time lecturers in the 'minor specialties' already referred to. Crucially, however, a new category of teacher was created - the 'clinical lecturer and examiner' (who still survives) - who was *ex officio* a member of faculty and also an internal clinical examiner. Holders were annual appointments and there were initially four, one in each of medicine, surgery, gynaecology, and ophthalmology, each (almost) invariably a senior attending consultant and nominated by the 'recognised' hospital concerned (not necessarily the Royal), and rotated so that many clinicians became involved in the business of the medical school. In the first five years, 1909-1914, for example, 17 different doctors filled the 20 available posts (4 posts, 5 years) and included, in 1912, and for the first time, a staff member of the Belfast Union Hospital, Dr Robert Hall,[57] the Union Hospital having been 'recognised' for general teaching since 1910, though for 'fevers' and 'vaccination' earlier (in 1899). (I should add, parenthetically, that the question of clinical teaching in the Union Hospitals in Belfast, Dublin, Cork and Galway, was a lively issue during the nineteenth century. In Belfast the professor of materia medica (1857-1890), James Seaton Reid, formerly an attending physician at the Royal until appointed medical officer at the Belfast Union Hospital, and then until the year he died a consulting physician at the Royal, was allowed by the board of guardians to teach students in the Union Hospital, but this was an *ex gratia* personal concession which he only exercised for five years up to 1862. There was some further sporadic and spasmodic teaching from 1924, but systematic teaching was not instigated until after World War II).[58] Some clinical lecturers and examiners were members of the staff of more than one hospital so that the number of hospitals represented at the faculty of medicine was greater than the number of representatives. The annual number of posts was increased to six or seven from 1921,[59] and in 1941 increased again to sixteen,[60] (four in each of medicine, surgery, obstetrics and gynaecology, and ophthalmology, the major final MB subjects) to reflect the number of teaching units and hospitals and the growing need for internal examiners.

These changes must be seen against a European and American backdrop of closer college/hospital relations generally arising from the seminal Flexner Reports in USA[61,62] and R.B. Haldane's Royal Commission in UK in 1913[63] which *inter alia* led to the creation of full-time university professorial clinical units housed adjacent to, or even 'embedded' in (to use the later University Grants Committee jargon) the general teaching hospital as we see in Belfast to- day (first) at the Royal and (later) at the City. Just as every schoolboy knows (as Macauley has it) who imprisoned Montezuma and who strangled Atahualpa, so every doctor knows, or should do, that the first such academic clinical units in the English-speaking world were in Johns Hopkins in 1913 under Halsted (surgery), Janeway (medicine - Llewellys Barker, the first choice, declined[64]), and Howland (paediatrics)[65]. Because of World War I no unit was created in Britain until 1920 when full-time chairs of medicine and surgery were established not in London, as Haldane had expected, but in the newly founded Welsh National School of Medicine (the prime minister, Lloyd George, was Welsh!) occupied by respectively Professor Kennedy and Professor Sheen[66,67]. Few followed until the nineteen-forties and though essentially a pre-World War I concept they were in Britain mainly a post-World War II creation. It was partly in line with this Flexnerian/Haldanian concept that the Royal staff in August 1909 wrote to Queen's expressing 'its approval and appreciation of the principle of the association of ... clinical hospitals ...

with [Queen's]',[68] and the new faculty of medicine at its very first meeting resolved 'It is the earnest desire of the Faculty to associate more closely than in the past the ... clinical hospitals with the University'.[69]

