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The Ulster Medical Journal

The Journal of the Ulster Medical Society. First published in 1932.
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The Ulster Medical Society was founded in 1862
by the amalgamation of the Belfast Medical Society (founded 1806)
and the Belfast Clinical and Pathological Society (founded 1853)

THE ULSTER MEDICAL JOURNAL

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2. Manuscripts including references should be typewritten in double spacing, with wide margins and page numbers. They should be fully corrected and alterations in proof may be disallowed or charged to the author. A sample typescript showing layout is available on request from the editorial office. Three copies of each manuscript should be submitted, including tables and figures.

3. The text should indicate the purpose of the paper, and should include an introduction, sections on materials and methods, results, and a discussion relevant to the findings. A brief factual summary should be provided at the beginning of the paper.

4. Scientific measurements should be in SI units *(Units, symbols and abbreviations; a guide for biological and medical editors and authors,* 3rd ed. London: Royal Society of Medicine, 1977). Blood pressure may be expressed in mmHg and haemoglobin concentration as g/dl.

5. Tables must be kept simple and vertical lines should be avoided. Tables and illustrations must be kept to a minimum and data should not be given in both text and tables. Line drawings should be used where possible and symbols must be large enough to be legible when reduced to text size. Where possible, size of illustrations and tables should be planned so that one or more can easily fit the page size of 19·5 x 12·5 cm. Photographs and other illustrations should be unmounted. Authors' names and the top of the figure should be marked in soft pencil on the back.

6. References should be restricted to those really necessary and useful. This journal uses the 'Vancouver' style (see British Medical Journal 1982; **1**: 1766 -70 and Lancet 1979; **1**: 429 - 30). Text references are numerical. Each reference should include:

   i) a list of all authors when six or less (when seven or more only the first three should be listed followed by *et al).*

   ii) the title of the article.

   iii) the title of the journal (abbreviated to the form published by Index Medicus).

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   eg

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The Ulster Medical Journal, Volume 72, No. 2, pp. 67, November 2003.

Ulster Medical Society
Programme 2003 – 2004

President Dr Elizabeth Mayne MD, FRCPath, FRCP (Glas), FRCP (E), FRCPI, FRCP

"REFLECTIONS ON THE CHANGING FACE OF MEDICINE, PAST, PRESENT AND FUTURE"

Thursday 9th October 8.00 pm — North Lecture Theatre MBC QUB — PGEA Approval – 2 hrs Category C
PRESIDENTIAL ADDRESS
"The Gender Trap"
Dr. Elizabeth Mayne, Honorary Consultant Haematologist, Royal Victoria Hospital

Thursday 23rd October 8.00pm — South Lecture Theatre MBC QUB — PGEA Approval – 2 hrs Category C
"The Rise and Rise of Haematology – but Whither Haematologists?"
Professor Sir John Lilleyman, Immediate Past President Royal College of Pathologists

Thursday 6th November 8.00 pm — Ulster Medical Society Rooms — PGEA Approval – 2 hrs Category C
"Masters of Irish Medicine"
Dr. Desmond Canavan, Immediate Past President of the Royal College of Physicians of Ireland

Thursday 20th November 8.00 pm — South Lecture Theatre — PGEA Approval – 2 hrs Category C
ROBERT CAMPBELL ORATION
Joint meeting with the NORTHERN IRELAND MEDICO-LEGAL SOCIETY
"Medicine and the Law"
Rt. Hon. Sir Robert Carswell, Lord Chief justice of Northern Ireland

Thursday 4th December 8.00 pm — Ulster Medical Society Rooms — PGEA Approval – 2 hrs Category B
Joint meeting with the ULSTER OBSTETRICAL AND GYNAECOLOGICAL SOCIETY President: Dr Allan Ritchie
"Thrombosis – From the Foetus to the Grave"
Professor Gordon Lowe, Department of Medicine, Glasgow Royal Infirmary

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Thursday 8th January 8.00 pm — Ulster Medical Society Rooms — PGEA Approval – 2 hrs Category C
Joint meeting with the ULSTER PAEDIATRIC SOCIETY President: Dr Chris Corkey
"Caring for Children – Is it just for Paediatricians?"
Professor David Hall, Professor of Community Paediatrics, Sheffield

Thursday 5th February 8.00 pm — Beechhill Country House Hotel — PGEA Approval – 2 hrs Category B
THE DESMOND WHYTE LECTURE — Londonderry
"From Shadows to Virtual Reality"
Dr. Teddy McIlwrath, Honorary Consultant Radiologist, Royal Victoria Hospital

Friday 13th February 7.15 for 8.00 pm — Great Hall, QUB
Annual Presidential Dinner

Thursday 26th February 8.00 pm — Ulster Medical Society Rooms — PGEA Approval – 2 hrs Category B
"Blood Transfusion with vCJD – Implications for Donors and Patients"
Professor Christopher Ludlam, Professor of Haematology, Edinburgh Royal Infirmary

Thursday 4th March 8.00 pm — Ulster Medical Society Rooms — PGEA Approval – 2 hrs Category B
Joint meeting with the ULSTER NEUROPSYCHIATRIC SOCIETY President: Dr Stanley Hawkins
"Multiple Sclerosis –The Future Looks Bright"
Professor Michael Hutchinson, Consultant Neurologist, St. Vincent's Hospital, Dublin

Thursday 18th March 8.00 pm — Ulster Medical Society Rooms
JUNIOR MEMBERS FORUM

Thursday 13th May 2.00 pm — (Malone Golf Club)
ANNUAL GOLF COMPETITION for the Victoria Challenge Cup

Thursday 20th May 5.00 pm — Ulster Medical Society Rooms
Annual General Meeting

THE ULSTER MEDICAL SOCIETY

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If you are not a member of the Ulster Medical Society, we would appeal to you to give the question of joining your consideration. The Society was formed in 1862 through the amalgamation of the Belfast Medical Society (founded in 1806 and revived in 1822) and the Belfast Clinical and Pathological Society (founded in 1853). Meetings are held in the Society's room in the Whitla Medical Building at fortnightly intervals from the autumn to the spring. There is an opportunity to meet informally after each lecture and enjoy a cup of tea. *The Ulster Medical Journal, the official organ of the Ulster Medical Society, is issued to all Fellows and Members free of charge.*

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Degrees ____________________ Date of Graduation ____________

Proposer (Print) ____________________ Seconder (Print) ____________________

Your proposer and seconder should be Fellows or Members of the Ulster Medical Society. Please contact the Honorary Secretary if you have difficulty in finding a proposer or seconder.

The Ulster Medical Journal, Volume 72, No. 2, pp. 69-72, November 2003.

Editorial

Prevention of hyponatraemia in children receiving fluid therapy

Severe hyponatraemia (serum sodium <130 mmol/1) has become increasingly recognised in recent years as a potential complication of fluid therapy in children,[1] and at least two children in Northern Ireland have died in recent years as a result. Worldwide, death or neurological morbidity related to this condition has recently been reported in more than 50 children.[2] Hyponatraemia has also been reported in as many as 5% of adults undergoing elective surgery[3] and in 25% of children following spinal fusion.[4] It has been suggested that menstruant women and prepubertal children are particularly at risk of brain damage in this situation.[5] Although risk factors include vomiting, pain, anxiety, disturbances of the central nervous system and metabolic and endocrine disorders, it has become recognised that any child receiving intravenous fluids or oral rehydration is potentially at risk. The particular risks associated with the post-operative period were highlighted by Arieff who pointed out that plasma levels of vasopressin (antidiuretic hormone, ADH) are elevated in virtually every child in the post-operative period.[5] If such children are given fluids containing less than 140 mmol/1 of sodium there will always be a tendency towards post-operative hyponatraemia.

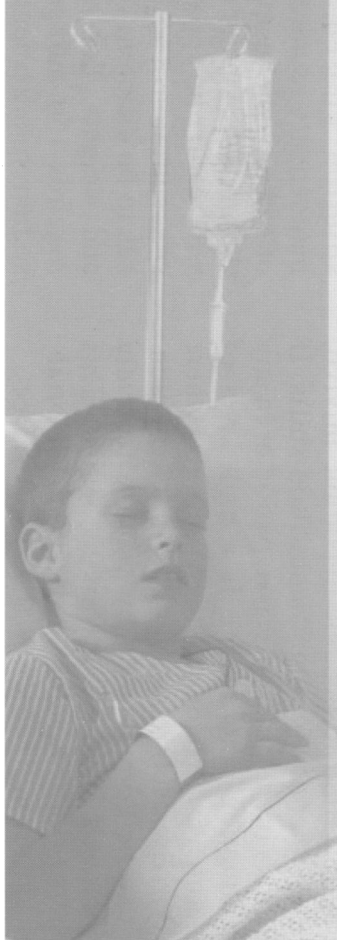
The complex inter-relationships between multiple factors influencing decisions regarding fluid and electrolyte management in children are described in standard texts. These result in difficulty in establishing simple guidelines for fluid administration in children. A solution containing 0.18% sodium chloride in 4% glucose has commonly been used in paediatric practice and is generally held to be isotonic. However, in the catabolic child the glucose is metabolised rapidly causing the fluid to become hypotonic in vivo, with the potential for significant fluid shifts. If the child is in the post-operative period or in any other situation where there is a high level of circulating vasopressin a situation can arise where excess free water is retained within the circulation. This can be compounded by water effectively administered in the intravenous fluids. This condition has been called "dilutional hyponatraemia" because the "free" water component of the serum has increased, causing dilution of the major cation, sodium. This "free" water will pass rapidly and unhindered across cell membranes with the particular risk of development of cerebral oedema. Children may be at particular risk of brain damage due to increase in intracranial pressure in this situation.[2]

GUIDANCE AND ADVICE

A Working Group in Northern Ireland has developed guidelines (figure), which have been published by the Department of Health, Social Services and Public Safety, and can be downloaded from the internet.[6] These guidelines emphasise that every child receiving intravenous fluids requires a thorough baseline assessment, that fluid requirements should be assessed by a doctor competent in determining a child's fluid requirement, and fluid balance be rigorously monitored. They emphasise the value of accurate measurement of body weight and monitoring of serum urea and electrolytes in any child requiring prescribed fluids after 12 hours, together with the importance of assessment of fluid balance and prescription at least every 12 hours by an experienced member of clinical staff. This assessment needs to take account of all oral and intravenous intake, together with the measurement and recording of all losses (including urine, vomiting, diarrhoea, etc.) as accurately as possible.

While general guidance can be given regarding *maintenance* fluid requirements in children of different weights, these must be assessed in the clinical context of each individual child. Requirements for water and electrolytes should be considered separately and an appropriate solution chosen. Although the baseline maintenance requirement for 2 to 3 mmol/kg/day of sodium can be applied to children of all ages, the amount of water needed varies with weight. It will readily be apparent that this means that the concentration of sodium in the maintenance fluid has to be different for children of different ages and weights. For example, an infant of 5 kg requires 150 ml/kg/day of water, so the daily sodium requirement will be provided by a fluid

any CHILD is AT RISK OF RECEIVING PRESCRIBED FLUIDS HYPONATRAEMIA



INTRODUCTION

- **Any child on IV fluids or oral rehydration is potentially at risk of hyponatraemia.**
- Hyponatraemia is potentially extremely serious, a rapid fall in sodium leading to cerebral oedema, seizures and death. Warning signs of hyponatraemia may be non-specific and include nausea, malaise and headache.
- Hyponatraemia most often reflects failure to excrete water. Stress, pain and nausea are all potent stimulators of anti-diuretic hormone (ADH), which inhibits water excretion.
- Complications of hyponatraemia most often occur due to the administration of excess or inappropriate fluid to a sick child, usually intravenously.
- Hyponatraemia may also occur in a child receiving excess or inappropriate oral rehydration fluids.
- Hyponatraemia can occur in a variety of clinical situations, even in a child who is not overtly "sick". Particular risks include:
  - Post-operative patients
  - CNS injuries
  - Bronchiolitis
  - Burns
  - Vomiting

BASELINE ASSESSMENT

Before starting IV fluids, the following must be measured and recorded:

- **Weight:** accurately in kg. [In a bed-bound child use best estimate.] Plot on centile chart or refer to normal range.
- **U&E:** take serum sodium into consideration.

FLUID REQUIREMENTS

Fluid needs should be assessed by a doctor competent in determining a child's fluid requirement. Accurate calculation is essential and includes:

Maintenance Fluid

- 100mls/kg for first 10kg body wt, plus
- 50mls/kg for the next 10kg, plus
- 20mls/kg for each kg thereafter, up to max of 70kg [This provides the total 24 hr calculation; divide by 24 to get the mls/hr].

Replacement Fluid

- Must always be considered and prescribed separately.
- Must reflect fluid loss in both volume and composition (lab analysis of the sodium content of fluid loss may be helpful).

CHOICE OF FLUID

- **Maintenance fluids** must in all instances be dictated by the anticipated sodium and potassium requirements. The glucose requirements, particularly of very young children, must also be met.
- **Replacement fluids** must reflect fluid lost. In most situations this implies a minimum sodium content of 130mmol/l.
- **When resuscitating** a child with clinical signs of shock, if a decision is made to administer a crystalloid, normal (0.9%) saline is an appropriate choice, while awaiting the serum sodium.
- The composition of oral rehydration fluids should also be carefully considered in light of the U&E analysis.

Hyponatraemia may occur in any child receiving any IV fluids or oral rehydration. Vigilance is needed for all children receiving fluids.

MONITOR

- **Clinical state:** including hydrational status. Pain, vomiting and general well-being should be documented.
- **Fluid balance:** must be assessed at least every 12 hours by an experienced member of clinical staff.

  Intake: All oral fluids (including medicines) must be recorded and IV intake reduced by equivalent amount.

  Output: Measure and record all losses (urine, vomiting, diarrhoea, etc.) as accurately as possible.

  If a child still needs prescribed fluids after 12 hours of starting, their requirements should be reassessed by a senior member of medical staff.
- **Biochemistry:** Blood sampling for U&E is essential at least once a day - more often if there are significant fluid losses or if clinical course is not as expected.

  The rate at which sodium falls is as important as the plasma level. A sodium that falls quickly may be accompanied by rapid fluid shifts with major clinical consequences.

  Consider using an indwelling heparinised cannula to facilitate repeat U&Es.

  Do not take samples from the same limb as the IV infusion.

  Capillary samples are adequate if venous sampling is not practical.

  Urine osmolarity/sodium: Very useful in hyponatraemia. Compare to plasma osmolarity and consult a senior Paediatrician or a Chemical Pathologist in interpreting results.

SEEK ADVICE

Advice and clinical input should be obtained from a senior member of medical staff, for example a Consultant Paediatrician, Consultant Anaesthetist or Consultant Chemical Pathologist

- In the event of problems that cannot be resolved locally, help should be sought from Consultant Paediatricians/ Anaesthetists at the PICU, RBHSC.

The Department Of Health, Social Services And Public Safety. Guidance is also available on the Departmental website : www.dhsspsni.gov.uk

containing 15 to 20 mmol/1 of sodium. The standard 0.18% saline solution contains 30 mmol/1 and so will adequately provide for this requirement. On the other hand, a child of 40 kg requires 50ml/kg/day, so a solution containing 3 times as much sodium will be needed to provide adequate maintenance sodium. A solution containing 0.18% saline will thus not provide adequate sodium to maintain the normal plasma level in the older child unless there are clinical reasons to limit sodium intake. This would require instead a solution containing 40 to 60 mmol/1. Half normal saline contains 75 mmol/1 of sodium.

Replacement fluids must reflect fluid loss, and in most situations this will imply a minimum sodium content of 130 mmol/1. This must be considered and prescribed separately, reflecting the fluid loss in both volume and composition. In some situations laboratory analysis of the electrolyte content of the fluid lost may be helpful.

It is important to remember that, while children receiving intravenous fluids are at particular risk, children receiving oral rehydrating fluids may also be at risk as these are invariably hypotonic. Vigilance is therefore required for all children receiving fluids. Medical and nursing staff need to be aware of risks in this situation, and of early signs of developing cerebral oedema such as vomiting, deteriorating level of consciousness or headache before more serious symptoms such as seizures occur, as deterioration to this extent is associated with significant morbidity and mortality.

Particular attention needs to be given to fluid management in specific situations such as diabetic ketoacidosis, renal failure and in the newborn, but attention to detail in assessment and management of intravenous and oral fluids in all children where these are required for medical or surgical reasons is essential to minimise the risks associated with hyponatraemia. It must be clearly recognized that prevention is quite different from treatment of hyponatraemia. All those working with children must be familiar with good practice to *prevent* hyponatraemia but not all will have the necessary expertise in *treating* a child with hyponatraemia which can be extremely complex. If concern is raised regarding clinical deterioration or biochemical abnormality then advice and clinical input should be obtained from a senior member of medical staff, for example a Consultant Paediatrician, Consultant Anaesthetist or Consultant Chemical Pathologist.

We recommend that complications and critical incidents related to intravenous fluids are reported to the Medicines Control Agency (MCA) in the same way as drug side-effects, by using the "yellow card" system. Fluids are included in the British National Formulary and are under the regulatory authority of the MCA. This will permit a nationwide analysis of the problem and also direct information to clinicians. When one of the deaths locally was reported to the MCA the Agency was asked to consider issuing a "hazard warning" about the use of a solution containing 0.18% sodium chloride in 4% glucose in children following surgery. After due consideration the MCA replied that electrolyte imbalance is a risk with the use of all intravenous solutions. The MCA Working Group on Paediatric Medicines advised that there should be no amendments to product information (personal communication).

CONCLUSION

It is important that all doctors caring for children are aware of current literature and advice in relation to the rare but serious condition known as "Dilutional Hyponatraemia". A complex neuro-endocrine response in susceptible children can occur where the "free" water component of intravenous fluids can cause a sudden and unheralded decrease in the serum sodium concentration. Preventative measures to avoid this potentially fatal condition need to be instituted in all units caring for children.[7]

JG Jenkins, B Taylor, M McCarthy

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The Ulster Medical Journal, Volume 72, No. 2, pp. 73-79, November 2003.

A road less travelled by

A review lecture given to the Royal Irish Academy on the occasion of the Award of Merit and Silver Medal by the Consultative Committee for Pharmacology & Toxicology on 22 November 2001

David J King, MD, FRCPsych, FRCP(I), DPM

A ROAD LESS TRAVELLED BY

"Two roads diverged in a wood, and I
took the one less travelled by,
And that has made all the difference."

Robert Frost (1874-1963)

In his book "Genome" Matt Ridley has said *"scientists are not interested in knowledge – only ignorance and mysteries"*. My review will therefore be unlikely to inform but rather to bewilder!

My title is taken from Robert Frost's famous poem and indeed I believe I have explored not one but many rarely frequented avenues of research in neuropsychopharmacology. Looking back over 30 years, however, I think I can discern a pattern of sorts which, I trust, I will be able to persuade you to see as well. The total "journey" is summarised in Table 1.

The story started with an aspect of my MD thesis ("Some aspects of the role of cortisol in relation to affective disorder", 1971) in which I examined a possible link between elevated cortisol (a known finding in depressive illness) and decreases in brain serotonin (5HT). The idea was that raised cortisol levels by inducing a liver enzyme, tryptophan oxygenase, diverted circulating tryptophan down the kynurenine pathway, so reducing the amount of tryptophan available for 5HT synthesis in the brain, thus leading to depression.[1] Since the rate limiting enzyme in 5HT synthesis was tryptophan hydroxylase I first demonstrated that there was a reduced level of this enzyme in the brain of rats which had been injected with cortisol in comparison with those which had not: an effect which was prevented by the co-administration of allopurinol (which inhibits tryptophan oxygenase in the liver). I was further able to show, in a longitudinal study in

TABLE 1

A road less travelled by: Highways and Byways

1969-87	Neuroendocrinology (Transcortin and dexamethasone suppression in depression; cortisol and tryptophan hydroxylase in rat brain).
1975-82	Pharmacovigilance (inter and intra-regional differences in psychotropic drug prescribing).
1979-89	Viruses and mental illness (Serum and CSF viral antibodies in psychiatric patients).
1979-2001	Biological Psychiatry (CSF amines, peripheral adrenergic receptors, neurological soft signs, CT scans, eye movements).
1980-97	Drug trials of new/novel antipsychotics (propranolol, ondansetron, remoxipride, quetiapine, sertindole, zotepine, ziprasidone, M100907).
1982-95	Pharmacokinetics of antipsychotic drugs in patients (haloperidol, remoxipride, zotepine).
1985-2001	Pharmacodynamics of antipsychotic drugs in healthy volunteers (eye movements, "McCollough Effect', EEG, psychomotor function, cognition, auditory and visual latent inhibition, pre-pulse inhibition, heart rate variability).
1993-	*Neuropharmacology (animal studies using latent inhibition, *in vivo* microdialysis, quantitative autoradiography).
2000-	*Functional neuroimaging (SPECT studies of acute tryptophan depletion in patients and healthy volunteers).

** Combined programme: "The role of the pre-frontal serotonin system in cognition".*

The Queen's University of Belfast, Department of Therapeutics and Pharmacology, Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL.

DJ King, Professor of Clinical Psychopharmacology.

which rats were sacrificed every two hours for a twenty four hour period, that this effect could be explained by a phase shift in the activity of tryptophan hydroxylase. This was particularly interesting since the abnormality in cortisol levels reported in mood disorders was an exaggeration of the normal diurnal variation or a phase shift in this circadian rhythm.

