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Case Reports

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The Ulster Medical Journal, Volume 69, No. 2, pp. 83-89, November 2000.

The declining autopsy rate and clinicians' attitudes

M B Loughrey, W G McCluggage, P G Toner

Accepted 5 May 2000

SUMMARY

The autopsy rate has been declining worldwide for decades. This study determined the overall and differential autopsy rates for the Royal Victoria Hospital, Belfast for the years 1997-1999 inclusive. Trends were examined by comparison with previously collected data for the years 1990, 1991 and 1993. Reasons for the decline in autopsy rates as perceived by hospital clinicians were assessed by means of a questionnaire. Over the last decade, there has been a steady decline in the overall autopsy rate from 30.4% in 1990 to 18.4% in 1999. This is due to a decrease in the hospital autopsy rate from 21.6% in 1990 to 7.9% in 1999. The coroner's autopsy rate has remained comparatively unchanged at around 11%. The decline in the overall and hospital autopsy rates involves all of the principal bedholding directorates, but is most dramatic in medicine, surgery and intensive care, where hospital autopsy rates are currently 7% or less. The main reasons for this decline as perceived by clinicians are difficulty in obtaining consent from relatives and advances in modern diagnostic techniques. The findings of this enquiry are in keeping with trends elsewhere, despite repeated studies which clearly demonstrate the continuing value of the autopsy in clinical practice. Recent publicity concerning the retention of organs can only have an adverse affect. Pathologists and clinicians who value the autopsy must become actively engaged in both public and medical education. Renewed emphasis must be placed on the importance of the autopsy in teaching, training and clinically relevant research, and as a means of medical audit.

INTRODUCTION

Autopsies performed by hospital based pathologists fall into two categories. Hospital or non-coroner's autopsies require the consent of relatives and are requested by clinicians in a variety of situations. Medicolegal autopsies are performed on behalf of local coroners, who may request an autopsy for various reasons. Relatives' consent for a coroner's autopsy is not required. With regard to deaths occurring outside hospital, only in the minority of cases reported to the coroner will there be any likelihood of an autopsy. General practitioners do not normally request autopsy permission and indeed generally do not have contractual access to a routine autopsy service. The adverse connotations associated with the coroner's autopsy may encourage general practitioners to issue a death certificate in cases where there is only circumstantial evidence of the underlying cause of death. Overall, therefore, in numerical terms, autopsies on hospital patients remain the principal source of pathologically verified causes of death and any decline in autopsy practice within hospitals is a matter for concern.

The autopsy rate in hospitals has been declining for decades, a fact which has been documented both worldwide and locally.[1-3] There are many reported reasons for this decline.[4,5] The situation is obviously complex, but it has been suggested that the most important single factor is the level of interest amongst individual consultant clinicians.[6,7] In this study we examined figures for adult autopsy rates in the Royal Victoria Hospital (RVH), Belfast, over the last three years. These figures were compared with records which were available for the years 1990, 1991 and 1993. In addition we circulated a questionnaire among consultant clinicians in an attempt to investigate local attitudes to the decline in the autopsy rate.