Little happened either on-stage or behind the scenes for another dozen years: World War I and its aftermath saw to it that the social and economic climates were unpropitious Then in 1921 the Belfast Lunatic Asylum relinquished to the Royal the lease on the last six acres of its Falls Road/Grosvenor Road site and was finally demolished in 1930 leaving a substantial acreage onto which moved the Belfast Hospital for Sick Children (from Queen Street) in 1931 and the Royal Maternity Hospital (from Clifton Street) in 1933 forming, with the Royal, a formidable concentration of clinical facilities yet leaving considerable space for the further developments which have since taken place. This potential for concentration on such a large site adjacent to the Royal was not lost on Queen's and on 11 July 1928 they resolved to move their existing department of pathology and bacteriology from University Road to the Royal site 'in view of the close interdependence between the practical work of hospitals and the scientific study of the phenomena and causes of disease ...'[70] There were only two dissentients at senate - Rev J McCaughan, president of St Malachy's College and a crown nominee, and Mr J B Moore, FRCSI, a co-opted member, former consultant surgeon at the Mater and father of Brian Moore, the distinguished novelist. Clearly they saw this proposed development as inimicable to the Mater's interests since it physically joined a core Queen's department with the Royal.[71] This Institute of Pathology was opened in 1933 as a two-storey building (the present third storey was added after World War II) and came to house both the Queen's facilities and those of the hospital pathology and bacteriological services as a joint enterprise. In 1937 John Henry Biggart was appointed as professor, consultant pathologist, and *de facto* director of the Institute (the *de jure* post was not created until 1948), an event of incalculable importance. Biggart was not the first professor of pathology to be a consultant at the Royal - all his predecessors had been - but with the unimportant exception of his immediate predecessor, the Scotsman, John Young, he was the first *full-time* professor in the medical school to go to his daily work at the Royal and not at Queen's. The opening of the Institute in fact marked a crucial and not just a symbolic shift in the clinical medical schools' centre of gravity from being university-based to being hospital-based.

It is easy to be hagiological about Biggart and equally easy to shrink from understanding the competing antinomies in his nature. He was a product of the Queen's/Royal system and he loved them both, as he did his profession, to the point of a romanticism at which few could only then as now guess. He was an able scholar proud of his cultural background taking at Inst the Sullivan (for mathematics), the Hyndman (for Latin and Greek), the Musgrave (for French) as well as the Blair Prize (for physics and chemistry), followed by many awards at Queen's and second place in his final year behind the late Freddie Kane, former superintendent of Purdysburn Fever Hospital. For his Ulster Medical Society presidential address as late as

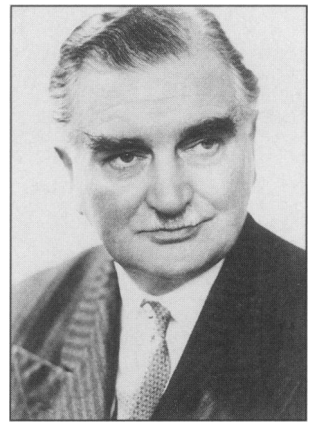


Figure 5 Sir John Henry Biggart (1905-1979). Professor of pathology at Queen's and pathologist to the Royal, 1937-1971, director of the Institute of Pathology, 1948-1971, dean of the medical faculty, 1944-1971, pro-vice-chancellor and then pro-chancellor of Queen's, and much more besides. The most significant figure in recent Ulster medicine. (Courtesy, the Royal Victoria Hospital).

1971 he chose as his topic the competing philosophies of the various schools of medicine of ancient Greece. He combined the scholar's perspective with high executive skills and he had a very clear vision of the future of medicine in Ulster around an integrated Queen's/Royal axis though with the due autonomies of each partner preserved. He was a superb judge of people and though a quintessential Ulsterman he was also by intellectual inclination and personal experience an internationalist, an especial enthusiast for Johns Hopkins in Baltimore (who had been the pioneers of full-time academic clinical units) where he himself had worked for two years. In consequence he did much to influence Queen's, and indeed more directly to reverse the century-old practice of appointing clinical professors exclusively from among the local fraternity (see below). As dean of the faculty of medicine from 1944 he ensured a smooth adoption by Queen's of the radical Goodenough Report proposals for introducing such academic clinical units and their 'appropriating' of teaching beds. As early as 1946, on Biggart's prompting, the Royal Belfast Hospital for Sick Children discussed whether if the new full-time professor of child health was not a member of staff he or she should automatically be made one and given appropriate clinical facilities[72] (in