At this point I had to leave laboratory research but was eventually very fortunate in being able to combine my interest in biochemistry and pharmacology with clinical psychiatry, by being appointed jointly to the Department of Therapeutics and Pharmacology at Queen's University, Belfast (perhaps the only pharmacology department in the country with its own psychiatrist!) and a local general adult psychiatric hospital (Holywell Hospital, Antrim). Building on the earlier work of Owen Wade and Peter Elmes in that department I took an interest in monitoring the use of psychiatric drugs in the community from GP prescribing data. It was clear, and the cause of some alarm at the time, that this was rising, particularly the use of benzodiazepines and antidepressants. This was in the early 1970s at the peak of our civil unrest, and there were many newspaper headlines suggesting that our increased use of these drugs was an inappropriate response to the troubles and was producing a "tranquillised province". Careful analysis of our data showed, however, that these trends continued long after the worst of our troubles; were similar in England and other Western European countries; and could just as readily be explained by the increase in the availability of new compounds.[2] Indeed the rise in antidepressant prescribing continues and has now exceeded that of benzodiazepines. We now believe much depressive illness was previously being unrecognised and is now more often successfully treated by family practitioners in the community, rather than as a specialist disorder requiring psychiatric in-patient treatment.

Nevertheless, I was primarily concerned with the biological substrates of psychiatric illness and began a series of studies on the neurotransmitter metabolites found in cerebral spinal fluid (CSF) of patients with psychotic disorders. Lumbar puncture studies would now be regarded as unjustifiably invasive but this was the best we could do before the advent of *in vivo* neuroimaging. Together with Dr Stephen Cooper, we were able to show that ECT (Electroconvulsive Therapy) and a standard antipsychotic drug, haloperidol, were both associated with a transient increase of the dopamine metabolite (HVA) in the CSF of schizophrenic patients.[3] ECT, despite its detractors, is still the "gold standard" by which other treatments for severe psychotic depression have to be measured. It is also effective, albeit temporarily, in otherwise treatment-refractory schizophrenia. We had thus demonstrated that ECT was having an antipsychotic action through a similar effect on the dopamine pathways as standard antipsychotic drugs. An interesting sequel to these CSF studies was a follow up carried out on the subsequent course of those schizophrenic patients who had had lumbar punctures eleven years previously.[4] We found that ten of the original thirty patients had subsequently made a suicide attempt and that these had had significantly lower CSF levels of the 5HT metabolite, 5-HIAA, at the time of the original illness. This was consistent with the previous depression literature, but seemed to point to a link with the depressed mood itself rather than impulsivity, since there was no association between low CSF 5-HIAA and more violent suicide attempts or other forms of violent behaviour.

We were driven by two convictions: (1) the need to find an objective, measurable correlate of psychotic illness and (2) that new antipsychotic drugs could be found which would be both more effective and better tolerated than existing treatments.

We did indeed confirm that neurological "soft signs" were present in schizophrenic patients and, in collaboration with John Waddington, correlated the cognitive impairment in these patients with increased lateral ventricular size on CT (Computerised Tomography) scans.[5] We also replicated by objective measurement, an observation which had first been made in 1908,[6] that these patients had abnormal eye movements when carrying out simple "smooth pursuit"[7] or "antisaccade"[8] tasks. We measured both smooth pursuit tracking and saccadic eye movements using a simple electro-oculographic (EOG) system. Saccades are rapid eye movements which occur when visual attention is switched between objects of regard and are the fastest movements of which the body is capable, reaching peak velocities of up to 600°/sec. The speed of these is unchanged in schizophrenia but when the task is to inhibit the tracking and instead to look in an

equal and opposite direction (the antisaccade paradigm), schizophrenic patients make many more errors. We were not, however, able to distinguish between treatment responsive and treatment refractory patients using this method.

Our quest for new and better treatments led us to try new compounds, or new uses of old compounds (propranolol) and also to explore the possibility that pharmacokinetic differences between patients led to their resistance to treatment. The propranolol story demonstrated that its apparent efficacy in schizophrenia was due to a positive or beneficial pharmacokinetic interaction whereby the addition of propanolol, by inhibiting the metabolism of the adjunctive antipsychotic, increased the plasma levels of those drugs.[9, 10] This encouraged us to embark on a somewhat "heroic" study of very high levels of haloperidol in an attempt to improve treatment refractory schizophrenic patients — perhaps this is where the toxicology comes in!. There was, however, a negative result in that, although we achieved somewhat hazardous serum haloperidol levels of up to 100 ng/ml, there was no additional response with levels above 20 ng/ml.[11] This has repeatedly been found with subsequent studies which show that there is no additional response to haloperidol in doses above 20 mg per day.

The other drug studies carried out at Holywell Hospital over this period of time are listed in Table 2. Clozapine, the first "atypical" antipsychotic which had been shown to be effective in otherwise treatment-resistant patients and to have a low incidence of adverse extrapyramidal side-effects, but which also carried a substantial risk of potentially fatal agranulocytosis, was re-introduced in the United Kingdom under limited licence procedures in 1990. We started using it in February of that year and published the first series of 24 patients to be given clozapine in Ireland.[12] 71% of these previously, very disturbed and treatment-resistant patients improved, one third markedly. However, because of the risks with this drug a range of "new atypicals" were being developed and we participated in the early trials of a number of these. An example is the remoxipride study. Remoxipride is a selective D_2 antagonist which was subsequently withdrawn due to aplastic anaemia. Crucial to its development was a multicentre study which we carried out in Northern Ireland, which proved to be the only placebo controlled trial to be done with this drug. We demonstrated that when chronic schizophrenic inpatients were randomised to remoxipride or placebo the relapse rate was significantly reduced in the remoxipride group.[13] This study was deemed to be ethical at the time since the patients had had a minimal response to standard treatment and had shown no signs of relapse during a previous one month placebo "wash out" phase. These studies underline the great change that has come about in the organisation of drug trials within the last twenty-five years. It is even more remarkable to read Heinz Lehmann's account of the first trial with chlorpromazine about fifty years ago as recorded by David Healy in his book on "The Psychopharmacologists" (1996).

"So the next morning, which was a Monday, the first resident I met was Dr Hanrahan and I asked him 'Do you want to start some research with me on a new drug?' and he said 'yes'. So we did it ... We decided we would try it out on about 70 or 75 patients. Nowadays, of course, this would take years but in those days it didn't take very long. We just chose 70, and we did them all, practically simultaneously, within one or two months. Also, I didn't have to ask permission from the Director of the Hospital. I didn't have to get permission from the FDA or the Government. There were no ethical committees at the time, no guidelines, laws or regimentations ...I don't remember – this was in 1953 – whether I even asked the patients. Certainly there was no such thing as informed consent at that time. I might have, but I don't think so. I just ordered it. I might have told the families if they visited ... We started in May and by August we had written the paper ..."

Increasingly, however, I was becoming persuaded that psychotic illness was associated with a localised brain abnormality and that a full understanding of the condition required a proper description both of the psychological function that was disturbed and the location of this abnormality within the brain. This, of course, raises the old Cartesian chestnut but we are beginning to see that a true account of pathophysiology will avoid separating "mind" from "body" by understanding that the integration of all somatic, endocrine and neural functions provides the subjective experience of consciousness.[14] I was also convinced that a proper understanding of the mode of action of antipsychotic drugs would lead to important clues about the nature of the illness itself.

TABLE 2

Antipsychotic Drug Trials
Holywell Hospital 1975-1997

	Novel Compounds
• propranolol	(ß adrenergic antagonist)
• ondansetron	($5HT_3$ antagonist)
• M100907	(selective $5HT_{2A}$ antagonist)
	New atypicals
• remoxipride	(selective D_2 antagonist)
• quetiapine	($5HT_2$ & D_2 antagonist)
• sertindole	($5HT_2$ & D_2 antagonist)
• zotepine	($5HT_2$ & D_2 antagonist)
• ziprasidone	($5HT_{1A}$ agonist, $5HT_2$ & D_2 antagonist)

The great challenge was to understand how it was that antipsychotic drugs could have profound effects on such a fundamental human function as thinking. So I embarked upon a review of the effects of antipsychotic drugs on cognition and found that the literature was in a real mess.[15] It was quite clear there was no general agreement as to what was meant by "cognition" and in particular there was no consistency in the way trials were being carried out. Pharmacologists controlled the pharmacological aspects of their studies but used very simplistic measures of cognition and took no account of neuropsychological subtleties such as practice effects, while on the other hand psychologists had sophisticated measures of cognition but no proper control over or understanding of the importance of controlling for dose and the timing of their tests. It was quite clear also that many of the studies in patients were confounded by these and other variables particularly the severity and nature of the illness itself. There was also an apparent paradox in that those drugs which improved thought disorder in patients generally had adverse effects on cognitive function in normal healthy people.

Thus I embarked on a series of studies of the effects of antipsychotics in healthy volunteers. This was not without its hazards, because, as was well known, healthy volunteers tolerated such drugs poorly. In particular haloperidol caused very unpleasant dysphoria and akathisia.[16] Nevertheless, it was interesting that the dose at which we found these effects emerging was very similar to the "neuroleptic threshold" i.e. the dose at which there were the first signs of parkinsonian adverse effects in patients, i.e. 3.7 mg.[17] Among other things these studies led me to realise that a great deal of "dysphoria" was being dismissed in psychiatric patients as part of their illness rather than an adverse drug effect. We found that healthy volunteers could in fact tolerate most other antipsychotics, including chlorpromazine as well as the newer atypicals, quite well. We started with studies of saccadic eye movements, demonstrating that peak saccadic velocity was a good correlate of the sedative properties of these drugs.[18, 19] We then went on to show that the antisaccade paradigm, which recruited a "cognitive" component, was paradoxically spared any impairment in spite of clear evidence of slowing of the saccadic velocity and of substantial subjective sedation.[20, 21] This "sparing" of cognitive function was very similar to that which had been previously observed by Mirsky and Kornetsky in the 1960s using a simple digit symbol substitution test (DSST).[22] We also confirmed that memory was largely unaffected by single doses of antipsychotics in healthy volunteers.[19, 23] More recently we have attempted to replicate an animal model of the attention deficit seen in schizophrenia, known as "latent inhibition", and have, once again, found that this is relatively unaffected by antipsychotic drugs.[24, 25] Indeed, chlorpromazine actually *improved* selective or focused attention as measured by this task. However a limitation of all these studies was that we could not give the drugs chronically for long enough in healthy volunteers to simulate the situation of therapeutic dosing in patients.

Turning once again to animals we followed up the theme of cognition by first establishing the latent inhibition paradigm. This is supposed to have "construct" validity in that it appears to model a key deficit in schizophrenic thought disturbance, namely the inability to ignore extraneous and largely irrelevant stimuli. This is done by having parallel groups of rats one of which is "pre-exposed" to a flashing light while the other is not. Following this training both groups are exposed to an aversive stimulus which had previously been linked with the "pre-exposed" stimulus. The response to the aversive shock is much less in the "pre-exposed" rat and the difference is "latent" inhibition. We found that both haloperidol and clozapine were effective in this model [26] and also some novel compounds such as antagonists of cholecystokinin,[27] a neuropepitide co-transmitted with dopamine, but

not selective dopamine D_1 antagonists.[28] Since the latter had not been found to be clinically effective either, these results strengthened the relevance of the latent inhibition model.

But in order properly to understand the neuropharmacology of what was happening when the brain was exposed to antipsychotic compounds we decided to look at the effects of these compounds on the neurotransmitter release in the core and shell of the nucleus accumbens using *in vivo* microdialysis. The shell of the nucleus accumbens links with the mesolimbic areas of the brain while the core is closely linked with the nigrostriatal areas. Thus the parkinsonian extrapyramidal adverse effects of antipsychotics are linked with increased dopamine turnover in the core of the nucleus accumbens while we believe that the beneficial effects are associated with a similar increased turnover in the shell. Robert Moran, who set up this technique, was then able to demonstrate a separation between the effects of haloperidol and clozapine (the first "atypical" antipsychotic drug which is virtually devoid of extrapyramidal side effects) on these two areas of the nucleus accumbens.[29, 30]

We have also established another way of looking at receptor pharmacology in rat brain through radioligand binding in membrane homogenates and by quantitative receptor autoradiography, and Marie Cahir is currently looking at the differential effects of typical and atypical antipsychotics on α_1 and α_2 noradrenergic receptor subtypes.[31, 32, 33] In the autoradiography technique, after animals have been treated with different antipsychotics, the brain is removed and sectioned by microtome. The sections are incubated with a radioligand (in this case tritiated prazosin, a selective α_1 adrenoceptor ligand), washed, dried and then apposed to a radioactive sensitive film for up to 6 weeks. The resulting images are examined by a computer linked digital camera system (Computer Assisted Image Analysis), which produces colour-coded pictures revealing the distribution and density of the receptors of interest. Marie has shown that clozapine causes an increase in α_1 receptors in a wide range of cortical regions, which may reflect part of the mechanism of its "atypical" action. Comparisons with other atypical antipsychotics and with chlorpromazine are ongoing. We will now be starting to use this technique to examine the effects of manipulating brain 5HT by tryptophan depletion, on both serotonin, noradrenergic and dopamine receptors in rat brain.

Finally in collaboration with Dr Stephen Cooper, we are currently developing functional neuroimaging with Single Photo Emission Computerised Tomography (SPECT), with the hope of also being able to use Position Emission Tomography (PET) scanning in Belfast in the near future. We have been manipulating central 5HT using acute tryptophan depletion in both healthy volunteers and schizophrenic patients, and, using ^{99m}Tc-HMPAO SPECT, have demonstrated that this procedure causes similar decreases in regional cerebral blood flow (rCBF) in healthy volunteers as have been previously demonstrated in depressed patients, but without the concomitant subjective reaction of depression.[34] Thus a fall of serotonin seems to be a necessary but insufficient explanation for depression.

In schizophrenic patients, however, we found *increases* rather than decreases in rCBF in those same prefrontal areas following acute tryptophan depletion.[35] Since these rCBF changes principally reflect glutamatergic function, these findings are consistent with the theories of a glutamatergic abnormality in this condition.

Furthermore, we have recently gathered evidence that this fall in serotonin following acute tryptophan depletion is associated with *improved* rather than impaired cognitive performance using a "gambling" or decision making paradigm, which is probably associated with increased activity in the orbital frontal cortex or the ventro-medial pre-frontal cortex. This is the area of the brain which when damaged leads to undirected and uninhibited behaviour, as in the classical case of Phineas Gage and many others now referred. It may also be impaired in psychiatric disorders with cognitive dysfunction such as schizophrenia and even, perhaps, in psychopathic personalities. Intriguingly, a recent study has found elevated kynurenate (a metabolite of kynurenine and ultimately of tryptophan) levels in one of these prefrontal areas (Brodman area 9) in schizophrenic brain.[36] Since kynurenate is a glutamate receptor antagonist, tryptophan depletion might improve cognition by reducing the levels of this metabolite.

We are now combining our animal work with these more recent human neuroimaging studies and have set ourselves the task of defining "The role of the pre-frontal serotonin system in cognition", and this programme of research has

been funded as part of a recently successful bid to establish a Recognised Research Group (RRG) in Neuroscience by the R & D Office of the Northern Ireland DHSSPS. We hope to demonstrate using the animal studies exactly what happens following acute tryptophan depletion not only to 5HT but also to other neurotransmitter systems. We trust that this will map on to the changes we see in regional cerebral blood flow in healthy volunteers after tryptophan depletion. We will then be in a position to interpret the changes in regional cerebral blood flow in schizophrenia.

Thus I have come full circle, back to tryptophan, serotonin and psychosis: a road now more travelled by!. It has been a fascinating journey. I do not know what it all means and I am just as puzzled as I was 30 years ago, but I still have the conviction that this is one of the greatest challenges we face in medical science and that further exciting glimpses of the truth about the brain and its most important functions lie ahead.

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Self-administration of epinephrine in children: a survey of current prescription practice and recommendations for improvement

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SUMMARY

The prevalence of peanut allergy is increasing rapidly and many children are now prescribed self-injectable epinephrine as part of their management. We aimed to examine the current extent of self-injectable epinephrine dispensing to children in the Eastern Health and Social Services Board (EHSSB), Northern Ireland, including indications for prescription, investigations performed, information and training provided and actual usage. Dispensing records held by the EHSSB were examined for the period May to August 1998. All general practitioners prescribing 'Epipens' during this period were contacted and asked to identify the patient and provide contact details. Information was gathered using postal questionnaires sent to General Practitioners and parents. A total of 104 'Epipen' prescriptions were dispensed. Thirty-seven (36%) general practitioners responded to the initial questionnaire; of these 36 (35%) were suitable for analysis. Thirty-four parents were then contacted; 28 (82%) returned questionnaires were reviewed. The commonest indication for 'Epipen' prescription was peanut allergy (32 of 36 (89%) general practitioner responses; 25 of 28 (89%) parent responses). Twenty-six (72%) children had been seen by a specialist; all except one had either blood or skin tests. Six of the remaining eight children had no investigations. General practitioners reported 14 (39%) parents to have basic life support training, compared with six (21%) parents. Eighteen (64%) parents had been given written information regarding their child's allergy, nine (32%) had been referred to a dietician and seven (25%) children wore a medical warning bracelet. The Epipen had been used by three children; all three had multiple food allergies. This study has identified a great variability in the management of children with allergy including the need for specialist referral, further investigation, written allergy advice, referral to a dietician and formalised training in basic life support and administration of epinephrine. It suggests a lack of consensus amongst health care professionals as to the best practice in the management of potentially life threatening food allergy and indicates, at least, a need for better multidisciplinary communication.

INTRODUCTION

Food allergy is common in childhood, with a prevalence between 0.3% and 8% [1] and the suggestion that the incidence is increasing.[2] In particular, over the last 10 years the prevalence of peanut allergy has doubled, and it now affects approximately 1% of British preschool children.[3] Once a child develops nut allergy it is usually lifelong,[4] although recent reports have challenged this idea.[5] In the majority of cases, the diagnosis has far reaching implications for the child, their family and carers.

To date there is no consensus on the best management for a child presenting with a history suggestive of peanut allergy.[6] Guidelines produced by the Royal College of Physicians of

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London and the Royal College of Pathologists UK [7] have recommended that Paediatricians should always be involved in the care of children with allergic disease. In individual cases there may be further consultation with or referral to an adult allergy specialist. In peanut allergy, children presenting with a clear-cut history of an acute reaction following the ingestion of peanuts may need no additional tests to confirm the diagnosis,[8] but specialist referral is still important for education of the family and child. Children with a less conclusive history require further investigations.[9] Skin-prick testing and allergen specific IgE are useful additional tests,[10] but not diagnostically efficient in all cases. Therefore, a careful clinical history with judicious use and interpretation of these tests is required. In some cases it is necessary to proceed to open or double blind placebo controlled food challenge in order either to confirm or to exclude food allergy. Such investigations should only be undertaken by experienced personnel.

This study examined some aspects of the current management of allergy among children by a questionnaire survey of their general practitioners (GPs) and parents. We surveyed GPs in the Eastern Health and Social Services Board which commissions care services for approximately 680,000 people. In particular we looked at the extent of epinephrine prescription for home use, in the form of the 'Epipen Autoinjector'. The indications for prescribing the 'Epipen', information and training given to parents and follow-up data on actual usage were obtained.

METHODS

Eastern Health and Social Services Board dispensing records for a 4 month period from May 1998 to August 1998 were examined and GPs prescribing the 'Epipen' were identified. Prior to this date no computer code was available for 'Epipens', hence GPs could not be identified. These GPs were contacted by letter on two occasions and asked to identify the child receiving the 'Epipen', complete a short questionnaire on circumstances surrounding the prescription and either forward the parent questionnaire to the family or give permission for the parents to be approached and return contact information. Two GPs did not consent to their patient being approached and one parent did not wish to be sent a questionnaire.

- **General Practitioner Questionnaires**

GPs were questioned on the indication for the 'Epipen' prescription, either peanut or other specified allergies, who prescribed the 'Epipen' and how many were prescribed for each child. They were also asked to provide information on investigations performed (full blood count (FBC) and differential white cell count (DWCC), total IgE, RAST Specific IgE, skin prick testing and/or oral food challenge) and by whom, and what information was given to parents after the prescription of the Epipen (recognition of allergic reactions, when and how to use the 'Epipen', and basic life support (BLS)). Details of usage of the 'Epipen' were also requested. Finally, GPs were asked to record their perceptions on 'Epipen' prescription and allergies.

If contact information and consent to approach the parents was provided, they were contacted in writing and asked to complete and return a short questionnaire.

- **Parent Questionnaires**

Information obtained from parents included their perception of why the 'Epipen' was prescribed, who prescribed it, investigations undertaken, information and training given in the recognition of allergic reactions, when and how to use the 'Epipen' and BLS. Objective data included the number of 'Epipens' held by each child, where they were kept and use to date. Information on referral to dietician, contact with school, provision of written information and use of Medical Warning Bracelet was obtained.

RESULTS

A total of 104 'Epipen' prescriptions were dispensed by 104 GPs during the four months of the study. All GPs were contacted and a total of 37 (36%) responded to the questionnaire. Names and addresses of two children were not supplied and one parent did not consent, leaving 36 (35%) GP responses for analysis. Thirty-four parents were sent questionnaires, two were returned as wrong addresses, one had to be discarded as not applicable, and three were not returned by parents, leaving a total of 28 parent questionnaires. The age range of children involved in this study was two to $16^{1}/_{2}$ years, median age eight years (information available in 30 cases). There were 19 boys and 15 girls (information available in 34 cases). The commonest indication for 'Epipen' prescription from GP questionnaires was peanut allergy (32/36, 89%) either singly (25, 70%) or

with other allergies (7, 19%). Allergies other than peanut (egg protein allergy, anaphylaxis to rabbit fur and a reaction to antibiotics in a child with cystic fibrosis) accounted for three (8%), with no information returned in the final case. The commonest indication for 'Epipen' prescription from parent responses was peanut allergy (25/28, 89%) either singly (20, 71%) or with other allergies (five 8%). Allergies other than peanut (egg protein, rabbit fur and antibiotic reaction) accounted for the remaining three (11%).

In 23 children, where the GP stated that the indication for the 'Epipen' prescription was for peanut allergy alone, parents reported peanut plus other nut allergies.