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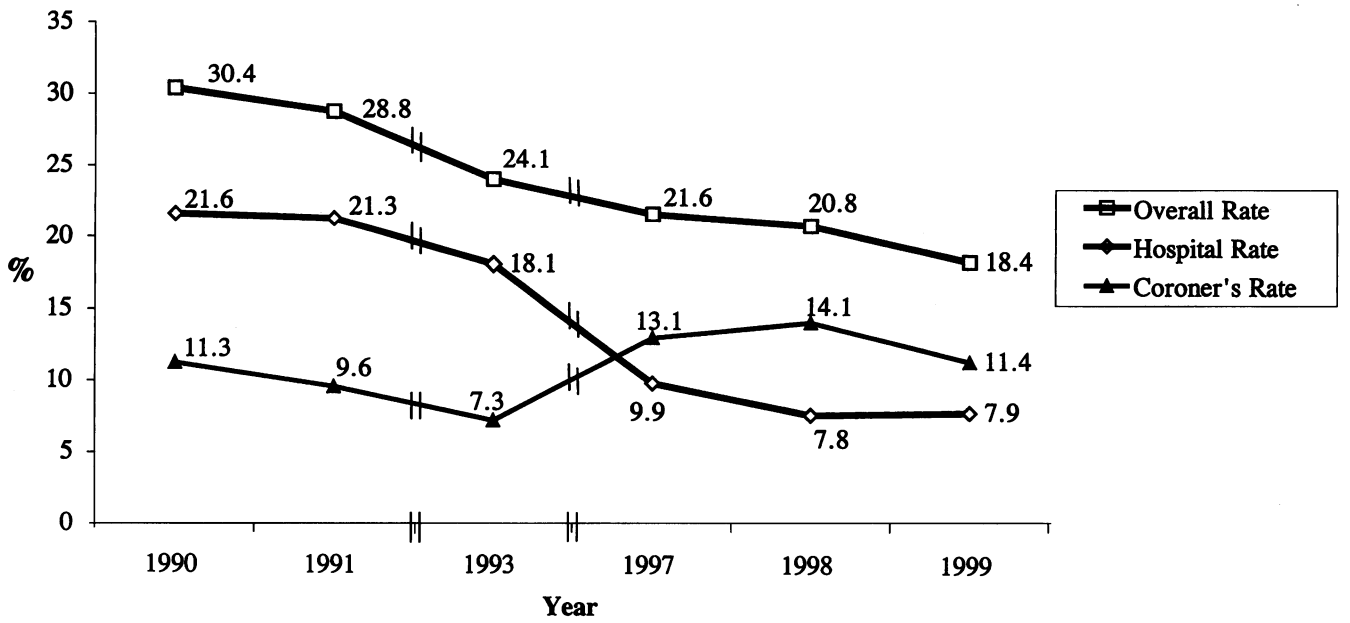
Fig 2 Autopsy rates per year – overall and differential



METHODS

We identified all hospital deaths occurring in the RVH in the years 1997-1999 inclusive. These data were retrieved from the hospital Patient Administration System (PAS) and from log books held within the hospital mortuary which contain a record of all hospital deaths and of all autopsies performed. Deaths occurring in the Royal Maternity Hospital and the Royal Belfast Hospital for Sick Children were excluded.

The overall autopsy rate was calculated, as well as the coroner's and hospital autopsy rates. These are known as the differential autopsy rates. In this study, the coroner's autopsy rate is defined as the total number of coroner's autopsies divided by the total number of deaths. The hospital autopsy rate is defined as the total number of hospital autopsies divided by the total number of deaths, excluding those cases which underwent a coroner's autopsy. This is because it cannot be assumed that, in a case which underwent a coroner's autopsy, a hospital autopsy would not have been asked for had the coroner not intervened. The autopsy rates were determined for the hospital as a whole, and also for each individual bedholding directorate. Patients were assigned to directorates according to the consultant in charge at the time of death. These records were already available for the years 1990, 1991 and 1993. The directorate structure within the hospital has not changed significantly within the period of this study.

The second part of the study involved examining clinicians' attitudes towards the autopsy by means of a questionnaire circulated among consultant clinicians within the RVH who have access to the autopsy facility. Clinicians were asked to score each of nine possible factors, using a visual analogue scale from 0 to 9, according to how important they felt was its contribution towards the decline in the autopsy rate (fig. 1). These statements were adapted from relevant literature published on this subject.[4,5] Mean scores were calculated for each factor. Respondents were also given the opportunity to express any additional comments. Since replies were anonymous, variations in response between individual directorates could not be examined.

RESULTS

Table I shows, for each year included in the study, the total numbers of hospital deaths; the total numbers of autopsies performed, with their breakdown into coroner's and hospital categories; and the overall and differential autopsy rates. There has been a steady decline in annual total autopsy numbers from 281 in 1990 to 169 in 1999, with only minor variations in the numbers of hospital deaths, which ranged from 827 to 923 per year. Examination of the numbers of coroner's and hospital autopsies reveals the changing pattern in autopsy practice, with a greater proportion of coroner's autopsies and a marked decline in the hospital autopsy rate. The overall and differential autopsy rates are demonstrated graphically in

TABLE I

Total numbers of hospital deaths, numbers of autopsies and autopsy rates per year