fact this was not tested as, true to the then form, in 1948 the senior consultant F.M.B. Allen was appointed!). But it soon was tested, and the decision of the Royal staff on 24 July 1947[73] automatically to appoint the new professor of surgery, the Englishman Harold Rodgers, to the Royal staff (with 25 beds in wards 11 and 12) opened the way for other imports to senior clinical posts - Dick Welbourn, Graham Bull, Richard Womersley, Owen Wade, Philip Stoy, Peter Elmes, Ivo Carré, and others, who would most assuredly not have been appointed before the war. When a local graduate was preferred he or she was expected to have had significant experience abroad, a credential, as we have seen, which Biggart valued and actively promoted - Jack Pinkerton, John Dundee, John Gibson and later Desmond Archer, come at once to mind. Biggart combined all this with an ability to conjure problems out of existence, and these attributes allied to personal integrity and a strong and attractive personality enabled him to win the complete confidence, indeed often something approaching eulogy,[74] of Queen's, the Royal, and his colleagues alike and by the end of my period, 1949, he had attained a unique position of power and influence in the local medical scene approached only by Andrews in the 1840s on a much smaller canvas. Indeed this paper could have been, and nearly was, subtitled 'From Andrews to Biggart'. It is pointless here to litanize his many offices: quite simply he stood at every crossword and although he had not fully entered his kingdom by 1949 he was very close to the gates. Of course the times were propitious. World War II saw the great reports on which a brave new medical world was to be built. Furthermore, the Hospitals Authority had to deal with only one medical school so that Biggart could - and did - hold strategic pluralities encompassing both bodies. Much of what came about would have come about anyhow as it did throughout Britain, but Biggart's was the sure hand which guided the special meeting of the faculty of medicine of 18 February 1948 into accepting a blueprint for allocating medical and surgical professorial teaching beds as between the Royal and the City:[75] the Mater was not at that time in the national health service (NHS). This was the first significant erosion of the Royal's monopoly with respect to medicine and surgery teaching and made this meeting one of the more important in the faculty's history. This opened the door to the joint appointment system for academic (mainly but not exclusively clinical academic) staff, which was accepted by both parties in principle on 11 May 1949,[4] and also to professorial teaching wards with clinical instruction and lectures by professors on-site and of right and not through the hospital's grace and favour, exactly as Drummond had proposed in 1826! Ironically the very changes to the service which greatly strengthened the Queen's/Royal axis in the short term up to 1949 weakened it in the longer-term through the NHS corollary of uniformity of service Province-wide, and this ultimately stripped the Royal of its near exclusivity with Queen's and it came to share resources, services, and academic units with other hospitals in Belfast and beyond, clearly evidenced to-day.

Epilogue

Finally, Chairman, 'alliance' or 'special relationship'? The Oxford English Dictionary says that an alliance is a 'combination for a common object'. The medical faculty, and the teaching hospitals in their instructional mode, clearly represent a series of co-ordinated co-operatives, and their commonality of purpose and objectives, their shared cultures, and their cross memberships though without surrender of ultimate autonomy, fulfill the definition of 'alliance' rather than, for example, a superior and vassal state or, as was the case of Russia and the Western Powers in World War II, 'associated powers' (and not 'allies') because they shared nothing except one thing - the defeat of Hitler. In fact I would call the faculty and the hospitals 'a grand alliance', borrowing the term from 'la Grande Alliance' of the late seventeenth century European powers against Louis XIV of France, and within this the Royal clearly is the leader on the grounds of history, of size, of range of facilities, of having the senior clinical academic units, and much more besides. It is more than *primus inter pares*; it is within the grand alliance a 'special relationship'.

It is not however integration nor anything like it. Macro-structural factors inhibit this, predominantly the vertical and horizontal fault lines in medical education: vertical, in that the academic bodies are under the purview of the Department of Education for Northern Ireland, and the service and training bodies under that of the Department of Health and Social Services; and horizontal in that undergraduate medical education is conducted and very largely regulated by academic bodies and institutions, whereas graduate training is conducted largely inservice and regulated exclusively by professional bodies - with a few grey areas scattered here and there. Much ingenuity has gone into devising effective collaborative and bridging structures but as long as the basic regulatory and funding dichotomies remain it is hard to see how

closer association can take place. In fact where responsibility has been shared, as in the pre-registration year, amiable chaos has been a feature! Since 1849, 'connexion' has evolved into a 'grand alliance' with an additional 'special relationship' for the Royal within it; but not into 'integration'. I personally believe that integration may be undesirable as well as impossible. At the 300th celebrations, chairman, I hope to be invited to defend this viewpoint!