General practitioners reported that 11 (31%) 'Epipens' were prescribed by a consultant paediatrician, eight (22%) by an unspecified hospital consultant eight (22%) by the GP, seven (19%) by a consultant immunologist and two (6%) by an unknown source.

General practitioners reported that a total of 26 (72%) children had at least one investigation performed, more commonly in children referred to a secondary specialist. Nine children (82%) prescribed an 'Epipen' by a consultant paediatrician, six (86%) prescribed by a consultant immunologist and seven (88%) prescribed by an undefined hospital consultant had at least one investigation performed, compared to three children (38%) prescribed an 'Epipen' by their GP. Six children (17%) had no investigations performed; five had 'Epipens' prescribed by their GP. Investigations performed were not documented in three cases. The commonest test ordered was allergen specific IgE (n=24/26 (92%) of children who had investigations performed) and five children were reported to have had oral food challenge. General Practitioners reported that 29 (81%) parents had received training in recognition of allergic reactions, 28 (78%) on when to use the 'Epipen' and 27 (75%) on how to use the 'Epipen'. Fourteen (39%) parents were

TABLE

General practitioner and parent responses and percentage concordance of responses

Question asked	*GP response*	*Parent response*	*% Concordance*
Number of respondants	36	28	28
Indication for prescription			82%
Peanut alone	25(69%)	20(71%)	
Peanut & other	7(19%)	5(18%)	
Other	3(8%)	3(11%)	
Prescriber			50%
Consultant paediatrician	11(31%)	5(18%)	
Hospital consultant	8(22%)	2(7%)	
General practitioner	8(22%)	17(61%)	
Consultant immunologist	7(19%)	4(14%)	
Unknown	2(6%)	0	
Investigations performed			89%
Yes	26 (72%)	22(79%)	
No	6 (17%)	6(21%)	
Unknown	4 (11%)	0	
Training received			
Recognition	29(81%)	20(71%)	57%
When	28(78%)	23(82%)	57%
How	27(75%)	23(82%)	54%
BILS	14 (39%)	6 (21%)	36%
Usage	3(8%)	3(11%)	100%

reported to have been taught BLS. Most parents reported receiving information on the recognition of allergic reactions (n=20/28, 71%), when to the use the 'Epipen' (n=23/28, 82%) and how to use the 'Epipen' (n=23, 82%). Six parents (21%) said they had been trained in BLS.

In only two cases (of 28 where information was available) was there agreement between GP and parental responses on information and training (Table). The number of 'Epipens' owned by each child ranged from one to eight. Modal number was four. Pens were kept at home, in school and with grandparents. Eighteen (64%) parents said they have received written information about allergies, nine (32%) children had been referred to a dietician and seven (25%) wore a Medical Warning Bracelet. Twenty-two (85%) schools had been informed that the child used an 'Epipen'. Three (11% of 28) children prescribed an 'Epipen' had used it. These children all reported multiple allergies including peanut allergy, and all had been admitted to hospital on at least one occasion following the use of the 'Epipen'. General Practitioners were asked to record their perceptions on 'Epipen' prescription and allergies. Thirty (83% of those responding) GPs felt that the prescription was appropriate. In the cases where the 'Epipen' was known to be prescribed following hospital assessment, 21/26 (81%) felt that they had received adequate information from the hospital following the prescription of the 'Epipen'. Overall, four (11%) felt that there was over-prescription of 'Epipens' to children.

DISCUSSION

Food allergy is common in childhood with a current prevalence between 0.3% and 8%.[1] Increased public and parental awareness, with high profile media coverage of the potential life threatening complications make it likely that the demand for home treatment of anaphylaxis will continue to increase. This study not only highlights differing perceptions of parents and general practitioners as to why an 'Epipen' was prescribed, but also a variation in practice. This suggests poor communication between parents and the medical professionals. We appreciate that our study involves small numbers but feel that important lessons can be learnt from our results if misinformation and inappropriate management are to be avoided.

Once a child develops nut allergy it is usually lifelong, although recent reports have challenged this idea.[5] Unnecessary dietary restrictions and lifestyle adaptations can be minimized by accurate diagnosis. The prescription of epinephrine for home use has resource implications with each 'Epipen' costing just under £30, and ideally each child should have a minimum of four prescribed at the time of diagnosis. The shelf life is often well under a year, thus making frequent renewal an added consideration.

A clear history of an allergic reaction immediately following ingestion of peanuts should be adequate to make a definitive diagnosis of peanut allergy, but assessment by a specialist is recommended prior to the prescription of epinephrine for home use.[7] In this study we found that one in three children were not seen by a hospital consultant. This may be acceptable if the GP involved has extensive experience in the management of allergy, but may indicate a lack of awareness of the need for referral. For children in whom the history is less certain, investigations are indicated. Both allergen specific IgE and skin prick testing have historically been limited by false positive and negative results but recent reports document the use of food specific IgE concentrations to diagnose symptomatic food allergy with 95% certainty.[13] The gold standard test for children presenting with a suspected food allergy is double blind placebo controlled food challenge.[14, 15] This test is not without risk and must only be performed by experienced staff in a centre with full resuscitation procedures. In this study GPs reported that 6 (17%) children had no investigations performed and of these 5 were not referred for assessment by a hospital consultant. The commonest test performed was allergen specific IgE (n=24 of 26 (92%) that were known to have investigations performed).

Not all reactions to peanuts are life-threatening, and oral antihistamines are adequate treatment for such reactions. However, epinephrine is the treatment of choice for life threatening anaphylaxis, but must be given at the first sign of a reaction.[6, 16] Intramuscular injection is the preferred route of administration as it provides rapid peak concentrations in most children.[17] Deficiencies in the actual carriage of prescribed epinephrine and its successful usage have been identified.[18] In a study of 101 families previously prescribed epinephrine for food allergy only one third of patients/parents knew how to administer their epinephrine correctly.[19] When epinephrine is indicated, it must be available at all times and

parents and all carers must be trained in the appropriate timing and safe use of the Epipen. Complications have been described following its use,[11, 12] albeit in the adult population. Despite this study having small numbers, a relatively high proportion (3/28 or 11%) reported using the Epipen. All three reported receiving instruction on the use of the Epipen but none on BLS. Again discrepancies were found between GP and parent responses.

Epinephrine administration is only one aspect of the management of food allergy. Indeed, the ready access to an Epipen may provide false reassurance and decrease vigilance in preventing exposure. Our study suggests that professionals fail to emphasize other aspects of management. Dietary avoidance is a key aspect of peanut allergy management and referral to a dietician should be made as peanuts and other nuts are frequent hidden ingredients in many foodstuffs. Medical Warning Bracelets allow easy identification of the medical condition and allow appropriate treatment to be given early. Comprehensive advice in drawing up a training package for an individual patient and carers is available and should be adhered to[20] and communicated to parents and carers.

On the basis of our study results we would recommend the following:

All children, suspected to have food allergy, should be referred for specialist assessment either by a suitably experienced paediatrician or Immunologist. Testing, when indicated, should involve the most appropriate and informative investigation. Review should be arranged to monitor effectiveness of avoidance, adequacy of treatment and continued sensitization.

If the diagnosis is confirmed, a multidisciplinary team approach should be adopted, and include

- Paediatrician +/- Immunologist
- Dietician
- General practitioner
- School Health Team

The child, their family and other carers should be instructed in the recognition and treatment of allergic reactions including training in basic life support. Regular review of 'Epipen' and BLS technique is advisable.

Written information on peanut allergy, individualized for each child, must be given to parent and other carers, including schools if of school age.

Dietary advice on avoidance of nuts or other relevant food allergens.

A minimum of 4 'Epipens' in the household: two for home and two for school.

Each child must wear a Medical Warning Bracelet (Medic Alert, SOS) for easy identification of their medical condition.

CONCLUSION

This study has identified a lack of consensus in the management of anaphylaxis, including specialist referral, investigations, written allergy advice, referral to a dietician and formalised training in administration of epinephrine and basic life support. We recommend the development and dissemination of clear guidelines, improved communication between health professional and carers and continued evaluation of outcomes.

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Impact of serum troponin measurement on triage of chest pain in a district hospital

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SUMMARY

Aim: To evaluate the impact on the clinical service of incorporating cardiac troponin T (cTnT) measurement into the existing chest pain care pathway in our district general hospital.
Methods: We randomised 200 consecutive patients admitted with acute chest pain, but without ST elevation on ECG, either to our existing chest pain care pathway (pathway 1) or to a new pathway incorporating semi-quantitative cTnT measurement (pathway 2).
Results: In comparison with pathway 1, in pathway 2 there was a strong trend towards reduced length of stay (3.13 v 4.36 days, p=0.08), and reduced usage of low molecular weight heparin (LMWH) (4.59 v 5.45 doses per patient, p=0.05). The number of cardiac events at three months in care pathway 1 (14/92) and care pathway 2 (22/108) did not significantly differ, p=0.34. In patients with atypical chest pain, there was a tendency for cardiologists to discharge earlier (1.75 v 2.03 days, p=0.07) and use less LMWH (2.04 v 2.97 doses, p=0.06) than general physicians.
Conclusion: In this study, incorporation of cTnT measurement into a chest pain care pathway resulted in a strong trend towards reduced length of hospital stay and LMWH usage.

INTRODUCTION

Chest pain is one of the commonest presentations to the accident and emergency department. The traditional risk factors obtained from the clinical history and abnormalities on the electrocardiogram (ECG) discriminate poorly between cardiac and non-cardiac pain, resulting in some 4-8% of patients with an acute myocardial infarction being discharged.[1] This may be catastrophic for the individual, and it accounts for 25% of litigation against emergency departments in the US.[2] For this reason, a large proportion of patients presenting with chest pain are admitted, although fewer than half of these have an acute coronary syndrome.[3] As chest pain accounts for 20-30% of acute medical admissions,[3] patients at low-risk of a cardiac event constitute about 10% of all hospital admissions.

Measurement of cardiac troponins may aid risk stratification and triage of this large group of patients. Several studies have shown that elevated troponin levels are associated with increased risk of subsequent cardiac events.[4-7] However most of these studies have been carried out in high-risk populations in clinical trials, or in cardiology units. The true value of a troponin assay in the assessment of unselected patients in a district general hospital is less certain.

In our hospital, as in many district general hospitals, initial management of chest pain has been performed by general physicians, with higher risk patients subsequently being referred to a cardiologist. In order to standardise care, a care pathway for patients admitted with chest pain without ST-elevation on the ECG was in operation. Patients were risk stratified on the

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basis of history, conventional risk factors for coronary disease and presence of ischaemic changes on the ECG. In an effort to improve the efficiency of the service, we devised a new care pathway incorporating serum cardiac troponin T (cTnT) measurement into the risk assessment algorithm. The care pathways represented alternative accepted management strategies for acute chest pain. The purpose of this study was to compare the clinical effectiveness of the pathways in an unselected population presenting to a district hospital. Specifically we sought to address the question of whether inclusion of cTnT in the risk stratification algorithm would influence length of hospital stay or use of low molecular weight heparin (LMWH).

SUBJECTS AND METHODS

Patient selection

The study population consisted of 200 consecutive patients admitted with chest pain to the Mater Hospital between May 22nd and October 12th 2000.The study was designed to be as inclusive as possible; however, patients with a history of myocardial infarction (MI) in the previous two weeks, ST elevation on the admission ECG, pleuritic chest pain, co-morbidity reducing life expectancy (e.g. advanced malignancy) and those unable to give an adequate history were excluded.

Study protocol

This was a prospective, randomised open comparison of two care pathways. Patients were randomised to Pathway 1 or Pathway 2 according to their accident and emergency number: odd numbers were allocated to pathway 1 and even numbers to pathway 2. Page 1 of both care pathways was filled in by the admitting doctor. It directed them to record clinical data, to take appropriate blood tests, and to assess the need for cardiac monitoring. In Pathway 2 they were directed to take two samples for point-of-care serum cTnT measurement: the first at least six hours after the onset of the most severe chest pain, and the second at 12 hours. If the patient presented more than 12 hours after the onset of pain, or if the first sample was positive, a single sample sufficed.

The first senior doctor assessing the patient made the clinical risk assessment. This may have been the registrar on the weekday evening ward-round, or the consultant on the ward round on the following morning. In Pathway 1, the assessment was made according to the character of the chest pain, presence of risk factors for ischaemic heart disease (IHD), and ECG characteristics. In Pathway 2, the assessment was based on character of chest pain, ECG characteristics, and serum cTnT levels. Those deemed to be at low risk were discharged early for outpatient exercise stress testing (EST) if appropriate, whereas those deemed to be at higher risk were kept as inpatients for intensive anti-anginal treatment and EST (see Fig. 1).

Risk factors for IHD were defined as: hypercholesterolaemia: total serum cholesterol >5.2mmol/1 or on statin therapy; hypertension: units mmHg on three occasions or on anti-hypertensive therapy; and diabetes mellitus: fasting blood sugar >7.0mmol/1 or on diabetic diet or medication. The patients were designated as current, ex- or non-smokers, according to their response at the time of admission. Family history of IHD was also obtained from the patient at the time of admission.

Data relating to in-patient episodes were obtained from the clinical notes. Follow-up data was obtained by a research nurse using a standard questionnaire administered by telephone three months post-discharge, and from the patient's GP or hospital records where necessary. Primary end-points were the number of doses of LMWH used and the length of hospital stay. Cardiac events during the follow-up period were a secondary end-point and included death from IHD, readmission with MI or unstable angina, and need for revascularisation. In order to compare our results with previous studies, MI was defined as the combination of typical chest pain with elevation in creatine kinase greater than twice the upper limit of normal, with or without dynamic ECG changes. Unstable angina was defined as a typical history compatible with type IIIB of the Braunwald classification.[8]

Analytical techniques

A semi-quantitative measurement of troponin T was made using the Cardiac Reader (Roche Diagnostics). 150μl of heparinised whole blood was applied to the reader, and a result was available after 12 minutes. A numerical value for cTnT was obtained in the range 0.1-2.0μg/l. Elevations of cTnT either less than 0.1μg/l or greater than 2.0μg/l gave readings LOW or HIGH respectively. If cTnT was not detected, a negative reading was obtained. Although the manufacturers

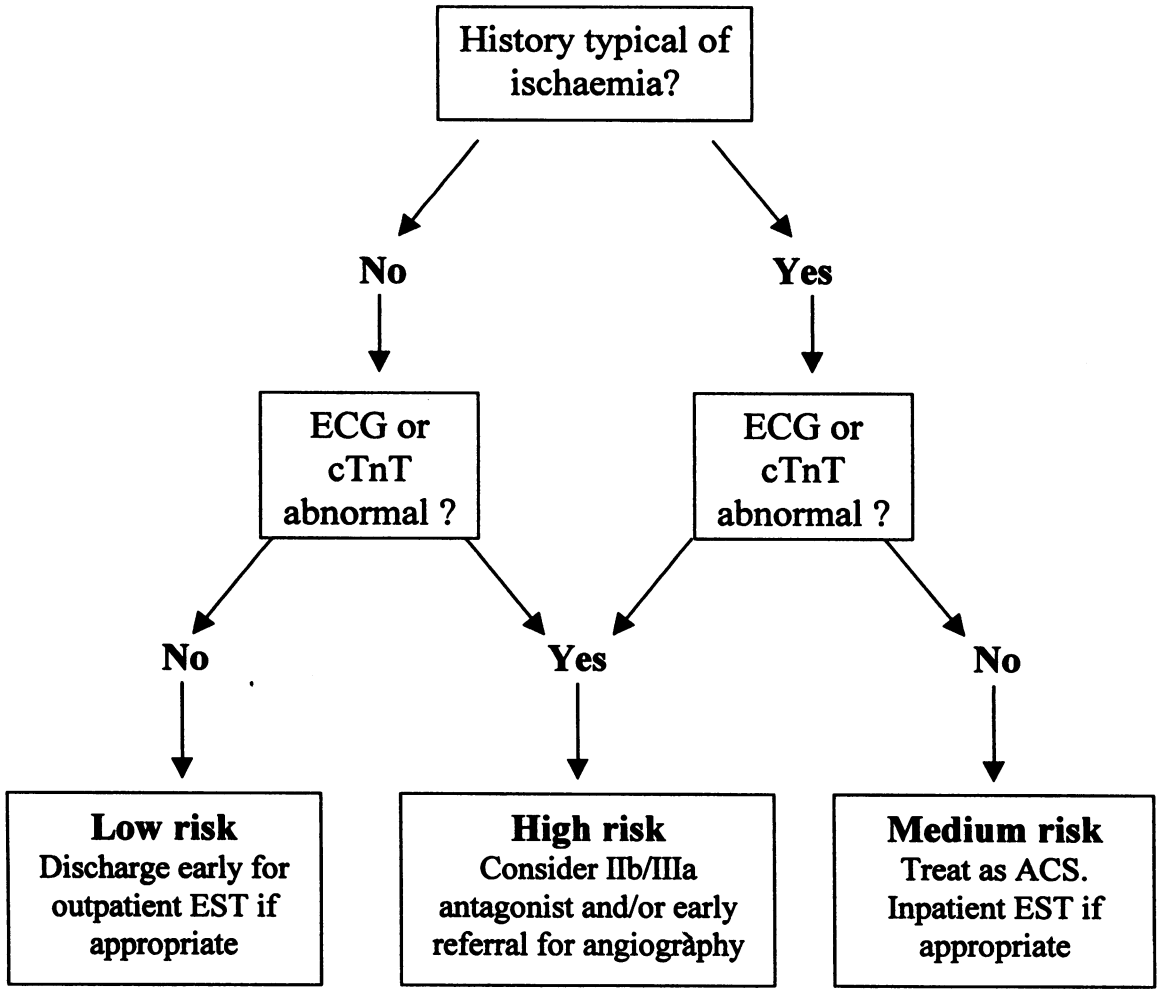

Fig 1. Algorithm for the management of chest pain in Care Pathway 2. (EST – Exercise Stress Test)

cut-off value for a positive result was >0.1μg/l, for this study we designated the test as being positive if any troponin T was detected. This is in light of studies showing that troponin T levels in the range 0.06-0.1μg/l are associated with increased risk of cardiac events,[5] and is consistent with a recent paper that recommended a reduction in the cut-off value to 0.05μg/l.[9] Quality control was assured by testing one kit in each batch of 10 against standards. All house officers were trained to perform the analysis. There are several cardiac Troponin I assays, each with their individual characteristics, available on the market but only one cTnT assay is available. The cTnT assay was chosen so that the current results could be more easily compared with those from previous trials.

Statistical analysis

All results for continuous variables are expressed as means. The student's t-test and the Mann-Whitney test were used to compare continuous variables between groups when the distributions were normal and non-parametric respectively. The χ^2-test with the appropriate number of degrees of freedom was used to compare categorical variables. Analyses were performed on SPSS (version 10.1) software package. Recruitment of 200 patients was sufficient to have 80% power to detect a difference of 1.5 days in length of stay between the groups at the 5% level of significance.

RESULTS

Of the 200 patients enrolled, 92 (46%) were randomised to pathway 1, and 108 (54%) to pathway 2. Baseline characteristics were similar in both groups (Table).

14 patients (7.0%) were diagnosed with myocardial infarction based on elevation of cardiac enzymes within the first 24 hours of admission. Unstable angina was diagnosed in 97 patients (48.5%), and the remaining 89 patients (44.5%) were considered to have non-cardiac chest pain.

TABLE

Patient characteristics at baseline

Characteristic	*All Patients number %*	*Care pathway 1 number %*	*Care pathway 2 number %*	*p-value*
Mean Age (years)	62.3	63.4	61.4	0.28
Male	106(53)	46(50)	60(56)	0.43
Smoking Status				
Current	54(27)	24(26)	30(28)	0.57
Ex-smoker	21(11)	14(15)	7(6)	
Hypertension	78(39)	39(42)	39(36)	0.36
Diabetes mellitus	23(12)	13(14)	10(9)	0.28
Hypercholesterolaemia	118(59)	53(58)	65(60)	0.71
Family history IHD	144(72)	67(73)	77(71)	0.75
Mean no. of risk factors	2.45	2.55	2.36	0.22
Personal history IHD	101(51)	49(53)	52(48)	0.47

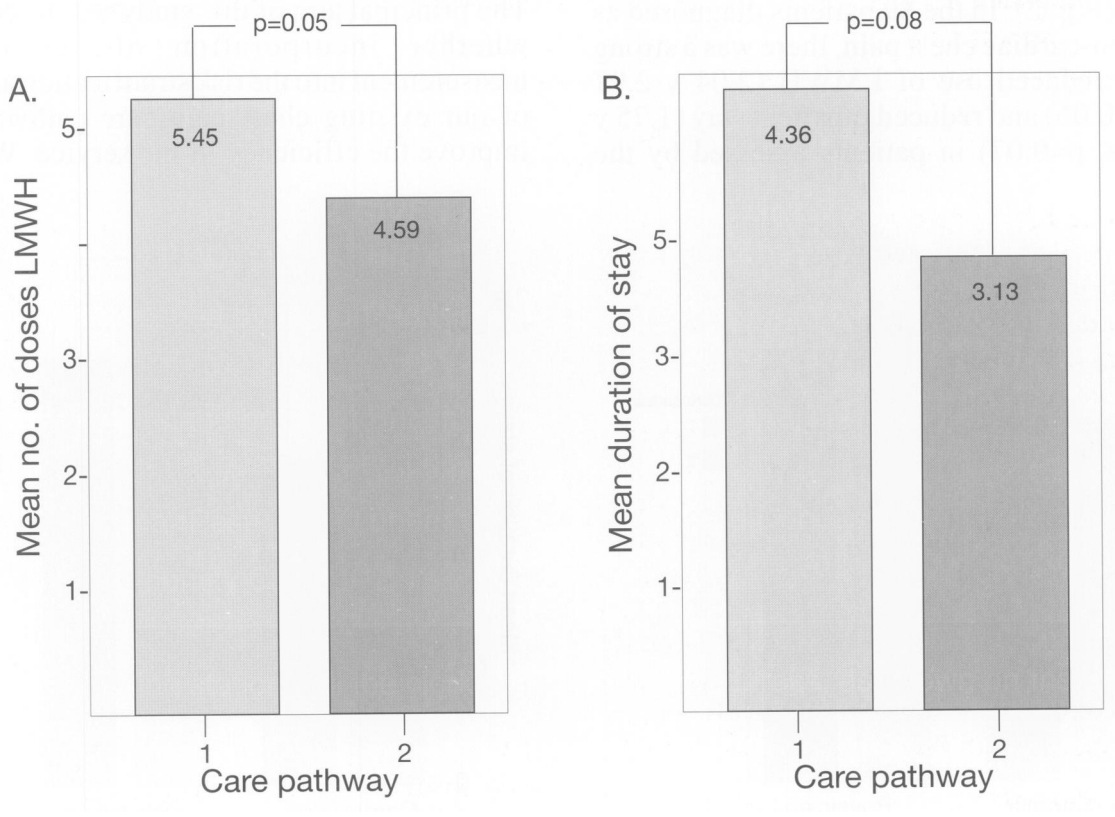

Fig 2. Mean number of doses of Low Molecular Weight Heparin (A) and duration of hospital stay (B) in care pathway 1 compared to care pathway 2.