Year	*Total Deaths*	*Autopsy numbers*			*Autopsy Rate (as % of deaths)*		
		Total	*Hospital*	*Coroner's*	*Overall*	*Hospital*	*Coroner's*
1990	923	281	177	104	30.4	21.6	11.3
1991	874	252	168	84	28.8	21.3	9.6
1993	827	199	139	60	24.1	18.1	7.3
1997	850	184	73	111	21.6	9.9	13.1
1998	849	177	57	120	20.8	7.8	14.1
1999	920	169	64	105	18.4	7.9	11.4

TABLES II-IV

Overall and differential autopsy rates as % of deaths per year for each directorate of the Royal Victoria Hospital

* Small numbers of deaths in ENT and opththalmology preclude meaningful interpretation

TABLE II

Overall Rate as % of Deaths

Directorate	*1990*	*1991*	*1993*	*1997*	*1998*	*1999*
Surgery	39.2	31.3	21.2	28.3	20.2	23.6
Medicine	19.1	19.3	22.5	13.5	12.2	11.8
Neuroscience	62.7	41.7	37.7	42.6	35.3	46.2
Cardiothoracic	40.5	38.6	29.9	19.7	27.1	20.0
ICU	51.9	51.9	21.2	41.1	39.2	25.9
*ENT	9.5	0	6.7	0	20	0
*Opththalmology		0	0	100	0	0
Entire Hospital	30.4	28.8	24.1	21.6	20.8	18.4

TABLE III

Hospital Rate as % of Deaths

Directorate	*1990*	*1991*	*1993*	*1997*	*1998*	*1999*
Surgery	23.1	20.2	11.9	13.2	4.6	6.9
Medicine	16	15.3	17.8	7.6	5.7	6.1
Neuroscience	50	36.4	26.7	25.0	10.8	22.2
Cardiothoracic	36.3	31.7	26.2	12.1	17.3	12.2
ICU	19.6	30.9	11.8	9.9	8.1	7.0
*ENT	9.5	0	6.7	0	11.1	0
*Opththalmology		0	0	0	0	
Entire Hospital	21.6	21.3	18.1	9.9	7.8	7.9

TABLE IV

Coroner's Rate as % of Deaths

Directorate	*1990*	*1991*	*1993*	*1997*	*1998*	*1999*
Surgery	20.9	13.9	10.6	17.4	16.3	17.9
Medicine	3.7	4.7	5.7	6.4	6.9	6.1
Neuroscience	25.4	8.3	15.1	23.4	27.5	30.8
Cardiothoracic	6.6	10.0	5.1	8.7	11.9	8.9
ICU	40.3	30.4	10.6	34.7	33.8	20.3
*ENT	0	0	0	0	10	0
*Opththalmology		0	0	100	0	
Entire Hospital	11.3	9.6	7.3	13.1	14.1	11.4

FIGURE 1.

Nine statements were presented in a questionnaire to consultant clinicians, who were asked to score each from 0 to 9, using a visual analogue scale, according to how important they felt was its contribution towards the decline in autopsy rate. Mean scores are shown and the statements ranked according to perceived importance.

	MEAN SCORE	
1.	5.8	Difficulty obtaining consent from relatives because of their perceptions of the autopsy.
2.	5.5	Advances in modern diagnostic techniques reducing the need for autopsy.
3.	4.7	Unavailability of reports in "clinically relevant time" i.e. excessive time lapse between patient's death and receiving report.
4.	4.6	Lack of direct feedback between pathologist and clinician at the time of autopsy.
5.	3.9	The lower profile of the autopsy in the medical undergraduate curriculum.
6.	3.7	Inconvenience and inability to view autopsy material.
7.	2.9	Lack of enthusiasm for autopsy practice shown by pathologists.
8.	2.4	Increasing fear that unexpected autopsy findings may lead to litigation.
9.	2.0	Lack of satisfaction with the quality, content or format of reports.

figure 2. Over the decade, the overall autopsy rate has dropped from 30.4% in 1990 to 18.4% in 1999. This is due to the decrease in the hospital autopsy rate, from 21.6% in 1990 to 7.9% in 1999. The coroner's autopsy rate has remained relatively unchanged over this period at approximately 11%. Tables II-IV show the overall and differential autopsy rates within each directorate for the years studied. The fall in both overall and hospital autopsy rates affected even the neurosciences and cardiothoracic directorates, where autopsy rates are generally higher than average. The decline, however, was most dramatic in the medical, surgical and intensive care directorates, where hospital autopsy rates are currently only 7% or less.