Acknowledgements

Professor Robin Shanks, while the senior pro-vice-chancellor, honoured me in the invitation to give this lecture and, as acting vice-chancellor, in chairing it. Professor John Bridges and his colleagues on the Royal Victoria Hospital bicentenary committee facilitated my every need. Dr John F O'Sullivan shared with me his unrivalled knowledge of arrangements at the former Belfast Union Hospital (see note 58) as did Mr Peter Gormley with the Mater Infirmorum staff minutes which survive intact for the 'new' hospital from 1898 largely due to his prescience and careful custodianship (see note 50). As usual Mrs Julie Frost typed and edited the script with skill and patience.

Notes and Bibliography

1. Malcolm, AG. The History of the General Hospital Belfast and the other Medical Institutions of the Town. Belfast: W&G Agnew, 1851, pp.49-52 (Reprinted in: Calwell, HG. Andrew Malcolm of Belfast, 1818-1856. Physician and Historian. Belfast: Brough, Cox & Dunn, 1977). It is not clear whether the Dispensary apothecary, Mr Devlin, moved his residence as well as his medicines to Factory Row. (See also: Strain, RWM. Belfast and its Charitable Society. A story of urban social development. London: Oxford University Press, 1961, p.156).

2. Dr SM. Stephenson (physician), and Surgeons McClelland, McCluney and Bankhead.

3. Moody, TW, Beckett, JC. Queen's, Belfast 1845-1949. The history of a university. 2 vols. London: Faber & Faber, 1959.

4. QUB Senate Minutes, 1949, pp.53-4 (11 May 1949).

5. Allison RS. The seeds of Time: being a short history of the Belfast General and Royal Hospital, 1850-1903. Belfast: Brough, Cox & Dunn, 1972.

6. Clarke, RSJ. The Royal Victoria Hospital Belfast. A History 1797-1997. Belfast: Blackstaff Press, 1997.

7. Froggatt, P. Medicine in Ulster: The Belfast School. In: O'Brien, E, Crookshank, A, Wolstenholme, G. (eds). A Portrait of Irish Medicine: an illustrated history of medicine in Ireland. Swords (Dublin): Ward River Press, 1983, pp.183-213.

8. Froggatt, P. The distinctiveness of Belfast medicine and its medical school. *Ulster Med J* 1985; **54**: 89-108.

9. Froggatt, P. The foundation of the 'Inst' medical department and its association with the Belfast Fever Hospital. *Ulster Med J* 1976; **45**: 107-145.

10. Froggatt, P. The first medical school in Belfast 1835-1849. *Med Hist* 1978; **22**: 237-266.

11. Froggatt, P. The resignation of Robert Little from the chair of midwifery at Inst. *Ulster Med J* 1979; **48**: 19-31.

12. Froggatt, P, Wheeler, WG. Robert Little MA, MD, LAH, LM, professor of midwifery and diseases of women and children, Royal Belfast Academical Institution, 1835-1840: a biographical note. *Ulster Med J* 1983; **52**: 58-66.

13. Froggatt, P. The people's choice: the medical schools of Belfast 'Inst' (1835-1849) and the Catholic University (1855-1908) compared. *J Ir Colls Phys Surg* 1991; **20**:49-59.

14. Tait, PG, Brown, AC (eds). The Scientific Papers of the Late Thomas Andrews MD, FRS with a Memoir by PG Tait and A Crum Brown. London: MacMillan, 1889; Riddell, H. Dr Thomas Andrews: the great chemist and physicist. Proceedings of the Belfast Natural History and Philosophical Society (session 1920-1921) pp.108-138.

15. (Belfast) Newsletter, 7 November 1826.

16. Froggatt, P. Dr James MacDonnell MD (1763-1845). *The Glynns* 1981; **9**: 17-31.

17. Froggatt, P. MacDonnell father and son. James (1763-1845) physician of Belfast; John (1796-1892) surgeon of Dublin. *J Ir Colls Phys Surg* 1984; **13**: 198-206.

18. Froggatt, P. Thomas Ferrar, MB, LRCSI (1797-1837); the absentee professor of surgery at the Royal Belfast Academical Institution. *Ulster Med J* 1996; **65**: 152-161.