Troponin T measurements

Of the 108 patients allocated to pathway 2, 106 had serum cTnT testing completed as per protocol. cTnT was positive in 15 (14%), including all five patients with myocardial infarction, and 10 of 48 (21%) with unstable angina. Each patient with an elevated cTnT was subsequently diagnosed as having either a myocardial infarction or unstable angina. Hence, although the sensitivity of cTnT for acute coronary syndromes was low at 28%, it was highly specific (100%).

Three patients who had normal cTnT on initial sampling subsequently developed elevated cTnT on repeat sampling. Of the 15 patients with elevated cTnT levels, five had no rise in creatine kinase, four had no dynamic ECG changes, and a further four had neither a rise in enzymes nor ECG changes, and hence would not have been identified as being at high risk by traditional markers.

Comparison of care pathways and teams

In comparison with pathway 1, in pathway 2 there was a strong trend for a reduction in use of LMWH (p=0.05) and in mean length of stay (p=0.08) (Fig. 2). In the 89 patients diagnosed as having non-cardiac chest pain, there was a strong trend for reduced use of LMWH (2.04 v 2.97 doses, p=0.06) and reduced inpatient stay (1.75 v 2.03 days, p=0.07) in patients assessed by the cardiology team compared with those assessed by general physicians. This trend in the triage of non-cardiac chest pain was particularly evident when cTnT measurements were employed (see Fig. 3).

Follow-up

Cardiac events occurred in 36 patients (18%) in the 3-month follow-up period. 22 of the 106 (21%) patients who had cTnT tested had a cardiac event, including 5 of 15 patients (33%) who were cTnT positive and 17 of 91 (19%) of those testing negative. The excess rate of events in patients testing positive for cTnT failed to reach significance (p=0. 19). The positive and negative predictive values of an elevated cTnT for a cardiac event occurring within 3 months were 33% and 81% respectively.

In the 3-month follow-up, 14 of 92 patients (15%) on pathway 1 had an event, compared with 22 of 108 (20%) patients on pathway 2. There was no significant difference in the frequency of events between the two pathways (p=0.34).

DISCUSSION

The principal aim of this study was to determine whether incorporation of serum cTnT measurement into the risk stratification algorithm of our existing chest pain care pathway could improve the efficiency of the service. We found

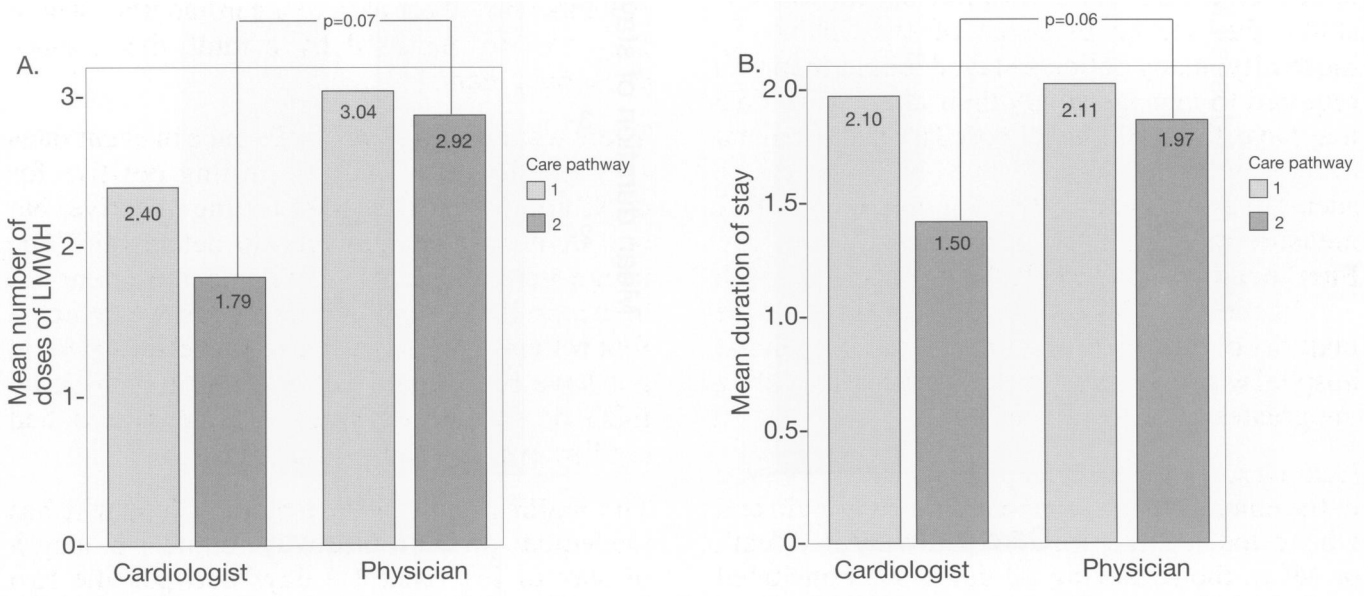

Fig 3. Mean number of doses of Low Molecular Weight Heparin (A) and duration of hospital stay (B) in patients with non-cardiac chest pain assessed by a cardiologist (n=24) compared to those assessed by a physician (n=65). There was a trend towards a greater reduction in these parameters when assessment was made by a cardiologist using pathway 2.

that there was a strong trend, which just failed to reach statistical significance, towards reduced length of hospital stay and usage of LMWH when cTnT measurement was employed.

This has major resource implications for a busy district general hospital. Assuming the pattern of admissions throughout the year was similar to that seen in the current study, over 500 patients with chest pain would be admitted to our hospital. As patients randomised to Care Pathway 2 spent on average 1.23 less nights in hospital, over 600 bed nights would be made available for other patients.

Most previous studies of serum troponin measurements in the assessment of chest pain have been carried out in high risk populations[5-7] or in cardiology units.[10,11] Our study had minimal exclusion criteria and therefore more accurately reflects the characteristics of patients admitted to a district general hospital with chest pain. Elderly patients were included (age range 28-94 years), as were those with significant co-morbidity (other than dementia and advanced malignancy). The difference between our study population and those of previous trials which required dynamic ECG changes for inclusion, is illustrated by a cardiac event rate of 18% at 3-month follow-up in our study, compared with 72% and 52% event rates at 30 days in the GUSTO-IIa and TRIM studies.[6,7] The impact of cTnT measurement in these high risk populations cannot be extrapolated directly to the district general hospital setting. In our study, due to the presence of significant co-morbidity, many patients stayed longer than was required to manage solely their chest pain. This may have diluted the benefit of cTnT measurement in improving efficiency, but would give a more accurate assessment of the true impact of cTnT measurement in a district general hospital. Furthermore, by excluding patients with nondiagnostic ECG's, these studies excluded the majority of patients presenting to a district general hospital with chest pain, including those providing the greatest diagnostic challenge.

Hamm found that 1.1% of patients who presented to the emergency department with chest pain and who tested negative for cTnT had a cardiac death or MI in the following 30 days.[4] He concluded that a negative result could therefore allow rapid and safe discharge of patients from the emergency department. Our study raises some doubts as to the validity of this approach. Firstly, three patients, including one patient with evolving infarction, who tested negative for cTnT greater than six hours after the onset of most severe chest pain subsequently tested positive on repeat sampling at 12 hours. This reflects the delay in release of cTnT from damaged myocardial cells, and is in keeping with other studies.[7] Secondly, a negative cTnT does not rule out the presence of an acute coronary syndrome or the occurrence of subsequent cardiac events. Only 21% of patients diagnosed with unstable angina in our study had raised cTnT levels, a proportion similar to that seen in other studies.[4,6,10] 19% of patients testing negative for cTnT had an event by three months, including one cardiac death in a patient who also had a negative EST pre-discharge. Furthermore, in Hamm's study, all patients diagnosed with unstable angina were admitted and treated with LMWH, including those testing negative for cTnT. The event rate may have been greater if these patients had been discharged directly from the emergency room.

Our study showed that members of the cardiology team tended to be more efficient than general physicians in managing patients with non-cardiac chest pain, particularly when cTnT measurements were employed (see Fig. 3). The addition of cTnT measurement to the decision-making process had little impact in reducing the LMWH usage or the length of stay for patients with non-cardiac chest pain assessed by a general physician. This provides a strong argument for admitting all patients with chest pain to a cardiac unit, where they can be managed by a multi-disciplinary chest pain team.

There was no significant difference in event rates at 3 months in the patients testing positive for cTnT compared with those testing negative, but our study was not powered to detect this. The prognostic value of cTnT measurement is, however, illustrated by the fact that we detected four patients with elevated cTnT levels who would not have been identified as being high risk by ECG or cardiac enzymes. Of these, two had cardiac events during follow-up.

The major limitation of the study is that it has inadequate power to detect differences in length of stay of less than 1.5 days between the two groups. Therefore, although the improvement in efficiency with cTnT measurement fails to reach significance in the study, we feel that if we were to ignore the strong trend towards improved

efficiency, we would be committing a type two error, and be discounting a smaller but still clinically important effect. We had anticipated that the impact of cTnT would have been greater than that seen. A recent randomised trial of patients admitted to a coronary care unit showed a 66% reduction in length of stay when a cTnI-based algorithm was compared with standard risk stratification.[11] However this trial did not include the time spent on the general wards following discharge from the coronary care unit, which as seen in our study, dilutes the impact of troponin measurement on overall length of stay, but more accurately reflects the overall expenditure.

In conclusion, our study supports the hypothesis that incorporating serum troponin measurement into a risk stratification care pathway improves service efficiency and is safe. This is likely to be most efficient in the setting of a chest pain unit or cardiac unit, where patients are assessed by those most experienced in the management of acute coronary syndromes.

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Ovarian cancer – the need for change in service delivery in Northern Ireland

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SUMMARY

This paper provides local data on the provision of services for patients diagnosed with ovarian cancer in 1996 prior to the reorganisation of cancer services. It documents a service for 140 patients provided by 80 consultant teams and illustrates the need for reorganisation to meet the evidence base already in existence for improvement in survival and will serve as a baseline for future audits in this area.

INTRODUCTION

Driven by some of the worst survival rates in Western Europe[1] there has been widespread reorganisation in recent years of the way cancer services in the UK are delivered.[2] Given the need to improve service quality and to justify the massive resource commitment required, monitoring and evaluation of the changes in terms of care processes and outcomes are clearly required. These may be measured using the patient care pathway. We report here an example relating to ovarian cancer.

In 1996 the Campbell report[3] made wide-ranging recommendations for change in the way cancer services were organised in Northern Ireland. Broadly in line with those made by the Calman Hine report for the NHS in England and Wales,[2] they included centralising care for the 1.7 million population within 5 cancer units and 1 cancer centre, providing care by designated specialists working in multidisciplinary teams and enhancing communication between primary and secondary care.

Recommendations specific to ovarian cancer were the use of ultrasound scanning and measurement of blood tumour marker levels as part of the assessment process, and the development of regionally agreed management guidelines to be used within a network of care. The latest regional guidance determines that treatment should only take place in the cancer centre or in a cancer unit and only under the care of a lead clinician in gynaecological oncology. If treatment is proposed to take place in a cancer unit the patient's management plan should be agreed with the multidisciplinary team at the cancer centre.[4]

Observational studies of patients with ovarian cancer lend broad support to these recommendations. The involvement of a gynaecologist at both presentation and treatment, and further management by a multidisciplinary team have been shown to improve survival.[5,6,7] Operation by specialist gynaecologists has also been found to improve survival among women with stage III disease.[8] However, the case for ensuring operators treat an optimum volume of patients is unproven to date.[7]

Part of a larger study of the overall cancer service changes in Northern Ireland, this paper aims to provide a baseline description of the care received

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by women diagnosed in 1996 with ovarian cancer, prior to anticipated service change.

METHODS

All ovarian cancer notifications for 1996 were extracted from the Northern Ireland Cancer Registry. This included both fully malignant and borderline malignant tumours, in accordance with the ICD-O-2 classification.[9]

A retrospective review of records was undertaken by one trained researcher (RM). For inclusion in the study each case was required to have at least one of the following: hospital case notes; General Practitioner records or histopathology reports.

In addition to the basic demographic information, details of presenting symptoms, the referral and assessment processes, diagnostic procedures, tumour information, treatment details, and outcomes were collected.

Information was recorded on a Microsoft Access database and analysed using SPSS software. Follow-up of patients was carried out up to 31 December 1999. Cox's proportional hazards regression model was fitted to the data, in order to investigate if age at diagnosis (under and over 65 years), stage of disease and treatment were significant predictors of survival.

RESULTS

144 incident cases of ovarian cancer and borderline malignancy were reported to the Northern Ireland Cancer Registry. Three cases of serous cystadenomas wrongly registered as "serous cystadenocarcinomas" and one case of pseudomyxoma peritonei were found on examination of notes; these cases were excluded from the study. 137 (97.9%) cases met our criteria for inclusion in the study. For four of these, only histopathology records were available.

Patient/disease characteristics

The mean age of the patients was 62 years (range 15 to 91, median 63). Surgical FIGO staging was recorded in the notes of only 69 (55.2%) cases. However, using the various data sources available it was possible for the researcher to stage 119 patients. Using the FIGO system 15 (12.6%) had borderline malignancy, 29 (24.4%) were stage I, 12 (10.1%) were stage II, and 63 (52.9%%) were stage III or IV.

Referral

The source of referral was available for 110 cases. 90 (81.8%) cases were referred by their GP. 56 (50%) cases were seen as an outpatient referral, with 49 (43.7%) as emergency admissions. Based on 108 cases, 58% of patients were seen the same day as referral, with 75% within 10 days of referral (range 0-164).

Assessment

Details of presenting symptoms were available for 117 patients. Abdominal pain 75 (64.1%) and abdominal distension 44 (37.6%) were the most common presenting symptoms. Others included weight loss 22 (18.8%), dyspepsia 18 (15.4%), urinary frequency 11 (9.4%), anorexia 5 (4.3%), altered bowel habit 5 (4.3%), and weight gain 4 (3.4%). Nine (7.7%) cases were asymptomatic at presentation. The median duration of abdominal pain at presentation to hospital was two months (range one week to two years).

Patients presented to 80 different consultant teams, 56 of whom assessed only one case each. The largest caseload at presentation was five patients. 16 cases were unattributable to a particular team. Initial assessment was by obstetricians or gynaecologists in 67 (55.4%) cases, general surgeons in 27 (22.3%), physicians in 21 (17.4%), and urologists in two (1.5%) cases. However, in 109 (79.6%) patients a gynaecological opinion was received, while in eight (5.8%) cases this was not sought. For 20 (14.6%) patients these details are unknown.

Details of pre-surgical assessment were available for 115 patients. Investigations included CA 125 in 59 (43%) cases, ultrasound scan 96 (70%), and CT scan in 35 (25.5%). 46 (40%) patients had both CA125 and ultrasound scan including transvaginal ultrasound performed.

Based on an analysis of 115 cases the median time from first hospital visit to diagnosis was 13 days, 70% were diagnosed within 33 days and 90% of within 108 days (range 0-399).

Surgical treatment

114 (83.2%) patients underwent some form of surgical procedure (see Table 1). In four cases this was limited to pleural tap or paracentesis.

The type of surgical procedure varied across the stages of disease. Table 2 gives details for cases where stage was derived by examination of notes.

Operator details

65 different clinicians operated on these patients with 43 operating on only one case each. Four

TABLE I

Procedures by FIGO Stage of Disease

Stage	*Pleural tap/ paracentesis*	*Biopsy/ laparotomy*	*SO/BSO*	*SO/BSO/ OM*	*TAH/ BSO*	*TAH/ BSO/ OM*	*Other*
Borderline	0	0	9	1	4	1	
Other							
Stage I	0	0	8	3	15	3	
Stage II	1	0	3	2	2	3	
Stage III	1	4	6	11	13	6	
Stage IV	2	1	1	3	0	0	3
Unknown	0	1	0	0	5	0	2
Total	4	6	27	20	39	13	5

so = Salpingo Oophorectomy
BSO = Bilateral S O
OM = Omentectomy
TAH = Total Abdominal Hysterectomy
Procedure Unknown = 11 patients

clinicians operated on five or more, with the highest caseload being nine. Operations took place at 21 different hospital sites across Northern Ireland.

Based on data for 99 cases, obstetricians or gynaecologists operated on 79 (79.8%). This includes three clinicians with specialist gynaecological oncology training who operated on 20 (20.2%) patients. General surgeons operated on 17 (17.2%), including four patients with stage I disease.

Adjuvant treatment

75 (54.7%) cases were discussed with an oncologist, while 22 (16%) were recorded as not discussed. In 40 (29.2%) cases this was not recorded or notes were unavailable. Although eight oncologists were involved, 58 of the cases were discussed with one oncologist who specialises in the treatment of gynaecological cancer. The median time from referral to being seen by an oncologist was one day (range 0-32).

75 (54.7%) patients had chemotherapy, eight (10.6%) did not, and in 54 (39.4%) cases this was not recorded or notes were unavailable. 23 (30.7%) patients were offered entry into a clinical trial: 18 (24%) accepted. Based on 69 case notes the median time from diagnosis to receipt of chemotherapy was 28 days (range 0-138).

Communication

In 63 (46%) cases, the diagnosis was discussed with the patient and in four (2.9%) the diagnosis was recorded as not discussed. For 70 (51.1%) this was not recorded or notes were unavailable.

There was evidence of a letter to the patient's GP in 114 (83%) cases. The prognosis was recorded in 53 (46.5%) of these. In 45 (39.5%) the letter recorded that the diagnosis was discussed with the patient.

Status at 30 days post operatively

After 30 days, 100 (88.0%) cases were alive, eight (7.0%) were deceased and the status of six (5.0%) was unknown for this period.

Survival

Whether a patient received radiotherapy and/or chemotherapy did not have a significant effect ($P>0.05$) on the hazard of ovarian cancer death; however the numbers of patients involved are small. Only the stage of disease was found to be a significant predictor of the risk of death from ovarian cancer ($P<0.05$). For each stage of disease, the hazard for ovarian cancer death was higher

TABLE II

Relative survival rates for ovarian cancer patients N.I. 1996 by stage of disease

Year	*Borderline*	*Stage 1*	*Stage 2*	*Stage 3*	*Stage 4*	*All Stages*
0-1	100	90	93	66	48	77
1-2	100	84	69	35	–	58
2-3	100	71	–	23	–	46
3-4	100	72	–	15	–	44

– Denotes intervals with unstable survival estimates due to too few individuals.

than the hazard of borderline ovarian cancer death. The relative survival rates for each stage of disease are given in Table II and Figure.

DISCUSSION

Against a background of the introduction of evidence-based recommendations for changes in cancer service provision in Northern Ireland, this study aimed to provide a baseline picture of the process of care and patient outcome for ovarian cancer prior to service reorganisation.

Service organisation

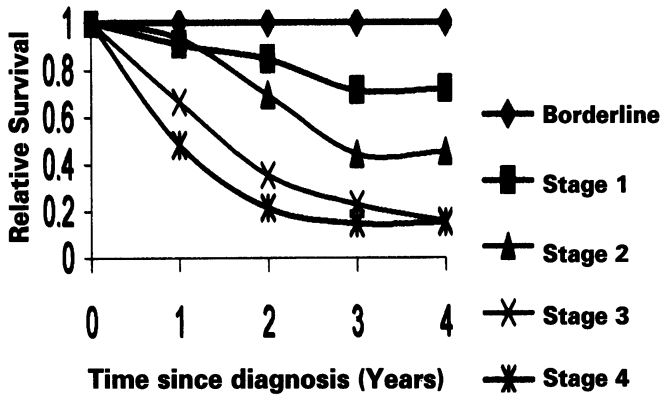
A large number of clinicians from different specialisms working in many different hospital sites were involved in diagnosing and treating women with ovarian cancer in Northern Ireland in 1996. Consequently the majority of individuals or their teams looked after only one such case per year. Similar patterns have been reported by audits conducted in England in 1991[10] and 1996.[11] While 80% of women received a gynaecological opinion during the process at least 5.8% (and possibly up to 20%) of cases did not, this despite published evidence of the benefit of such a consultation.[5, 6, 8]

Care processes

Variations in surgical practice exist although we must be careful in further interpretation, as the total information which could influence treatment including patient views were not available to us. While only 11.4% of women received the currently advocated surgical treatment of TAH/BSO/Omentectomy, this might be confounded by technical difficulties in advanced disease, by previous gynaecological surgery, or by younger women wishing to preserve their fertility. Omentectomy when considered in Borderline/Stage I disease is not subject to these confounders and may be a better marker of appropriateness.