QUESTIONNAIRE DATA

Of 71 questionnaires circulated, 32 replies were received, giving a response rate of 45%. The mean scores for each factor are as shown in figure 1, and the factors are ranked according to the overall perceived order of importance. Additional comments were invited and were offered by 60% of respondents.

DISCUSSION

This study confirms the progressive decline in the overall and, more specifically, the hospital autopsy rate within the Royal Victoria Hospital, Belfast. This is in line with the rest of the United Kingdom and with general experience elsewhere.[1,2] The most important reason for this decline, as perceived by consultant clinicians, is increasing difficulty in obtaining consent from relatives for a hospital autopsy. Comments suggested that consent was often declined because of a possible delay in the funeral, or a negative

view of the autopsy held by the relatives. This negative perception has perhaps resulted from the lack of involvement of the general public in dialogue concerning the autopsy.[8] Relatives may not appreciate the benefits of an autopsy and may prefer to "maintain the physical dignity" of their loved one, rather than determine the exact cause of death. It might be expected that recent controversy in the media regarding the retention of organs at autopsy will exacerbate this problem. The Royal College of Pathologists is currently considering this matter, with particular focus on modification of the consent format to include allowance for organ or tissue retention in appropriate cases and to ensure fully informed consent. Contributing to the problem is the fact that seeking consent for hospital autopsies still usually falls to the more junior members of the medical staff, who may "sign off" death certificates because no instructions have been left by the consultant that an autopsy should be requested. It has been previously shown that the approach used by clinicians to obtain consent affects the likelihood of a positive response from the relatives.[9, 10] If the clinician concerned is not convinced of the worth of an autopsy, this can only reduce the chances of obtaining a positive response from the relatives. Techniques of communication with the bereaved should be improved, a matter which should be addressed at both an undergraduate and postgraduate level.[11] A summary of the uses of the autopsy should be available in all clinical units (figure 3).

FIGURE 3

A summary of the main uses of the autopsy.

Post mortems are carried out primarily to determine the cause of death. They are important tor many reasons: -

Quality of Care

To assess the accuracy of clinical diagnosis
To assist in the audit of clinical care
To assist in counselling the bereaved

Quality of Statistics

To enhance the accuracy of death certification
To improve the quality of the Registrar General's cause of death statistics, for health services planning and epidemiology

Teaching and Training

To assist in medical undergraduate teaching
To assist in postgraduate medical training in all specialties
To assist in the professional training of pathologists

Research and Development

To advance medical research in the clinical, pathological and basic medical sciences
To validate new diagnostic procedures
To monitor the effectiveness and side effects of new medical and surgical therapies

Medico-Legal

To assist in the detection of crime
To assist the courts in legal actions for compensation for industrial injury or negligence

The second commonest reason cited by clinicians for the decline in the autopsy rate is the considerable advance in modern diagnostic techniques. Modern radiological methods of imaging and the ability to obtain tissue samples from deep-seated lesions either by trucut biopsy or fine needle aspiration have resulted in an antemortem diagnosis of malignancy in many cases where this would not previously have been possible. This has had a major effect on autopsy rates, notably within the surgical directorate, where a large number of deaths are due to advanced malignancy, in which a tissue diagnosis has already been made. In cases where the underlying diagnosis is thought to be reasonably clear, an autopsy rarely seems justified to clinicians. However, even where a primary diagnosis of malignancy is known, it has been shown that autopsy can often reveal unsuspected conditions and complications, particularly post-surgery, from which lessons can still be learned which are of relevance to the care of others.[12] Despite continuous improvements in diagnostic techniques, studies over a number of decades continue to show a surprisingly consistent rate of significant discrepancies between antemortem and postmortem diagnoses.[13-15] Major discrepancies, although difficult to define, occur in around 10% of cases. With the constant introduction of new investigative and therapeutic procedures, the autopsy remains of fundamental value in monitoring their efficacy and complications.