19. Report of the President of The Queen's College Belfast for the Academic Year 1852-3. H.C. 1854 [1804] xx.31-48 (p.12).

20. Report of Her Majesty's Commissioners appointed to Enquire into the Progress and Conditions of the Queen's Colleges at Belfast, Cork and Galway .... H.C. 1857-8 [2413] xxi. 53-572 (p.25)

21. Moody, TW, Beckett, C. Op. cit. (note 3 above), p.174.

22. Ibid., App. IIIB, pp.699-719.

23. Pinkerton, JHM. John Creery Ferguson 1808-1865: physician and fetologist. *Ulster Med J* 1981; **50**: 10-20.

24. Fraser, Sir Ian. Father and son: a tale of two cities, 1801-1902. *Ulster Med J* 1968; **37**: 1-37.

25. Froggatt, P. Two neglected Belfast medical professors: James Lawson Drummond (1783-1853) and James Drummond Marshall (1808-1868). In: Gray, J, McCann, W (edits). An Uncommon Bookman: essays in memory of JRR Adams. Belfast: Linenhall Library, 1996, pp.74-99.

26. Moody, TW, Beckett, JC. Op. cit. (note 3 above), p.119.

27. Froggatt, P. The early medical school: foundation and first crisis - the'college hospital' affair. *Ulster Med J* 1987; **56 (Suppl.)**: S5-S14.

28. Medical Charities Act, 1851. Previously the Poor Law Guardians and the medical charities authorities had a discretion in assessing the qualifications of applicants (Queen's College Commissioners. Op. cit. (note 20 above), pp.24, App. B. pp.337-8.

29. Ibid, pp.24-5.

30. Moody, TW, Beckett, JC. Op. cit. (note 3 above). pp.232-4, 257-267.

31. Ibid, pp.56-7.

32. Ibid, pp.192, 263-267, App. IIC (p.666).

33. Queen's College Belfast Calendar for 1853-4. Belfast: Alexander Mayne, 1853, pp.xxxiii et seq. These included several 'unchartered' schools in Dublin.

34. Malcolm, AG. Quoted in Allison, RS. Op. cit. (note 5 above), p.87.

35. Moody, TW, Beckett, JC. Op. cit. (note 3 above), p.126.

36. Registers of students enrolled at the Royal exist from 1866 and specify *inter alia* names and home addresses. They are lodged in the office of the Archivist, Royal Victoria Hospital.

37. Queen's College Commissioners. Op. cit. (note 20 above), App.B, pp.339-340. In the 1850s the clinical activity at the Royal was 'much below the required average as to render the withdrawal of recognition ... extremely likely [if] its actual condition was made known to any of the Licensing Bodies'. This was used by the College presidents to support the case for teaching at the 'Workhouse Hospitals in Belfast, Cork and Galway'.

38. Moody, TW, Beckett, JC. Op. Cit. (note 3 above), pp.228-232.

39. Ibid, p.259 et seq.

40. Macafee, CHG. The history of the chair of midwifery and gynaecology in the Queen's University of Belfast. *Ulster Med J* 1975; **44**: 93-115.

41. Butterfield, IK (edit). The Making of a Neurologist: the letters of Foster Kennedy MD. FRS Edin., 1884-1915, to his wife. Hatfield: The Stellar Press, 1981.

42. Dill, JR. The Dill Worthies (2nd edit). Belfast: published privately, 1892, pp.106-7; Moody, JW, Beckett, JC. Op. cit. (note 3 above), pp.215-6.

43. Kennedy, RF. Retrobulbar neuritis as an exact diagnostic sign of certain tumours and abscesses in the frontal lobes. *Am J Med Sci* 1911; **162**: 355-368.

44. Verner, JV, Morrison, AB. Islet cell tumor and a syndrome of refractory watery diarrhea and hypokalemia. *Am J Med* 1958; **25**: 374-380.

45. Froggatt, P. Competing philosophies in the nineteenth century. The'preparatory' medical schools of the Royal Belfast Academical Institution (1835-1849) and the Catholic University of Ireland (1855-1909). In press.