FIGURE

Ovarian Survival by Stage of Disease



This however was a component of treatment in only eight (18.2%) such cases, raising the potential for understaging and under treatment of disease.[10]

Again, audits elsewhere have emphasised the variation in surgical practice and shown similar results for cases with disease staging recorded,[10, 11] and the percentage receiving chemotherapy.[12] Poor availability of routine stage information at the time of diagnosis will result in problems interpreting reasons for change in survival overtime.

Communication

These results focus attention on communication at the hospital/primary care interface. While a letter to the patient's GP was found in the majority of cases, only a minority included whether the diagnosis or prognosis had been discussed with the patient. The Campbell report [3] is explicit in its recognition of the central role of primary care and its need for "timely and appropriate communication with the hospital sector".

Four patients had a written record indicating that non-discussion of their diagnosis was an active

part of their management. This has implications for the acquisition of informed consent, an issue currently under discussion in relation to research in general.

Study methodology

This work was carried out in a population-based cancer registry. Cancer registries are ideally placed to assist in the key public health function of service evaluation. Working in established partnerships with numerous reporting agencies they have considerable expertise in the collection, collation, analysis and dissemination of population-based data within a data protection framework.

The main limitation of the study lies in the fact that it was carried out some three to four years after the majority of patient treatment had occurred. Underreporting of the true picture can be a problem in any retrospective study, but is compounded in this case by our inability to differentiate between data genuinely "not recorded" and that missing because of unavailable casenotes, as we did not record which data sources were accessed for each case. In addition, there is the impression that notes tended to be unavailable for deceased patients as opposed to survivors. This missing data may therefore be more representative of women with advanced disease at presentation.

CONCLUSION

This population-based study documents both the process and outcomes of care for women diagnosed with ovarian cancer in Northern Ireland in 1996. The findings suggest a picture of service provision very different from that later recommended by the Campbell Report, yet similar to that seen elsewhere in the UK at that time. A study of cases incident in 2001 is now underway to close the audit loop.

ACKNOWLEDGEMENTS

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John Pemberton and the flax industry in Northern Ireland

P Elwood

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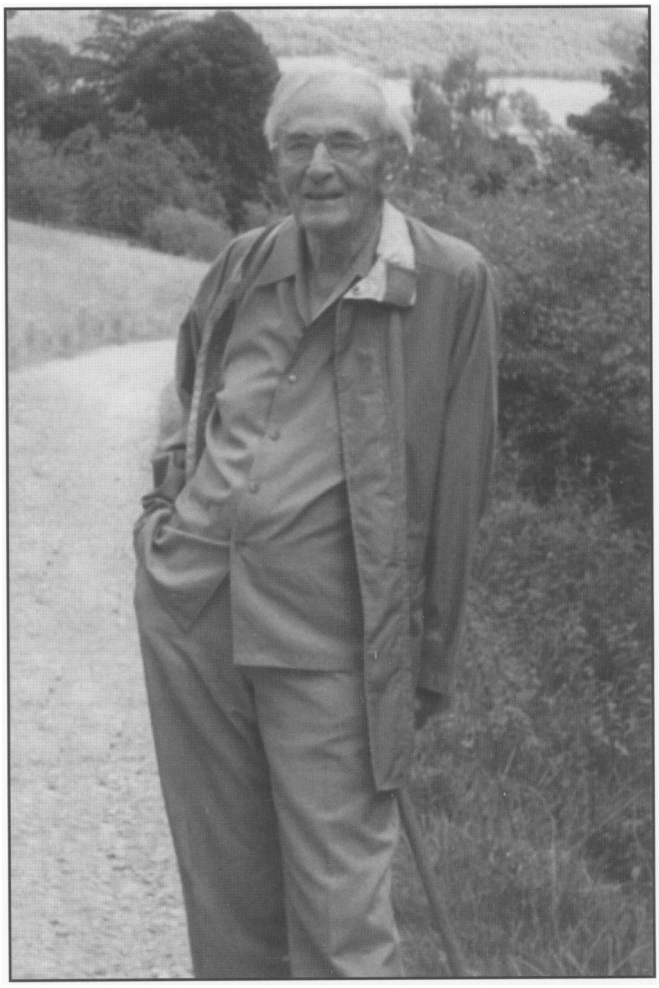
The following is based on a paper given at a meeting to celebrate the 90th birthday of John Pemberton in The London School of Hygiene and Tropical Medicine, London, on 22nd November 2002. John Pemberton was Professor of Social and Preventive Medicine in Queen's University 1958-1976 and the author had been Stuart Friar Fellow in his Department from 1960-1963.

Byssinosis is a syndrome of chest tightness and breathlessness which occurs in textile workers. Symptoms commence a few hours after returning to work after a week-end break away from the industry. The symptoms gradually ease during the day, but as the condition advances the symptoms become more severe and last for longer, sometimes for several days each week.

Ramazinni, in 1705,[1] was probably the first to record a description of the condition, though the term 'byssinosis', from the Greek for flax or linen, was not applied to it until 1908.[2] It was Richard Schilling, however, who, in two papers in 1956,[1] established the importance of byssinosis as a common disabling condition within the cotton industry,[3] and his work led to the inclusion of the condition under the Industrial Injuries Acts.

In this legislation, byssinosis was defined as occurring in cotton workers. Workers handling flax were not included either in this Act, which covered England, Scotland and Wales, or in the corresponding Act in Northern Ireland (National Insurance (Industrial Injuries) Act (Northern Ireland) 1946. In 1960, the Ministry of Labour and National Insurance (NI) asked Professor Pemberton of the Department of Social and Preventive Medicine in Queen's University, to conduct a survey of workers in the flax preparing industry to establish whether or not a 'counterpart to byssinosis amongst cotton workers' existed in workers in the flax industry in Northern Ireland.

In fact, towards the end of the survey undertaken in Northern Ireland, the Ministry in London asked



John to extend his survey to England and Scotland to give a basis for an extension of the relevant English Act to include flax workers in the definition of byssinosis. One flax mill in Halifax, one in Glasgow and one in Aberdeen were

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therefore visited by the team and a few workers examined in each – sufficient to identify a few workers with byssinosis!

The work was organised, and visits to the mills arranged by John. The field team consisted of Yvonne Duggeon, receptionist; Geoffrey Carey who performed respiratory spirometry on each man; Ian McAulay who made detailed dust measurements at randomly selected points within every flax preparing room and Peter Elwood, who interviewed each worker, completed the MRC Questionnaire on Respiratory Symptoms and recorded height, weight and an industrial history.

Twenty three of the 24 flax preparing mills in the Province were visited. Permission was not however given for the team to visit a mill which was owned by the then Minister of Commerce in the Government of Northern Ireland. In all, 2,528 workers over 35 years of age were examined, representing 83% of the total workforce of those ages in the 23 mills.

Statistical analyses were overseen by Eric Cheeseman, the first professor of medical statistics in the UK, and Desmond Merrett. The data were entered on Hollerith sorting cards by Mrs Jean McCabe and her staff. The questionnaire data were analysed on a Marchant electro-mechanical calculator and the lung function data on a DUCE computer, the first computer in the University. All these items are now museum pieces!

Overall, 17% of the workers reported respiratory symptoms which were identical to byssinosis as it had been defined in cotton workers. In the early flax-preparing stages the prevalence of the characteristic symptoms was 48%, while in the later stages, which were very much less dusty, the prevalence was low, and the symptoms were totally absent in spinning rooms in which the fibres were handled wet and dust was totally suppressed.

A report stating this, and giving evidence that the condition was clinically identical to cotton workers' byssinosis, was submitted to the Minister of Labour and National Insurance in the Government of Northern Ireland in November 1963.[4] This gave a basis for the enactment of legislation to provide benefits for flax workers. The results of the tiny surveys conducted in England and Scotland made possible the inclusion of flax workers in the relevant English Act.

John had however set aims for the survey which were additional to the one required to satisfy the Minister. These included the ascertainment of the prevalence of a range of respiratory symptoms in the workers, the determination of the distribution of lung function and the relationship of this, and of byssinosis, to the concentrations of airborne flax dust within the various departments in the mills.

A most important finding was that smoking powerfully potentiates the effect of flax dust and was a major factor in the development of all respiratory symptoms. In fact, byssinosis was rare in non-smokers,[5] and this finding was strongly supported by the data on lung function.[6] Published literature at that time however made no mention of this association. Once allowance had been made for the effect of smoking, there was evidence of a significant association between dust level and byssinosis, but not with chronic bronchitis.[7]

A problem became apparent as the survey progressed. This was, whether or not byssinosis is entirely an acute response to exposure to textile dusts, or whether exposure to the dust causes permanent respiratory changes, leading to continuing disablement of workers after they left the industry. It was clear that this was a most important question, fundamental to the understanding of byssinosis, and of direct relevance to the legislation and to claims for compensation by ex-workers who believed they had been disabled by having worked in the industry.

This issue could not be answered by a prevalence survey. Ten years after the initial survey all the workers who had been seen in the prevalence survey were therefore followed up in order to identify deaths. The analysis of these gave no convincing evidence that exposure to flax dust affects survival. Workers who had reported symptoms of byssinosis did show a very small excess mortality, their mortality rate, relative to the rate in all employed men of the same ages (the SMR) being 103 for deaths from all causes. Deaths from respiratory diseases in the flax workers were however raised (SMR 125) but there was no evidence of any gradient in mortality with increasing severity of byssinosis as reported during the survey. The numbers of deaths amongst workers with byssinosis were however small and it was not possible to take adequate account of cigarette smoking in these analyses.[8]

These data on mortality were presented at a number of conferences, and they led to a considerable controversy with Professor Schilling and others. Not surprisingly however, few colleagues found the evidence they provided convincing, and the general belief continued to be that byssinosis does cause permanent respiratory damage. This belief was fuelling a rapidly increasing number of claims by ex-textile workers against factory owners for compensation on the grounds of continuing disability.

Ten years after the study of mortality in the industry, that is, twenty years after the initial prevalence survey in the flax mills, opportunity arose for the situation to be examined further. A team based in John's old department in Queen's University, under the direction of Professor Harold Elwood, conducted a survey of subjects resident in towns in Northern Ireland in which flax processing had been a major source of employment. Random samples of the population were drawn from electoral registers, the MRC Questionnaire on respiratory symptoms applied, lung function measured and an occupational history recorded.

A prediction which had been made when planning this survey, namely that about half the older residents in the selected towns would have worked in the flax preparing industry, was confirmed. It was therefore possible to compare the respiratory symptoms and respiratory function of ex-flax workers with symptoms and function in subjects who had never handled flax. There was very little evidence that the ex-flax workers had any excess respiratory symptoms, or any impairment of respiratory function.[9]

The opportunity was taken at the same time to conduct identical surveys in Bolton and Oldham, in which cotton processing had been a major source of employment. Again, as with flax, very little evidence was found that former cotton workers had any excess respiratory symptoms, or any impairment of respiratory function.[10]

The three phases of this work therefore yielded evidence from which it seemed reasonable to conclude that byssinosis does occur in flax workers with a prevalence and severity similar to the condition in cotton workers, and that cigarette smoking is a powerful potentiating factor in the development of byssinosis. By far the most important conclusion was however that while workers can be disabled by byssinosis while exposed to textile dusts, once they leave the industry the symptoms disappear and there is no permanent disability attributable to the dust.

Following discussions with a number of people, including industrialists in the flax and linen industry and medical colleagues, a commentary on changes in the flax industry, with predictions of the likely future for the industry was submitted and published in the Lancet. In this it was stated that 'the future of the (flax) industry, perhaps even its very survival, probably depends more on medico-legal developments than on all the technical and other issues combined'.[11]

It has not been possible to obtain continuous data on claims for byssinosis. The condition had been included in the National Insurance (Industrial Injuries) Act (Northern Ireland) in 1966 and the total number of applications up to 1980 appear to have been well over 700. In the five years to the end of 1970, 35 claims were allowed. In the next five years 22, and in the five years 1976 to 1980, 168 claims were allowed. Although no further figures were available, it was stated that there had been no claims after about 1983. Strangely however, six patients were admitted to hospital in the 1990s, with a diagnosis of byssinosis.

Nor has it been possible to obtain details of common law claims. One of the managing directors of a mill was most helpful, and according to him the mills had been able to survive the claims for byssinosis because flax was then a highly profitable business, and insurance cover had been adequate. At the same time, the situation with byssinosis appears to have fuelled the 'blame culture' and this is now posing problems for the industry greater than byssinosis had ever been.

Epidemiologists are always interested in long-term outcomes, and so in order to get some details about the present state of flax growing and flax processing in Northern Ireland a number of medical colleagues and managers and others in the industry were contacted in 2002. It was also hoped to get information about claims for disablement by byssinosis under the Industrial Injuries legislation, and under common law on the grounds of negligence by mill owners.

It seems that no flax at all is now grown in Northern Ireland. Research on new methods of flax cultivation is going on in the Department of

Agriculture in Queen's University but the field work is being conducted in Belarus!

Two mills still process flax, but the raw fibres are all imported. The managing director of one of the mills stated that dust control in the mill is now so good that byssinosis is 'a thing of the past'.

Weaving and the production of Irish linen is apparently thriving, though on a much reduced scale compared with the early post-war years. Covers in seats in 'first class' are made from Irish linen in a number of airlines. Double damask linen is regularly supplied to the British Royal family, the Saudi Royal family, the President of the United States, and recently, an order was received from Number 10 Downing Street. Many hotels in London and abroad are supplied with Irish table linen. The mill which had made specially designed table linen for the Titanic in 1912 reproduced items with the same design to coincide with the launch of the film 'Titanic'. Linen dress fabrics are enjoying a marked revival with leading courturiers.

Most of the old mills have been demolished, but a few remain. One is now a historical and craft centre, run by a Trust. Another is a museum and houses many of the machines, the dust from which had been measured in the early 1960s by McAulay. The national Trust maintain the Wellbrook Beetling Mill at Wellbrook, in County Tyrone. In the Irish Linen Centre in the Lisburn Museum spinning and weaving are demonstrated. There are 'Linen Tours' in one of the former flax towns, and these include a visit to a working scutch mill, a weaving mill, but none of the processes which used to take place in the preparing mills – carding, hackling, drawing, doubling, spinning or reeling – appear to be demonstrated.

CODICIL

John is still active at ninety! He takes an active interest in a current follow-up of the Boyd Orr survey of the diets and health of school children in the 1930s. He and Gwen, John's wife, had been field workers in this survey.[12] Thirty papers arising out of this study are now listed in Index Medicus, many being based on a recent follow-up of the cohort by epidemiologists in the Department of Social Medicine in the University of Bristol.[13, 14] Recent papers have been published by John himself on the history of the Society for Social Medicine[15] and on a school diet in the 1920s[16] and he is currently working on other historical papers.

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Abstracts of the Association of Clinical Pathologists Irish Branch Annual Meeting 2003

A CASE OF CONSECUTIVE LYMPHOMAS

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A 33 year old male had an acute septic episode resulting in multi-organ failure and death. At age 13 he was diagnosed with lymphocyte predominant Hodgkin's disease of cervical nodes and treated with localised radiotherapy. This diagnosis was confirmed retrospectively by immunocytochemistry which showed the sparse large mononuclear cells to be CD15 –ve, CD 30 –ve and CD 20 +ve. He remained well and in remission until he was 30 years of age when he developed diffuse large B cell lymphoma (CD20 +ve, CD 3 –ve, CD30 –ve, CD15 –ve) of abdominal nodes. He received 6 courses of conventional CHOP chemotherapy and again had a complete remission which lasted for three years. A tissue diagnosis during his acute presentation proved elusive. However at postmortem examination a widespread large cell lymphoma of T cell type (CD3 +ve, CD20 –ve) with involvement of liver, lymph nodes and bone marrow. Ki-67 was >50%. Second lymphomas following HD are well documented, but on review of the literature we could find no case reports corresponding to the number and type of lymphomas which occurred in this patient. Immunoglobulin and T gene rearrangement studies of the diagnostic material from all three presentations are in progress.

AMYLOIDOSIS: SYSTEMIC OR LOCAL

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Amyloidosis is a disorder of protein folding in which normally soluble proteins are deposited as insoluble fibrils, disrupting organ function and causing disease. The deposited proteins may involve one single organ system or be widespread throughout the body. We present a case of laryngeal amyloidosis in a 62 year old man, and review the current literature on diagnosis and treatment of this unusual disease, with discussion of the difficulties in determining whether the disease is local or systemic. Laryngeal amyloid is reported in 100 cases in current literature, and presents difficulties in diagnosis and therapy.

AORTIC VALVE PAPILLARY FIBROELASTOMA IN A PATIENT WITH AN INCIDENTAL FINDING OF BRADYCARDIA

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We present a patient who, following investigation for asymptomatic, incidental bradycardia, was demonstrated to have a papillary fibroelastoma on his aortic valve.

The microscopic appearance of the lesion was of papilliform projections arising from the valve. They featured a central core, comprised of dense, paucicellular collagen with a varying degree of myxomatous matrix, lined by a surface layer of endothelial cells. The appearances were those of a papillary fibroelastoma, which is a relatively rare lesion: by 1991 only 132 cases had been cited in the literature.[1] However, if benign tumours of the heart are considered, they rank third in the adult population.[2] Constituting 11.6% of all histologically benign tumours.[3] A synopsis of knowledge regarding papillary fibroelastomata will be given including site of involvement, age and sex predilection, histogenesis, main differential diagnoses and clinical sequelae.

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CORRELATION OF PROSTATE NEEDLE BIOPSIES WITH PROSTATE-SPECIFIC ANTIGEN

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ABSTRACT

Introduction:

Prostate specific antigen has proven to be a good screening instrument for prostate cancer, which is the second leading cause of cancer death in males. Poor specificity and low predictive value have been some of the reported limitations.

Objectives:

To correlate the histopathological findings in Prostatic needle biopsies with level of total PSA and ratio of free to total PSA and to determine sensitivity, specificity and positive predictive value at different cut off levels.

Materials and Methods:

Prostate core biopsies received in the department of histopathology between 2001 and 2002 were retrieved from file and reviewed. All patients with available PSA results were included in the study. All patients have sextant biopsies, which were processed routinely.

Result:

187 patients were studied, mean age 71 years. 88 were benign and 99 malignant with mean age of 68 and 73 respectively. There was significant relationship between elevated total PSA and low PSA ratio and malignancy ($P<0.5$). We found optimal cut off value for total PSA to be 10ng/1 with sensitivity and specificity of 70% and 72% respectively and positive predictive value of 73%. The sensitivity rises to 96% but the specificity drop to 17% with positive predictive value of 57% at cut of value of 4ng/1. There is no significant improvement in sensitivity at cut off value of 2ng/1. The optimal cut off for PSA ratio is 10% with sensitivity and specificity 53% and 79% respectively and positive predictive value of 62%. PSA ratio is found to be useful in when total PSA fall in the grey zone of 4-10ng/1 for optimal result.

Conclusion:

Both total PSA and PSA ratio are useful in screening for prostate cancer. Total PSA should form the main anchor in making decisions.

CUTANEOUS MALIGNANT MELANOMA IN YOUNG PATIENTS UNDER 21 YEARS IN NORTHERN IRELAND – AN 18 YEAR RETROSPECTIVE REVIEW

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Malignant melanoma is a rare tumour in childhood and adolescence but some studies have shown an increase in incidence over the last 20 years which is felt to be independent of earlier clinical detection. Previously the majority of these lesions in childhood were thought to arise in congenital naevi but recent reports have highlighted new risk factors.

The hospital notes of patients aged under 21 years with a histological diagnosis of melanoma (n=20) were retrieved from the files of the department of pathology in the Royal Group of Hospitals, from January 1984 to December 2002 inclusive. The histological sections were reviewed by both authors to confirm the diagnosis.

The age of the patients ranged between 13 and 20 years with a mean age of 18 years. No cases in children under 12 years were present in the study. 55% (11 cases) were female with a mean age of 18 years and 45% (9 cases) were male; mean age 17 years. The majority were located on the upper limbs (30%) and head and neck (25%) with 20% involvement of the lower limb. Approximately 15% involved the trunk and back and in two cases (10%) no site was given. In 12 of 20 cases the histogenic type was superficial spreading melanoma, four were nodular, three were melanoma in situ and one represented a recurrence in a scar with no previous histology available for review. The majority (94%) were of epithelioid cell type with one of spindle cell type. Breslow's depth ranged from 0.1mm to 1.6cm with a mean of 2.4mm. 50% were Clarke level IV at presentation. Eight of 20 cases presented at pT1, 6 cases pT2, 3 cases pT4, 2 cases pTis and 1 case pT0.

In 30% of cases (6) a co-existing benign intradermal/congenital naevus was identified.

While malignant melanoma in young people remains a relatively unusual tumour the incidence of melanoma is rising in the general population and the incidence in teenagers is also increasing. While numbers are small pathologists need to be aware that melanomas do occur in teenagers and young adults.

AN UNUSUAL CAUSE OF DELAYED RUPTURE OF SPLEEN

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Splenic trauma is a rare fatal complication of colonoscopy. Awareness of this complication is essential for early diagnosis and management. We report a case of rupture of the spleen seven days following colonoscopy. A 72 year old female presented with recent onset of weight loss and anaemia. Colonoscopy was carried out amongst other investigations to exclude malignancy. No abnormality was found. Two days following this procedure her haemoglobulin level fell, necessitating blood transfusion. The patient developed severe left loin pain with tenderness in the left iliac fossa on day seven following colonoscopy. The clinical impression was of possible intestinal obstruction or intestinal ischaemia. Plain X-Ray of the abdomen showed distension of the bowel. She developed sudden cardiopulmonary arrest and resuscitation was not successful. A post-mortem examination was carried out. The relevant pathological findings were of rupture of the spleen with associated haemorrhage and fresh blood clot. Microscopically, there was associated abundant iron pigment. The relevance of this in relation to recent haemorrhage is discussed.