46. Medical Staff Minutes, Belfast Royal Hospital, 5 May 1882.

47. William Whitla to RUI of 10 June 1884 (cited in Allison, RS. Op. cit. (note 5 above), p.92).

48. Clarke, RSJ. Op. cit. (note 6 above), pp.69-72.

49. The Local Government Board of Ireland required that doctors who qualified after 1st May 1906 and who held a post of medical officer in a poor law dispensary district had to be in possession of a certificate of competence in vaccination (LGB (Ire.) Order of 20 December 1905). This survived until the advent of the National Health Service in 1948.

50. Medical Staff Minutes, the Mater Infirmorum Hospital, 18 Jan., 30 Jan., 19 May, 12 Oct., 1899. The approval from RUI is dated 18 Aug., 1899. (These minutes have been collated and bound by Mr Peter Gormley, FRCS, formerly consultant ophthalmologist at the Mater and to whose care and prescience historians of the hospital are forever grateful.)

51. Bishop Henry to Mater medical staff committee of 20 July 1900. (Ibid, 11 July 1900 et seq.).

52. Ibid, 25 Sept, and 13 Oct, 1908.

53. Ibid, 4 June 1915.

54. The subsequent minutes and Annual Reports are uninformative the standard wording being '... it is gratifying to report that a very large number of students are in attendance' (e.g. Annual Report Mater Hospital, 1943-4, p.l2). The numbers are unlikely to have averaged more than 40 by that time.

55. Cited in Allison, RS. Op. cit. (note 5 above), p.94.

56. 'Medical Faculty' Minutes, Queen's College Belfast, 6 January 1902, Sir William Whitla in the Chair (QUB library, Reginalia: Folio 848).

57. QUB Calendar, 1912-13.

58. Craig, DH. Belfast and its Infirmary. The growth of a hospital from 1838-1948. Belfast: Brough, Cox & Dunn, 1962, chap. 12. I am also indebted to Dr John F O'Sullivan for this information.

59. QUB Calendar, 1921-2.

60. Ibid, 1940-41

61. Flexner, A. Medical Education in the United States and Canada. A report to the Carnegie Foundation (Bulletin No. 4). New York: Carnegie Foundation for the Advancement of Teaching, 1910.

62. Flexner, A. Medical Education in Europe. A report to the Carnegie Foundation (Bulletin No. 6). New York: Carnegie Foundation for the Advancement of Teaching, 1912.

63. Royal Commission on University Education in London ('The Haldane Commission'). Command Papers 5911, 6717, 6718. London: HMSO, 1913.

64. Barker, LF. Time and the Physician: the autobiography of Llewellys F Barker, New York: Putnam's Sons, 1942, pp.185-206.

65. Field, J. Medical education in the United States: late nineteenth and twentieth centuries. In: O'Malley, CD (ed.) The History of Medical Education. Los Angeles: University of California Press, 1970, pp.501-530.

66. Froggatt, P. The university academic clinical unit: an opportunity for pharmaceutical medicine? *Pharmaceut med.*, 1988; **3**: 211-217.

67. Wade, OL. The legacy of Richard Burdon Haldane: the university clinical units and their future. *Ulster Med J* 1976; **45**: 146-156.

68. RVH Visiting Staff to Faculty of Medicine of 26 August 1909. Cited in Faculty of Medicine Minutes, 25 Oct. 1909.

69. Faculty of Medicine Minutes, 25 Oct. 1909.

70. QUB Senate Minutes, 1928, p.77 (July 11th).

71. Ibid, p.78.

72. Calwell, HG. The Life and Times of a Voluntary Hospital. The history of the Royal Belfast Hospital for Sick Children 1873 to 1948. Belfast: Brough, Cox & Dunn, 1973, p. 109.

73. RVH Medical Staff Minutes, 24 July 1947. Rodgers was also given access to the OPD, to the Musgrave and Clark Clinics, and was made a member of the visiting staff though junior to existing members.

74. Weaver, JA. John Henry Biggart 1905-1979 - a portrait in respect and affection. *Ulster Med J* 1985; **54**: 1-19.

75. Faculty of Medicine Minutes, 18 February 1948. This defined the professorial 'units' in terms of teaching beds in the Royal and City Hospitals including an agreed 'emphasis' on post-graduate training at the City.