CUTANEOUS NODULAR AMYLOIDOSIS – A 12 YEAR REVIEW

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Amyloidosis is a generic term describing a group of diseases, of both localized and systemic distribution, in which there is deposition of fibrillary proteins having a ß-pleated sheet configuration on X-ray crystallography.[1] Nodular amyloidosis is an uncommon pattern of amyloid distribution, thought to be due to localized plasma cell dyscrasias.[2,3] Records over a 12 year period (totalling 234,803) were reviewed: five patients had been diagnosed as having cutaneous nodular amyloidosis during this period. The affected sites were predominantly in the head and neck. Importantly, the histopathological appearances cannot be distinguished from those of systemic amyloidosis and consequently in all cases encountered the clinicians should be reminded to give consideration to the possibility of systemic disease, specifically multiple myeloma.[4] Skin lesions are detected in approximately 30% of patients with systemic amyloidosis.[5]

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ENDOMETRIAL ADENOCARCINOMA ON A BACKGROUND OF MIRENA COIL INSERTION

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We present the case histories of 3 patients who had a Mirena coil in situ at the time of diagnosis of endometrial adenocarcinoma. Two premenopausal women (48-49 years), who had the levonorgestrel intrauterine device inserted for the treatment of menorrhagia at the time of curettage, were found to have well differentiated endometrioid adenocarcinoma. They each proceeded to abdominal hysterectomy within the following 3 months. Both of the resection specimens showed a well differentiated endometrioid adenocarcinoma which was confined to the endometrium. One case showed focal lymphovascular space invasion while the other one had no adverse prognostic factors. Both tumours showed proliferation and mitotic counts ranging from 3 - 7 per 10 high power fields with mild to moderate nuclear atypia. The third lady (36 years of age) presented with menorrhagia and

was found at the time of initial curettage to have epithelial hyperplasia that was suspicious of malignancy. She had a Mirena coil inserted and repeat curettage 3 months later confirmed the diagnosis of adenocarcinoma. She proceeded to hysterectomy within 5 months of her initial curettage. The resection specimen had no residual tumour, but was the only specimen to contain simple hyperplasia. In two of the three resection specimens the background endometrium showed evidence of progesterone effect with stromal decidual change but gland atrophy was not identified in any of these cases. These cases highlight the fact that although the Mirena coil has helped to revolutionize the treatment of menorrhagia and has some proven benefit in the treatment of hyperplasia, it should not be used in the treatment of carcinoma, or relied upon to prevent the development of carcinoma. It also highlights the importance of proper investigation of persistent menorrhagia prior to the instigation of treatment.

METASTATIC CARCINOMA IN THE SKIN - A 12 YEAR REVIEW

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The skin is an unusual site for visceral metastases. It appears to be the eighteenth most frequent site for carcinomatous metastases.[1] We reviewed the incidence of cutaneous metastatic deposits of visceral metastases over a 12 year period: 47 cases of secondary carcinoma of the skin were found, the primary site including (in order of frequency): breast, adenocarcinoma of site unspecified, gastrointestinal adenocarcinoma, squamous cell, lung, hepatocellular and prostate. The use and limitations of immunohistochemistry in the identification of the primary source will be discussed.[2] One of the main differential diagnoses for metastatic adenocarcinoma is cutaneous adnexal neoplasm. These are often immunophenotypically similar; consequently immunohistochemical techniques are often unable to aid in distinguishing between primary and secondary cutaneous malignancies.[3]

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THE ROLE OF IMMUNOHISTOCHEMICAL EPITHELIAL MARKERS IN THE HISTOLOGICAL DIAGNOSIS OF INTRATUBULAR GERM CELL NEOPLASIA (ITGN)

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Introduction

The significance of ITGN, also known as *carcinoma in situ* of testis, is that 50% of patients developed invasive tumours by 5 years. Primary management is orchidectomy. The aim of the study was to assess the expression of immunocytochemical markers – PLAP, CAM5.2, AE1/AE3, EMA, Vimentin and CD30 and their use in the histological diagnosis of ITGN.

Methods

The pathology for orchidectomy patients (1995-2001) was reviewed and three groups identified – normal, or cryptorchid testis and germ cell tumours. New tissue sections were cut from stored blocks and an immunohistochemical panel examined.

Results

In all groups Vimentin, CD30, AE1/AE3, EMA and PLAP were as previously published. Of note in the normal group CAM5.2 stained tubules with absent spermatogenesis in the substance of the testis, discrete groups of tubules with absent spermatogenesis stained in cryptorchid testis, while CAM5.2 was positive in most tumours.

Conclusion

Our data confirm PLAP is a consistent marker for ITGN. Of particular interest is the CAM5.2 staining. It is found in tubules with abnormal spermatogensis both in normal and neoplastic testes but does not correspond to PLAP positive ITGN. However there is no proof that CAM5.2 expression in ITGN could predict cells that are committed towards non-seminomatous

differentiation. CAM5.2 staining pattern most likely reflects tubular injury.

VIRUSES AND TRANSPLANTATION

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Varicella Zoster virus (VZV) infection is potentially very serious in bone marrow transplant recipients, and may manifest as a disseminated visceral infection. This condition is generally accompanied by a vesicular rash. Reactivation of VZV is a common event in patients undergoing allogeneic bone marrow transplantation (BMT) and may lead to life-threatening complications. We describe here a patient who developed acute abdominal pain eight months post allogeneic bone transplant carried out for acute myeloid leukaemia. Gastroscopy revealed multiple, discrete and haemorrhagic ulcers. The patient received triple therapy (Lansoprazole, Amoxicillin and Clarithromycin) without improvement. Skin rash appeared very late in the course of the disease. The patient died due to disseminated varicella-Zoster infection after a brief admission to Intensive Care Unit. This rare presentation of VZV infection is potentially underdiagnosed. Testing for VZV viraemia by Polymerase Chain Reaction (PCR) can suggest the diagnosis although whether plasma-associated viraemia is truly pathognomonic of visceral disseminated infection remains to be established. As bacterial infections are becoming less of a problem because of new and effective antibiotics, viral infections have emerged as one of the main causes of mortality and morbidity. With fewer options available to treat severe viral infections, a need for more effective surveillance and prevention becomes very clear.

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Case Report

Palliation of terminal malignancy with shape memory alloy ureteric stents

KJ Ho, EJ McAteer, BT Little, A O'Brien

Accepted 24 September 2003

We report on the first case in Ireland of ureteric stenting with shape-memory alloy nickel-titanium (*Memokath 051*) stent in relieving malignant ureteric obstruction. Successful drainage was achieved and the patient required no further intervention indicating a clear place for these stents in the long-term management of malignant ureteric strictures. The use of ureteric double-J stenting in the long-term management of ureteric obstruction is associated with well-recognized complications. Consequently, metallic ureteric stents were developed to overcome the associated morbidity. We report on the first case in Ireland of ureteric stenting with shape-memory alloy Nickel-Titanium (*Memokath 051*) stents.

CASE REPORT A 72-year-old woman with inoperable gastroesophageal adenocarcinoma was found to have bilateral hydronephrosis on ultrasound scanning due to secondary disease. She had percutaneous nephrostomy tubes inserted and bilateral antegrade stenting with silastic double-J stents. However her renal function began to deteriorate after the nephrostomy tube became dislodged from the right kidney, which had 92% differential function. This showed that the silastic double-J stent was inadequate in draining the obstructed right ureter. She subsequently had bilateral percutaneous antegrade metallic ureteric stenting (Fig.1, Fig.2a and 2b). This was successful in providing comfort and continued ureteric drainage as monitored by her renal function. She required no further intervention. After six months of palliation, she succumbed to her primary disease.

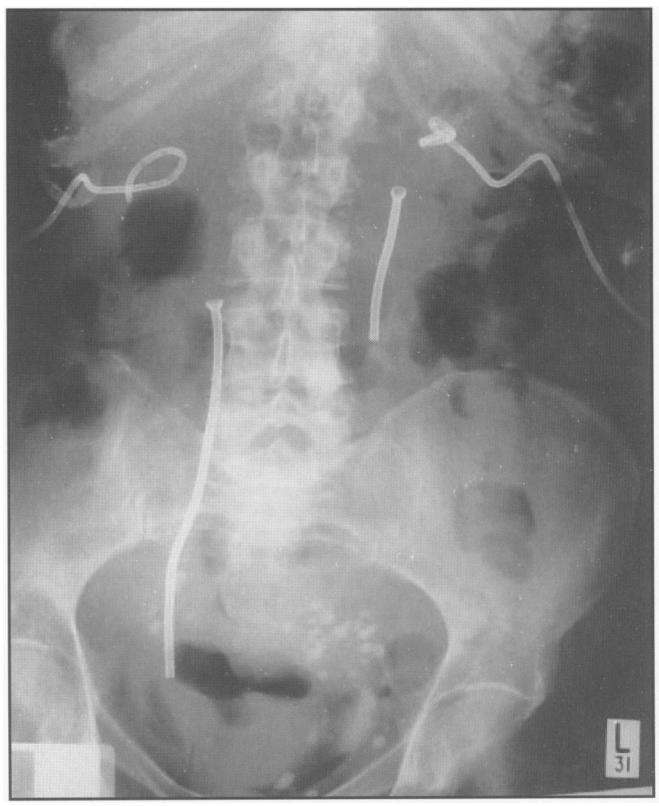

Fig 1. Post procedure radiograph demonstrates position of the bilateral *Memokath* ureteric stents prior to removal of the nephrostomy drains.

DISCUSSION

Long-term ureteric double-J stenting has been the only viable option to open urinary diversion in the management of ureteric obstruction caused

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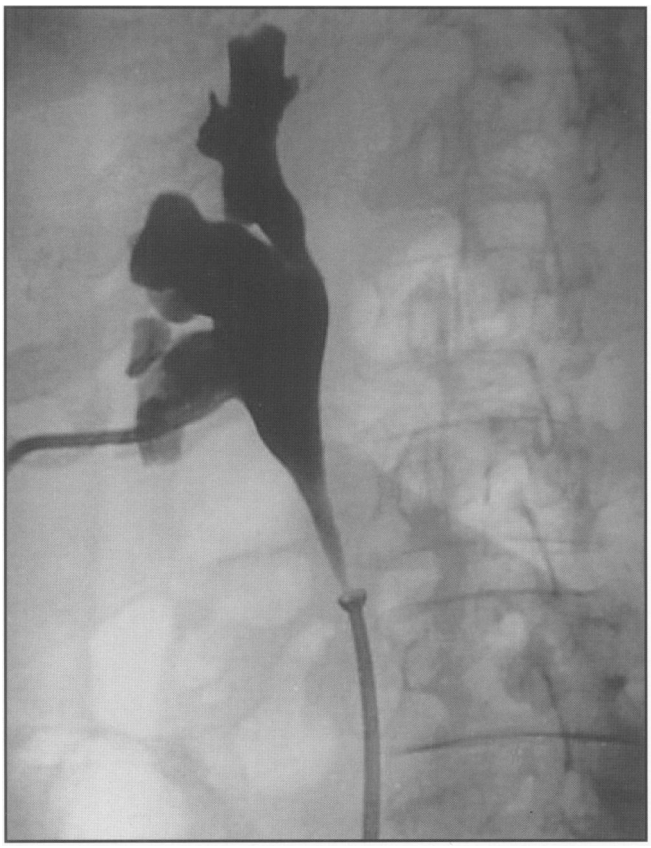

Fig 2a. Right nephrostogram showing phlanged upper end of the *Memokath* stent deployed in the ureter.

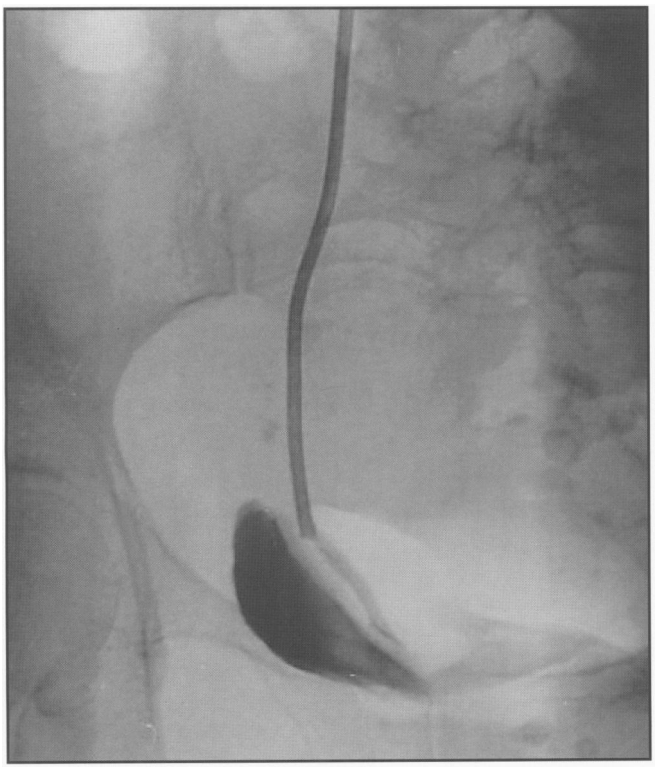

Fig 2b. Free drainage of the ureter with stream of contrast entering the bladder. Note the lower end of the stent lies in the ureter and not the bladder to prevent encrustation.

by recurrent benign disease or extrinsic compression by tumours. However there are recognised complications including encrustation, sepsis, haematuria, pain, reflux, fragmentation and migration.[1] Double-J stents require regular changes to maintain renal function, causing repeated hospital admissions. Metallic ureteric stents were developed to provide a solution to long-term stenting without the aforementioned complications.

Milroy *et al* reported the first use of metallic stents in the urinary tract in treating urethral strictures.[2] These stents were then used in the ureter for benign and malignant ureteric strictures.[3] However their usage in malignant ureteric obstruction was hindered by reocclusion due to endothelial hyperplasia and tumour ingrowth through the meshwork making removal virtually impossible.[4] A nickel-titanium alloy was then chosen to combat this because of the resistance of titanium to encrustation in the urinary tract.[5]

The stents used in this case were *Memokath® 051 (Engineers & Doctors A/S, Hornbaek, Denmark).* The nickel and titanium alloy affords it a unique thermal shape memory. It softens below 10°C and reassumes its predetermined shape when reheated to above 55°C. This can be repeated with no resulting shape distortion. It also has a tight spiral design to allow a degree of mobility and prevent endothelial and tumour regrowth.

Initial experience of the *Memokath 051* stent in the ureter is found in two published series. Kulkarni and Bellamy inserted 37 stents in 28 patients with ureteric strictures and followed them up post insertion for a mean of 19.3 months.[6] There was malignant disease in 18 patients and benign pathology in 10 patients. Upper tract decompression was achieved in all cases. Stent migration was noted in 3 patients but only after treatment for their underlying malignancy. There were no other stent related problems. Arya *et al* published a series of 13 stent insertions in 11 patients who had a mean follow up of 18 months.[7] This group of patients had ureteric strictures secondary to benign disease only. Once again there was relief of obstruction and no stent related symptoms.

These initial results show a clear place for these stents in the long-term management of malignant ureteric strictures. Repeated stent changes are avoided, easing pressure on hospital beds and

resources. With 3-6 monthly hospital admissions required for changing indwelling double-J stents, there are obvious financial advantages as well as advantages in patient comfort and hence quality of life.

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Case Report

Infectious mononucleosis, ruptured spleen and Cullen's sign

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Accepted 15 October 2003

Although Cullen's sign is usually associated with haemorrhagic pancreatitis, this report describes a case in which it occurred in a patient with infectious mononucleosis and non-traumatic rupture of the spleen. Thomas Stephen Cullen (1869-1953) professor of gynaecology at Johns Hopkins University Hospital, Baltimore USA, gave his name to a peri-umbilical ecchymosis resulting from a haemoperitoneum secondary to the rupture of an ectopic pregnancy. Over the years, it has usually been considered to be a sign of haemorrhagic pancreatitis, but it has also been associated with other conditions.[1] Although a similar case has been published,[2] we feel that its occurrence is rare enough to warrant mention, particularly in view of the opinion in a well-known medical text book that Cullen's sign is so infrequent in splenic rupture that it is academic,[3] and a later (17th) edition does not make any mention of an association.

CASE REPORT A 22 year old male presented with an acute abdomen. He complained of pain localised to his left upper quadrant. There was no history of abdominal trauma. The diagnosis of infectious mononucleosis had recently been confirmed by a Paul Bunnell test. The patient's vital signs were stable on admission. There was no evidence of any lymphadenopathy. Abdominal examination revealed moderate tenderness, mild rigidity and guarding together with hepatosplenomegaly. Liver function tests (LFT) were markedly abnormal with elevated ALP, ALT and GGT. Full blood count (FBP) revealed a mild anaemia, but white cell count, platelets, urea and electrolytes (U&E) and amylase were normal. Abdominal radiograph (Fig. 1) confirmed an enlarged spleen, measured by ultrasound scan as being 19 cm from pole to pole. Hepatomegaly was also noted. The patient remained haemodynamically stable and was treated conservatively with daily monitoring of FBP, U&E and LFTs.

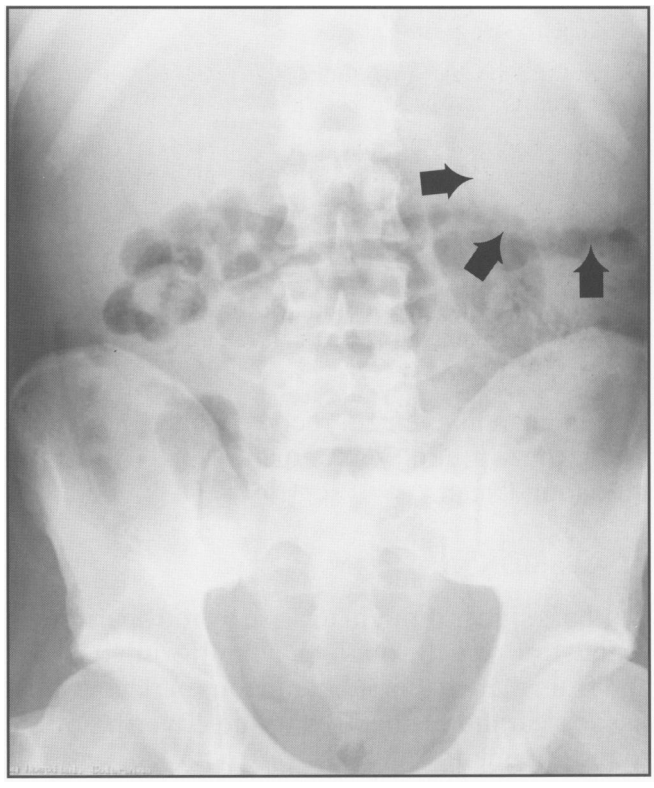

Fig 1. Abdominal radiograph demonstrating enlarged spleen.

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One week after admission, he had another episode of abdominal pain, which radiated to his left shoulder. Repeat bloods were unchanged. Abdominal examination now revealed a peri-umbilical ecchymosis, Cullen's sign (Fig. 2) Repeat abdominal ultrasound scan was unchanged. With the recurrence of his symptoms, the presence of Cullen's sign, and the ultrasound findings, a diagnosis of a further splenic rupture secondary to infectious mononucleosis was made. The patient remained haemodynamically stable, and the conservative approach to his management was continued.

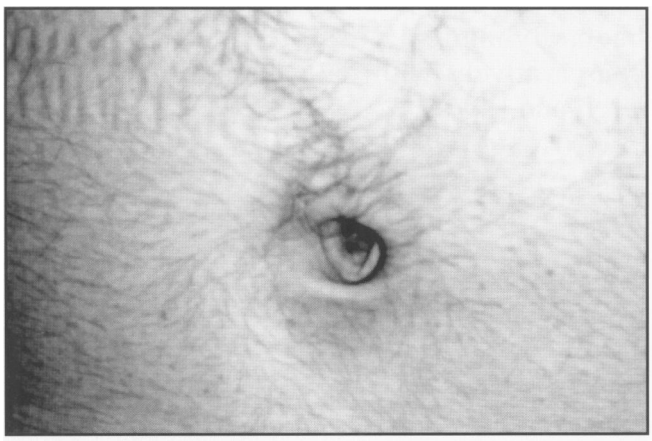

Fig 2. Periumbilical ecchymosis – Cullen's Sign.

He made an uneventful recovery and four weeks later the spleen was normal on follow-up ultrasound scan.

DISCUSSION

Cullen's sign is thought to arise by retroperitoneal blood tracking through the falciform ligament and from there to the subcutaneous peri-umbilical tissues via the connective tissue covering of the round ligament.[4]

Infectious mononucleosis is due to an infection with the Epstein-Barr virus (EBV). Transmitted primarily in saliva, its peak incidence occurs in the teenage years. It is usually a mild and self-limiting disease. Patients may, however, develop a variety of complications, some of which can be life threatening. The most common of these is spontaneous splenic rupture which occurs in 0.1-0.5% of cases.[5] It is important to note that an absence of a history of trauma may delay the diagnosis of this potentially fatal complication, increasing mortality to around 30%.[6] It is thought that rupture occurs as the result of infiltration by mononuclear leucocytes, which in turn weakens the trabecular and capsular structure of the spleen.[7]

In this case, the diagnosis of splenic rupture was easily and confidently made with the aid of an abdominal ultrasound scan and the presence of Cullen's sign. Abdominal computed tomography (CT) scanning can also be useful to differentiate between those patients requiring surgery from those who do not.[8]

Other potentially serious physical and psychological complications with long term implications may also arise.[9, 10]

There appears to be little benefit in the use of anti-viral treatment in treating uncomplicated infectious mononucleosis. Steroids have been used with some success in some complications.[11]

CONCLUSION

We would like to highlight that the presence of abdominal pain is an uncommon symptom in infectious mononucleosis and its occurrence is therefore a danger sign that a rare and potentially life threatening complication may have occurred.

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Case Report

Mycobacterium celatum pulmonary infection

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INTRODUCTION

Mycobacterium celatum is a nonphotochromogenic mycobacterial species, phenotypically similar to *M. avium* and *M. xenopi*, described for the first time less than a decade ago.[1] Several reports exist in the literature establishing this organism as a convincing pathogen among Human Immunodeficiency Virus (HIV) seropositive patients.[2-9] However, there is little evidence of its pathogenicity among individuals whose immune function is not profoundly impaired. We describe an episode of pulmonary infection with *M. celatum* in a patient whose clinical syndrome was compatible with a diagnosis of mycobacterial disease in whom there was no evidence of severe immune deficiency.

CASE REPORT

A 79-year-old man presented to hospital complaining of increasing dyspnoea over the preceding two weeks accompanied by drenching night sweats, general malaise and approximately 10kg weight loss during the preceding twelve weeks. He reported a prior history of tuberculosis affecting a cervical lymph node which had been resected 30 years previously. He also suffered from chronic obstructive pulmonary disease (COPD) having smoked 40 cigarettes per day for 60 years. His medications were oral salbutamol, inhaled salbutamol and inhaled beclomethasone.

He was found to be pyrexial on admission and continued to have fevers for seven days. Oropharyngeal mucocutaneous candidiasis was present. There were no abnormal findings on examination of the respiratory, nor any other, system. Analysis of peripheral blood revealed a leucocytosis with predominant neutrophilia. On the chest radiograph there was evidence of acute patchy consolidation with pleural thickening in the upper lobe of the right lung; there was also minor patchy consolidation affecting the upper lobe of the left lung. (Figure)

Initial empiric therapy was with intravenous coamoxiclav and clarithromycin for six days. Sputum direct microscopy findings of acid-fast

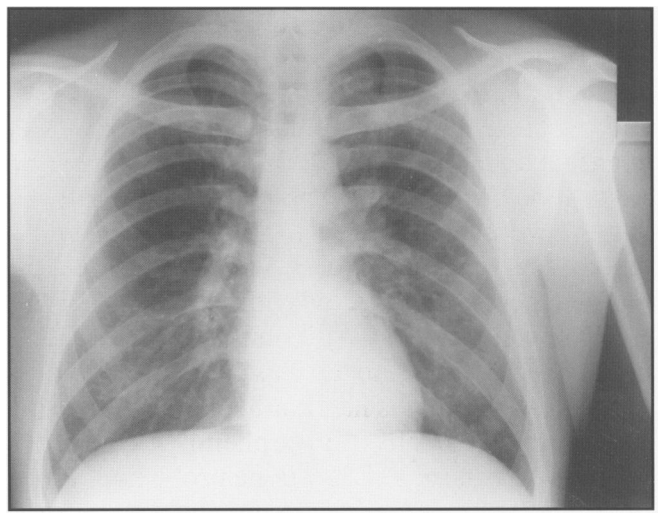

Fig. Chest Radiograph

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bacilli (AFB) resulted in a change to the patient's empiric therapy; isoniazid, rifampicin, pyrazinamide and ethambutol were introduced. The fever settled after 48-hours with later resolution of the leucocytosis following ten days of this regimen. When the identity of the isolate and its antimicrobial sensitivities became available therapy was changed to rifampicin, ethambutol and clarithromycin. This patient's symptoms of sweats and malaise have improved since this therapy was introduced; however he remains dyspnoeic as a result of continuing COPD.

MICROBIOLOGICAL INVESTIGATIONS

Three sets of blood cultures, processed using the BacT/Alert (Organon Teknica Corporation, Durham, NC, USA) system, were negative with the exception of a nonsignificant isolate of *Propionibacterium sp.* Five specimens of sputum were processed routinely for typical bacterial pathogens yielding only *Candida sp.* on two occasions in keeping with the clinical finding of mucocutaneous candidiasis. Atypical bacterial and viral respiratory pathogen serology was negative and urine culture failed to produce any pathogen. Eight specimens of sputum from the patient were handled by the mycobacteriology laboratory; although AFB were visualised on direct microscopy of only three of these, *M. celatum* was cultured in all instances. The search for an alternative pathogen was conducted without success. The isolates had not been identifiable to species level either by routine phenotypic methods or using commercial DNA gene probe kits for *M. tuberculosis* and M. *avium intracellulare.* Molecular identification was performed by PCR amplification and sequencing of a region of the 16S rRNA gene, using a previously described method,[10] with modification of the forward primer to PSL, as described by Campbell *et al.*[11] Upon anaylsis using BLAST alignment software (http://www.blast.genome.ad.jp/), the isolates were identified as *M. celatum* with 557/557 bases called (100% homology). This sequence has subsequently been deposited in GenBank with the Accession number AF433135.

DISCUSSION

M. celatum, first described in 1993,[1] is an established pathogen among seriously immunocompromised HIV-seropositive individuals [2-9] and belongs to the group of mycobacteria other than Tuberculosis (MOTT). Interestingly, its role in disease among other populations is less well described. The case we outline represents the first isolation of this organism in Northern Ireland and, of note, this patient had no markers of severe immune deficiency. Although HIV serology was not sought seropositivity, in the context of this man's risk profile, seems extremely unlikely.

It is accepted that the identification of *M. celatum* in routine practice is difficult since it is phenotypically similar to *M. avium* and *M. xenopi* [1-5] and, in addition, has been reported to cause false positive results with *M. tuberculosis* DNA-probe kits.[7, 12, 13] Correct identification is of importance since *M. celatum* is known to have low in-*vitro* susceptibilities to many antituberculous drugs [2, 3, 14] although the correlation between these and clinical outcome remains unclear. Furthermore, as evidence develops and therapeutic options increase, therapy for *M. celatum* infection may come to differ from therapy for other MOTT.

This report may serve to highlight that *M. celatum* can cause pulmonary infection in populations other than profoundly immunocompromised HIV-seropositive patients.

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Case Report

Entero-cutaneous-vesical fistula: an unusual presentation

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CASE REPORT A 75-year-old female patient presented with painless haematuria. IVP was normal and at cystoscopy a globular swelling found at the fundus of the bladder was resected. Histology revealed pan-mural inflammation with abundant submucosal oedema. The urothelium showed no evidence of dysplasia or malignancy. Two months later in the out patient clinic a periumbilical fistulous tract opened up spontaneously. On enquiry there was no history of altered bowel habit prior to or after resection of the bladder lesion. CT enema and small bowel series confirmed the presence of a fistula between the ileum, urinary bladder and the skin but the aetiology was not apparent. At laparotomy a transverse colonic mass adherent to a loop of ileum and the fundus of the bladder was found and resected. The bowel continuity was restored after dissecting off the bladder wall and the bladder closed in two layers. Histology revealed the mass to be a poorly differentiated colonic adenocarcinoma extending throughout the fistulous tract and invading the bladder. The patient developed bronchopneumonia and died on the 10th postoperative day.

COMMENT

The incidence of enterovesical fistulae is estimated at 3 per 10,000 hospital admissions.[1] Diverticula and malignant tumours of the colon are the most common aetiology. Carson *et al* reported an incidence of the various causes to be diverticulitis 51%, adenocarcinonia 16%, Crohn's disease 12% and primary bladder carcinoma 5%.[2] Gross haematuria is rare and recurrent cystitis with or without pneumaturia is frequently found. IVP is mandatory to exclude ureteral involvement. However, CT enema has the highest diagnostic yield. Spontaneous closure of the fistula occurs only in 2% cases and is most likely when trauma is the aetiology.[1] Good results are reported with a one-stage repair in a non- obstructed bowel with a mature fistulous tract. Having performed a comprehensive up to date literature search, to our knowledge this is the first case reported of an entero-cutaneous-vesical fistula.

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Case Report

Gastric Volvulus complicating Cerebral Palsy with Kyphoscoliosis

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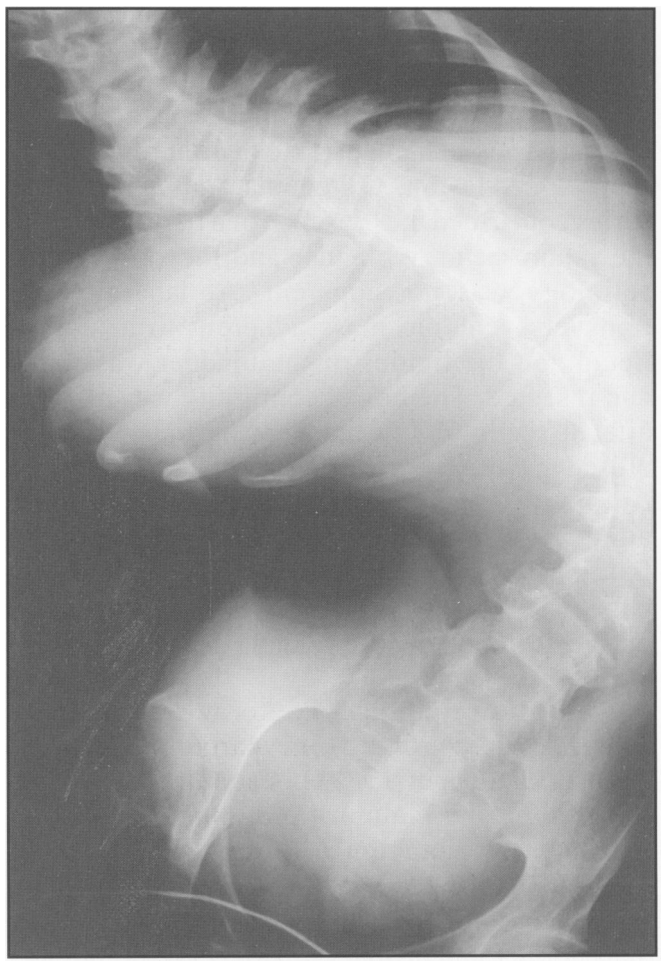
Acute gastric volvulus is a life-threatening condition associated with abnormalities of the stomach, surrounding viscera or spatial anatomy such as hiatus hernia (Millar *et al*, 1991). Our report of gastric volvulus highlights an aetiological association with severe secondary kyphoscoliosis. As cerebral palsy is the commonest cause of physical disability in paediatric patients, with high survival rates into adulthood (Hutton *et al*, 2000), it is essential that practitioners are aware of the potential complication, particularly given diagnostic difficulties in the presence of complex disabilities.

CASE REPORT An 18-year old male with mixed dystonic/spastic cerebral palsy, associated kyphoscoliosis, epilepsy treated with gabapentin, clonazepam and phenytoin, and oesophageal reflux treated with omeprazole, fed orally, presented to his local District General Hospital with twelve hours of laboured breathing, retching and hiccups. On admission he was shocked with a tender distended abdomen and tinkling bowel sounds. Severe kyphoscoliosis with distortion of anatomical landmarks made interpretation of his abdominal radiograph difficult. (Figure 1) A grossly distended gas filled viscus was interpreted as stomach and his condition improved with nasogastric (NG) aspiration of 1.5 litres of bile-free fluid. Laboratory investigations included normal glucose, electrolytes and amylase, with a mildly elevated urea. Blood and urine cultures were negative. The initial adult surgical opinion was acute gastric distension secondary to chronic duodenal ulceration or small bowel obstruction, and barium studies followed by oesophago-gastroduodenoscopy (OGD) were recommended. Pharmacy advice concluded that none of his drugs were aetiological factors. Barium studies revealed a normal duodenal cap with normal gastric emptying and movement of contrast. Feeds were restarted but acute obstruction recurred on day 9. OGD was performed on day 12. The adult



(Figure)

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gastroenterologist reported mild inflammation in the lower oesophagus and a normal stomach. When obstruction recurred on day 14 the telephone opinions of a paediatric surgeon and paediatric gastroenterologist were sought. These opinions, subsequently reinforced by the surgeon's clinical assessment, were that intermittent gastric volvulus was probable. Given the surgical risk, difficulty in establishing the diagnosis definitively, and the presence of deteriorating nutritional status, a palliative approach to management was agreed with the family. A therapeutic trial of gastrostomy tube insertion with the dual aims of providing a means of intermittent stomach deflation and stomach fixation by anchoring the stomach to the abdominal wall was proposed to overcome the presumed predisposition for volvulus recurrence. On day 27 a percutaneous endoscopic gastrostomy (PEG) tube was inserted under general anaesthetic without complication. At endoscopy the pylorus was noted to be cephalad consistent with increased stomach mobility. PEG feeding was introduced without complication and two years on, with no further episodes of gastric dilatation his family report a good quality of life.

DISCUSSION

Gastric volvulus is an abnormal rotation of the stomach about itself, either around a line between the pylorus and the oesophagogastric junction – organoaxial – or around the stomach's transverse axis – mesenteroaxial (Barr, 1994). We postulate that severe postural deformity resulting in intra-abdominal displacement can cause critical imbalance of the normal tensions between ligamentous attachments of the stomach, with secondary gastric hypermobility and volvular potential.

Presentation may be acute with complete obstruction, or chronic with partial obstruction. Prompt recognition and decompression are required to prevent infarction and perforation. While the classical Borchardt triad of unproductive retching, acute localised epigastric distension and inability to pass an NG tube is pathogmonic of complete obstruction (Cole and Dickinson, 1971), these signs are not always present and may be difficult to interpret especially in those with profound handicap.

Typically erect abdominal X-ray reveals a grossly dilated stomach with double fluid levels in the fundus and antrum, or a single air bubble with no additional bowel gas (Andiran *et al*, 1995). However, classical appearances may not be present with disturbed premorbid anatomy. Diagnostic difficulty was further compounded in this case by the intermittent nature of the recurrent presentation and unfamiliarity with the problem presenting in a profoundly disabled patient.

Normally definitive management includes surgical derotation and internal fixation. While the non-operative mortality of gastric volvulus is high, the risk of a major surgical procedure was unacceptable in our patient with his general debility. Cameron and Blair (1993) have reported a case of a neurologically impaired child with intermittent gastric volvulus managed with percutaneous gastropexy under combined laparoscopic and gastroscopic guidance while Tsang *et al* (1998) have described endoscopic PEG tube insertion to fix the stomach and provide a means of decompression in debilitated elderly patients. After consultation with the family of our patient PEG tube insertion was considered an acceptable option for a therapeutic trial.

There are important reasons to report this case. With increased survival of children with severe cerebral palsy into adulthood there is a need to heighten awareness of this potentially fatal complication arising in association with severe postural deformity. Further, where the patient's physical condition precludes definitive surgical management, the palliative option of PEG tube insertion offers a potentially life-saving option with the prospect of at least short term enhancement of quality of remaining life.

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Case Report

Squamous cell carcinoma of the bladder and prostatic urethra in a post renal transplant patient

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Carcinoma arising in the bladder following renal transplantation is extremely rare. We present a case of squamous cell carcinoma of the bladder and prostatic urethra in a post renal transplant patient and discuss the literature and management issues.

Immuno-suppressive treatments for transplantation interfere with host immunity predisposing to a variety of malignancies.[1] Lower urinary tract tumours are very rare accounting for only 2% of these malignancies.[2]

CASE REPORT An 80-year old male non-smoker who had undergone cadaveric renal transplantation for end-stage renal disease three years previously presented with irritative voiding symptoms and microscopic haematuria. His immunosuppression included cyclosporin for one year and tacrolimus subsequently. 27 years earlier he had undergone a left Orchidectomy for testicular seminorna and radiotherapy for para-aortic nodes. He was found to have microscopic haematuria six months following the transplantation, cystoscopy was normal. Flexible cystoscopy on current presentation showed yellowish tissue at the bladder neck. He developed acute urinary retention following this examination and underwent trans-urethral resection of this tissue in the bladder neck and prostatic urethra. Histological examination revealed moderate to poorly differentiated squamous cell carcinoma at

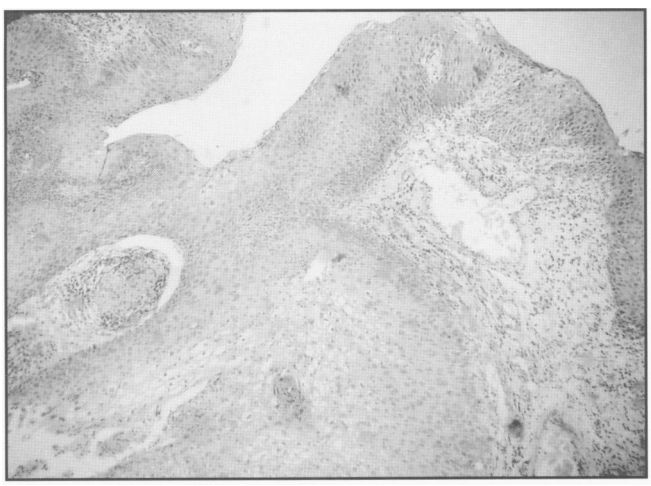

Fig 1. Squamous cell carcinoma at the bladder neck (Magnification X 30).

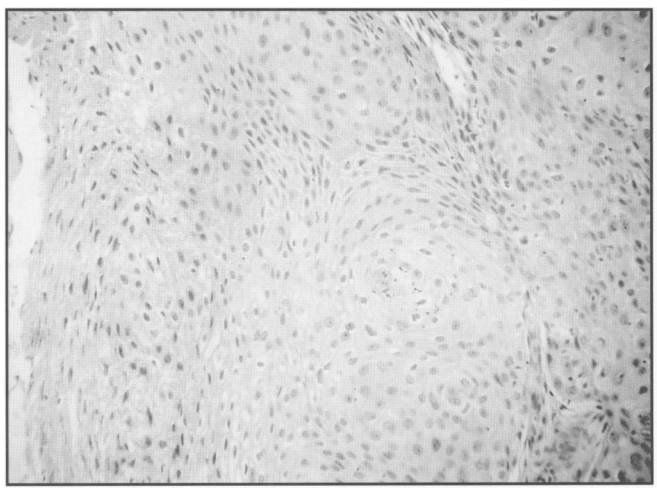

Fig 2. Infiltrating squamous cell carcinoma (Magnification X 120).

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the bladder neck infiltrating the prostate with squamous metaplasia and dysplasia in the adjacent urothelium (figs. 1, 2). Because of patient's age and co-morbidity, radical cystectomy was deferred and further palliative resection was done allowing successful voiding. He is currently maintained on low dose tacrolimus.

DISCUSSION

Host immunity is one of the well-known protective factors against carcinogenesis and immunosuppression interferes with this host ability. Rao and Anderson observed a 25% incidence of tumours during the second decade after transplantation.[1] Of newly diagnosed tumours in organ allograft recipients, 2% originate in the lower urinary tract according to the data from the Cincinnati transplant tumour registry.[2] There are few case reports of de-novo bladder carcinoma in renal allograft recipients. The most common type is transitional cell carcinoma, with squamous cell carcinoma being relatively rare.[3,4,5,6] Cyclophosphamide and azathioprine have been implicated in the aetiology of bladder cancer.[7,8]

The management of this tumour poses specific problems. Radical surgery would be needed in patients with high-grade invasive tumours. One should consider fate of the allograft and option of reconstructing reservoir or conduit for salvageable graft. Graft removal may be necessary to avoid the immunosuppression totally. An alternative option would be to modify immunosuppression such as discontinuing cyclophosphamide or reducing the dose of other immunosuppressants. There is no recognised standard approach and management should be tailored to the patient's medical condition in a multidisciplinary setting.

In our patient, the only identifiable risk factor is immunosuppression with tacrolimus and he has not been treated with cyclophosphamide. His immunosuppression is maintained with low dose tacrolimus without compromising graft function.

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Case Report

Acute osteomyelitis of the ilium mimics septic arthritis of the hip in children

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Osteomyelitis of the ilium is uncommon representing 2.3%[1] of all cases of acute osteomyelitis. It is far more common in children than in adults and the clinical features are similar to those of acute pyogenic arthritis of the hip joint. A lack of awareness of this clinical entity in the differential diagnosis of causes of pain around the hip means that physical examination is often inadequate and there are delays in obtaining the appropriate imaging studies. This leads to a delay in diagnosis, which is associated with significant and prolonged morbidity. We present two instructive cases of osteomyelitis of ilium in children and discuss the management of this uncommon condition.

CASE 1 A 13-year-old girl presented with a five-day history of left hip pain and difficulty in weight-bearing. There was no history of trauma. On admission her temperature was 38.2°C. She was tender over her left groin and iliac crest. Hip flexion was painful but she had no restriction of internal and external rotation. Initial investigations revealed a white cell count of $9x10^9$/L and ESR of 100 mm/hr. Plain radiographs of the pelvis and isotope bone scan were normal. Ultrasound scan was negative for an effusion within the hip joint. A CT scan of the pelvis showed periosteal elevation in the left ilium with an abscess in the iliacus and gluteus minimus muscles (fig.1). Percutaneous aspiration of the gluteal abscess was performed (fig. 2). Her blood and pus cultures were positive for Staph. aureus sensitive to flucloxacillin. Despite antibiotic therapy she remained febrile. Surgical drainage of the iliacus abscess was therefore undertaken through an apophysis-splitting sub-periosteal approach. She was treated with antibiotics for six weeks with complete resolution of her symptoms.

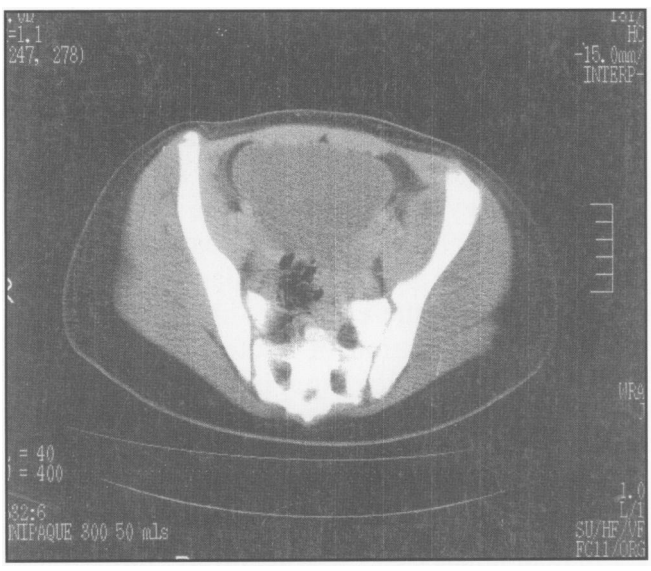

Fig 1. CT scan of the pelvis showing periosteal reaction left ilium and abscesses in the iliacus and gluteus minimus muscles.

CASE 2 A 10-year-old girl presented with an eight-day history of pain in the region of the left hip and low-grade pyrexia. She had a limp with difficulty in weight bearing. There was no history of trauma. Her temperature was 38°C and her left hip was held in flexion. She was tender over an area extending posteriorly from the greater trochanter to the gluteal region with pain on passive extension but none on internal and external rotation. Her white cell count was 14.5 x 10^9/L

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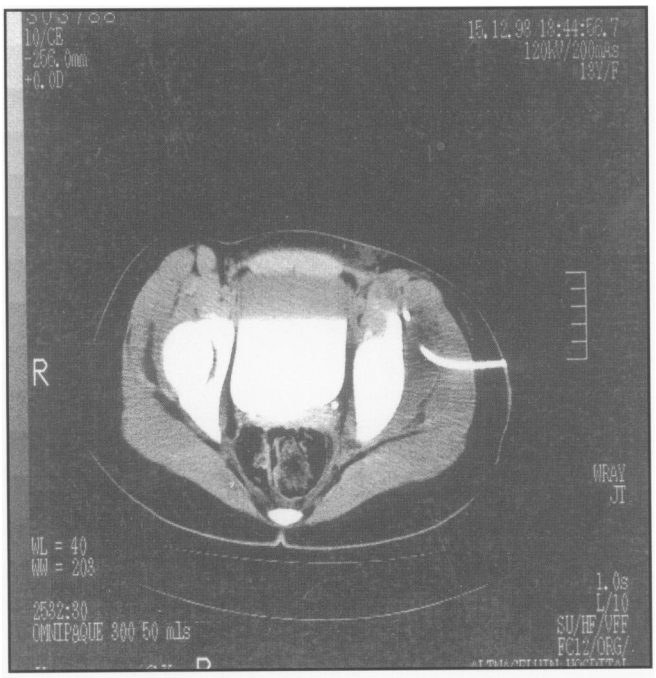

Fig 2. CT-guided percutaneous aspiration of gluteal abscess.

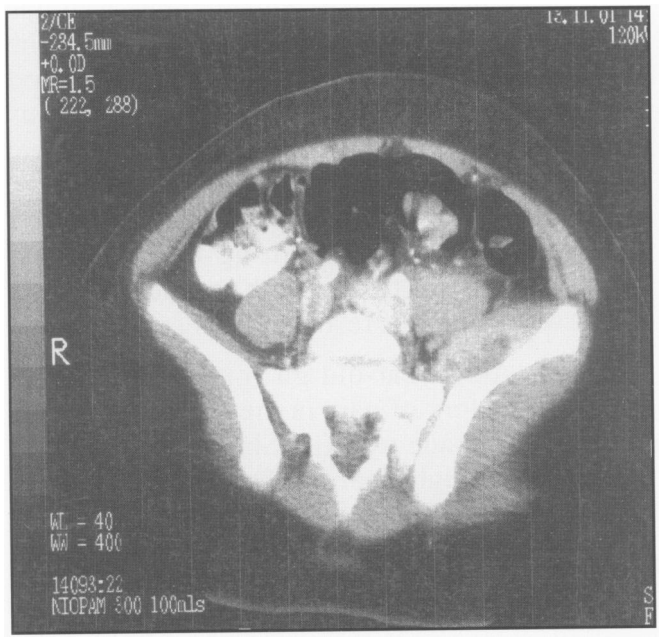

Fig 3. Contrast-enhanced CT scan of pelvis showing periosteal reaction left ilium and an iliacus abscess.

and CRP 102 mg/L. Plain radiographs and ultra sound scan of the hip joint were normal. CT scan showed periosteal elevation in the ilium with an abscess displacing the left iliopsoas muscle. (fig. 3). The abscess was drained and *Staphylococcus aureus* sensitive to flucloxacillin cultured from the pus. She was treated with antibiotics for six weeks and made a full recovery.

DISCUSSION

Osteomyelitis of the ilium is uncommon representing 2.3% of all cases of acute osteomyelitis.[1] It is far more common in children than in adults.[2,3] The clinical presentation is diverse, the major features being fever, pain, gait disturbance and limitation of movement around the hip joint. These are features suggestive of septic arthritis of the hip joint. The laboratory findings are also similar with the ESR and CRP both usually elevated. These can be used to monitor response to treatment.[4,5] The leucocyte count is raised in 65% of patients and blood cultures positive in 30-50%.[6]

The physical examination should help to distinguish between these two separate clinical entities. In osteomyelitis of the ilium it should be possible to put the hip joint through a relatively normal passive range of motion and if carefully sought a specific area of tenderness will be found. In septic arthritis of the hip, examination reveals the flexed abducted and externally rotated leg with an extreme reluctance to allow passive movement. Ultrasound will normally confirm the presence of a joint effusion with hyper-echoic synovial fluid and thickening of the joint capsule.[7]

Osteomyelitis of the ilium usually occurs through haematogenous spread of pathogenic organisms and in 95% of cases is caused by a single organism with Staphylococcus aureus causing 90% of infections in infants and children. Less commonly the infection is due to *Staph. epidermidis, Haemophilus influenza* and *Group B Streptococcus. Escherichia coli* and other gram-negative organisms may be the causative organisms in the neonatal period.[8,9] Plain radiographs and ultrasonography are not helpful in the diagnosis but are useful in ruling out hip joint pathology. Radioisotope bone scanning with Technetium-99 is sensitive in localizing areas of increased blood flow hence inflammation, but is non-specific and therefore is of limited diagnostic value in the situation of acute bone infection. Magnetic Resonance imaging (MRI) and CT scanning provide excellent anatomic detail and are therefore the investigations of choice in the diagnosis of osteomyelitis of ilium. MRI will show early intraosseous changes and small sub-periosteal abscesses.[10] CT scanning, though less sensitive in picking up early changes, is cheaper, more widely available and can also be used to guide percutaneous drainage (Fig. 2). A large

subperiosteal abscess may decompress into the surrounding tissues usually the iliacus and gluteal muscles. Surgical drainage is carried out via a retrofascial approach allowing access to the abscess without the risk of peritoneal contamination.

The choice of antibiotic is guided by bacteriological sensitivity but early empirical therapy is instituted with the most common causative organism (*Staph. aureus*) in mind.

The key problem in the management of osteomyelitis of the ilium is delayed diagnosis. This is generally the result of a lack of awareness of this clinical entity and leads to significant morbidity from spread to surrounding tissues, generalized sepsis and chronic infection requiring repeated surgical debridement and long term antibiotic therapy. The clinician must be prepared to look beyond pyogenic arthritis when considering the diagnosis in a patient presenting with acute pain in the area of the hip joint and systemic signs of infection. Meticulous physical examination and early use of the appropriate imaging studies will lead to an accurate diagnosis and the early institution of effective therapy.

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Case Report

Treatment of co-existing thoracic and abdominal aortic aneurysms using combined endoluminal stent grafts and conventional surgery

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We report three patients with a descending thoracic aortic aneurysm (DTAA) and a separate infra-renal abdominal aortic aneurysm (AAA) who had initial endovascular repair of the DTAA followed by repair of AAA. Endovascular stent repair of DTAA avoids the significant morbidity associated with thoracotomy and open repair. Hence more patients with multilevel aortic aneurysm may be eligible for surgical intervention. Aortic aneurysms most often present as a confluent dilatation, either of the thoracic, the thoraco-abdominal or the infra renal abdominal aorta. Co-existing multilevel aortic aneurysms are present in a small subgroup of patients. Of these, the combination of infra-renal abdominal aortic aneurysm (AAA) and an aneurysm of descending thoracic aorta is the most frequently encountered.[1] The usual method of open repair of these aneurysms is through simultaneous or sequential thoracotomy and laparotomy, which is associated with significant morbidity and mortality.

Endoluminal treatment of infrarenal AAA and descending thoracic aorta aneurysm (DTAA) is now feasible as an alternative to conventional open repair. This is especially true for the repair of DTAA. We report three patients with a descending thoracic aneurysm and a separate infra-renal AAA who had initial endovascular repair of the DTAA followed by repair of AAA.

CASE REPORT

Case 1 A 70-year-old woman with an AAA was suspected to have a concomitant thoracic aneurysm on her chest x-ray. This was confirmed with contrast enhanced spiral CT scan which also allowed detailed evaluation of the aneurysm for

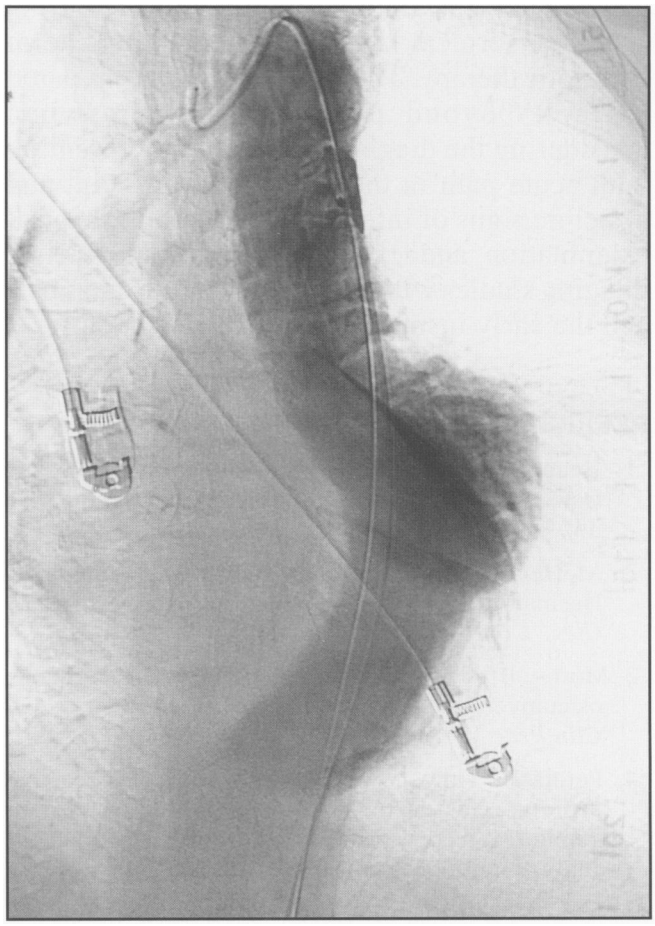

Fig 1. Intraoperative angiogram delineating the DTAA proir to stent graft placement.

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endovascular repair. It confirmed the presence of a saccular DTAA measuring 70mm in maximum diameter and 110mm in length. The aneurysm commenced 35mm distal to the left subclavian artery, terminating 40mm proximal to the coeliac axis. The diameter of the aorta distal to this aneurysm was 33mm, whilst the aorta at the left subclavian was 29mm. The infrarenal AAA was 56mm in maximum diameter, and was found unsuitable for endovascular repair due to a short conical neck.

The patient subsequently underwent endovascular stent-graft repair of the DTAA, using two modular stent-grafts, each 40mm diameter, 100mm long (Talent, Medtronic). The stent-graft was passed via the right common femoral artery which was exposed surgically. Imaging was performed through a catheter positioned in the arch of the aorta, inserted percutaneously through the left femoral artery. An intra-operative angiogram showed complete exclusion of the thoracic aneurysm with no endoleak. The post-operative period was uneventful. A follow-up CT scan six weeks later demonstrated the stent to be in a satisfactory position, with no evidence of endoleak. The abdominal aortic aneurysm was then repaired using a retroperitoneal approach with an 18mm tube graft. A repeat CT scan at one year revealed a satisfactory repair with no endoleak.

Case 2 A 78-year-old man was found to have a large abdominal and thoracic aortic aneurysm during investigations for prostatic symptoms. Subsequent contrast enhanced CT scan showed a DTAA 56mm in maximum diameter, 150mm in length, arising 90mm distal to the left subclavian artery. The upper abdominal aorta was normal in caliber. The infrarenal AAA measured 90mm in diameter. Angulation and conicity of the infrarenal neck made it unsuitable for endovascular repair. In addition, there were bilateral common iliac aneurysms measuring approximately 45mm in diameter, with the left iliac aneurysm extending into the internal iliac artery.

The thoracic aneurysm was repaired first using three 40mm diameter stent-grafts (Talent, Medtronic), each 150mm in length, inserted through a surgically exposed right common femoral artery. Imaging was again performed using a catheter passed percutaneously via the left femoral artery. A completion intraoperative angiogram showed no evidence of endoleak.

Due to a post-operative chest infection, the repair of the AAA was deferred for two months. This was then repaired through a transperitoneal approach using a bifurcated graft anastomosed distally to the origins of both external iliac arteries. The right internal iliac artery was revascularised using a 6mm Dacron graft from the left limb of the bifurcated graft. At 12 months the patient remained well and repeat CT scan of the chest showed no endoleak.

Case 3 A 76 year-old man was detected as having a DTAA and an AAA following investigation of a heart murmur. The thoracic aneurysm measured 68mm in maximum diameter, arising 50mm distal to the left subclavian artery. The diameter of the aorta below the aneurysm was 35mm. The infrarenal AAA measured 59mm in maximum diameter, with a 15mm parallel neck distal to the origin of the renal arteries. This was deemed suitable for endovascular stent-graft repair.

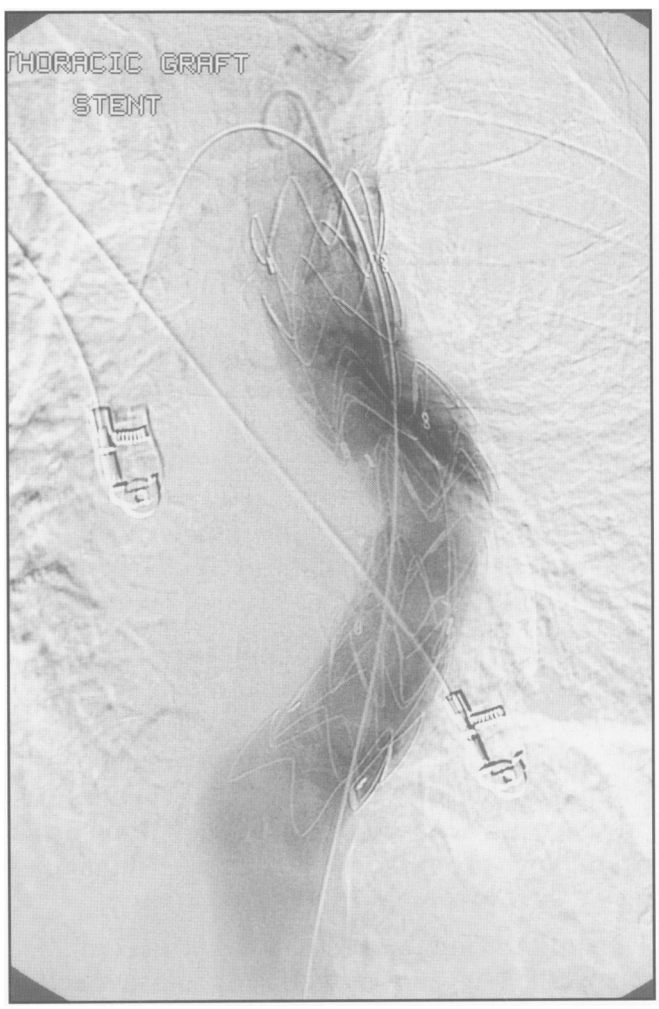

Fig 2. Intraoperative angiogram showed exclusion of DTAA after stent graft deployment.

The thoracic aneurysm was repaired using two 42mm diameter x 96mm stent-grafts (Talent, Medtronic) using the same technique as described above. Intraoperative completion angiography showed no evidence of endoleak. The AAA was repaired six weeks later using an endovascular bifurcated stent-graft system (Talent, Medtronic). It was inserted through the common femoral arteries after surgical exposure. No endoleak was detected at intraoperative angiography. A follow-up CT scan three months later showed no evidence of endoleak in either DTAA or AAA.

DISCUSSION

The coexistence of a DTAA in patients with AAA continues to pose problems in relation to the type of repair employed, and the option of simultaneous or sequential repair. Conventional open repair of the thoracic aneurysm carries a high rate of morbidity and mortality. Many of these patients have significant co-morbidity, rendering them ineligible for such open repair.[1]

The endovascular stent-graft was initially introduced for the repair of abdominal aortic aneurysm. In 1992, Dake *et al* reported the use of an endovascular stent-graft for the repair of DTAA.[2] With recent widespread use, the feasibility of this less invasive surgical alternative is now well established, despite the uncertainties over its long-term durability. The repair of synchronous aneurysms of the descending thoracic aorta and the abdominal aorta can be carried out simultaneously, or sequentially, with an interval of a few weeks. In sequential repair, although each operative episode is shorter, a small risk of rupture of the remaining aneurysm exists in the inter-operative period.[1] In asymptomatic patients, the DTAA which is considered the 'greater of the two evils' is stented first.

Paraplegia is a known complication with both conventional and endovascular repair of DTAA. However, in endovascular repair, the incidence of paraparesis is less than in conventional repair.[2,3] Endovascular repair of DTAA, even in the presence of severe co-morbid conditions, has been shown to be associated with good immediate results and low morbidity and mortality.[2]

The reported numbers of patients with combined repair of DTAA and AAA is small,[4] but favourable results have so far been reported when endovascular repair is utilized for one or both aneurysms.[1,4,5] The above three cases support the technical feasibility of treating these patients with endovascular repair of at least the thoracic component. The long-term durability of the thoracic stent-graft system for the exclusion of the aneurysm is yet to be established. However, endovascular repair provides an option of treating patients with multilevel aortic aneurysm, even in those who are otherwise unfit for conventional thoracic surgery. The availability of endovascular stenting should therefore increase the number of patients with DTAA and AAA that will be suitable for surgical intervention.

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Book Reviews

Familial Breast and Ovarian Cancer: Genetics, Screening and Management. Patrick J Morrison, Shirley V Hodgson, Neva E Haites. Published November 2002. ISBN 0 521 80373 X (hardback). £65.

This text book is a timely publication and it gives a splendid overview of the genetics and management of familial breast and ovarian cancer. The book is edited by Professor Morrison and his colleagues and they have drawn together a national and an international list of contributors well respected in their fields. The book begins with a series of book chapters on molecular biology of these tumours.

There then follows a further six chapters discussing screening for breast and ovarian cancer. Herein are a number of very important and up to date guidelines.

The final eight chapters discuss the management for patients with these difficult familial problems. The latter two chapters give a glimpse into the future discussing new therapies including gene therapy.

The book is well written in a uniform style despite the number of contributors. The two familial tumours are discussed in great detail and the chapters on management are practical, up to date and well referenced.

This book will be of interest to a wide range of specialists who are involved in managing these patients who require careful counselling. Colleagues managing patients with these cancers and their families will find this book to be of great benefit including nurses, counsellors, psychologists, surgeons, gynaecologists and geneticists.

The latter two sections of book will also be of interest to family doctors. The contributors, editors and indeed publishers are to be praised for their rapid speed of writing and subsequent publication. The references are up to date, timely and appropriate. The references are mostly 1990's up to the year 2000 with a sprinkling here and there of 2001 references, despite the publication date of the book being 2002.

This book will require a new edition within two years in such a rapidly changing field. Two small suggestions which may help the next edition would be either a chapter, or alternatively an appendix describing some of the more technical genetic phrases and their meaning. This would widen the scope and the readership of this book.

A second helpful chapter or an appendix would contain an up to date listing of what genetic tests are available for the various cancers and how widely they are available (ie generally available or only as a research tool) and some idea of their costs.

These are relatively minor points which the editors may wish to take on board for the next edition. I can recommend this book thoroughly to colleagues looking after patients with breast or ovarian cancer and their families.

Colleagues throughout the profession from a wide range of disciplines will find much in this book to interest them and will help them guide and manage their patients through the difficult decision journey of familial cancer

R A J SPENCE.

Gastrointestinal Emergencies. Tony CK Tham and John SA Collins. BMJ Books. ISBN 0-7279-1485-5. www.bmjbooks.com

The authors pitch this compact book at those practitioners who have no specialty training in gastroenterology but may nonetheless be faced with gastrointestinal emergencies. It is essentially a reference source for emergency management pending the early attention of a GI surgeon or physician. The book is divided into three sections, approaching in turn presenting symptoms, organ-specific conditions, and complications of GI procedures. The last in particular should be compulsory reading for all those, junior and senior, who request an ERCP with the same nonchalance that they might an ESR. Most PEG tube complications will present themselves in units outside gastroenterology, and there is a useful chapter on the subject here.

Specialists may nitpick details but there is little to criticise. In the interim between the authors' final draft and publication, MRI cholangiography has rapidly progressed from its "as yet undefined" role to rendering the diagnostic ERCP virtually obsolete, and no doubt will gain more detailed appraisal in the next edition. The statement that barium swallow is the preferred initial diagnostic test for dysphagia is outdated: the early OGD for the patient with dysphagia is safe, potentially therapeutic, and one of the few situations where the upper GI endoscopist approaches the procedure without a sense of impending futility.

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