The next most important perceived factors relating to the declining autopsy rate were the unavailability of the autopsy report in "clinically

relevant time" and a lack of direct feedback between pathologist and clinician at the time of autopsy. These were felt to be more important than the ability to view autopsy material directly. The quality of autopsy reports was not felt in general to be a problem, this statement receiving the lowest mean score, although there was occasional dissatisfaction with inconsistencies between the clinical course and the pathological findings. In addition, the clinicopathological correlation was sometimes deemed to be inadequate, with little attention paid to points of clinical interest. There have been previous reports documenting the inadequacies of communication between pathologist and clinician with regard to autopsies.[16] Direct contact before the autopsy, or improved completion of autopsy request forms, a task again usually left to the most junior medical staff, could help to ensure that the autopsy addresses the issues which interest the clinician, as well as simply recording pathological findings consistent with a cause of death. This would result in improvements in the clinicopathological correlation in the final autopsy report. On the part of the pathologist, the time taken to produce the final autopsy report should be reduced, and communication of the gross autopsy findings to the clinician should be improved. This can usefully be supplemented in appropriate cases by rapid diagnostic histology of selected sections.[17] In all cases, there should be direct contact between pathologist and clinician immediately following the autopsy, not least because relevant autopsy findings can be of assistance in counselling the bereaved.

The role of autopsy pathology in the new undergraduate medical curriculum has declined; many clinicians commented that they were unaware of this change. Many junior doctors have never attended an autopsy, while in general practice there is no tradition of autopsies by consent.[18] There is therefore an ever greater need for medical education at undergraduate and postgraduate level, to focus on the value of the autopsy as a useful investigative and teaching tool and as a means of medical audit. Autopsies provide excellent educational resources for interested clinicians at clinicopathological conferences. Many subscribers to this Journal will be aware of the long-established local tradition established by Sir John Henry Biggart, who is commemorated in the award of the Biggart Trophy at a major clinicopathological conference held annually by the Ulster Medical Society, under the auspices of the Royal College of General Practitioners. One of the present authors has participated in this event for the past fifteen years and, over this period, the challenge presented by these autopsy-based conferences has never failed to stimulate participants and audience alike.

Lack of enthusiasm for autopsy practice amongst pathologists and fears of litigation were not perceived as important reasons for the decline in the autopsy rate. The latter is perhaps surprising in these days of increased public and medical awareness of malpractice litigation.

In conclusion, the overall autopsy rate within hospitals continues to decline, mainly as a result of reduced numbers of hospital autopsies. The main reasons for this are perceived by clinicians to be difficulty in obtaining consent from relatives and advances in modern diagnostic techniques. With increasing media attention focusing on the retention of organs and tissues, consent may become more difficult to obtain. In the modern era of clinical governance and medical audit, we must not lose sight of the fundamental contribution which the autopsy makes to medical training and to quality assurance in clinical care. Action and commitment will be required from both pathologists and clinicians if the autopsy is to maintain its position as the "ultimate audit".

† The Royal College has recently produced a comprehensive publication dealing with these and related issues (Ref 19).

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Paediatric renal transplantation in Northern Ireland (1984-1998)

C Mayes, J M Savage

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SUMMARY

Over the last 20 years a comprehensive paediatric nephrology service has been developed in Northern Ireland, based in the academic medical unit at the Royal Belfast Hospital for Sick Children (RBHSC). In the 15 years 1984-1998 a total of 77 renal transplants have taken place in patients aged 18 years and under. Initially transplants were only considered in children over five years of age but in the past eight years children as young as two years have successfully received kidneys. Aggressive nutritional support combined with peritoneal dialysis has enabled survival to a size when transplantation is feasible. The 5 year graft survival was 64%, with two children dying following transplantation. The complexity of managing this age group is reflected by the fact that a total of 10 transplants (13%) failed in the first 30 days. These figures compare favourably with statistics reported by similar paediatric centres from across the United Kingdom and Republic of Ireland, and with local results in adult patients. This demonstrates that a successful end stage renal replacement programme for children is achievable in a relatively small population, which is geographically isolated.

INTRODUCTION

Paediatric renal transplantation began in Northern Ireland in 1980. Despite clinical experience being limited by a relatively small population, long term graft and patient survival rates are comparable to other centres throughout the UK and Republic of Ireland. This represents a beneficial initial sharing of adult nephrology expertise with the paediatric team, and subsequent development of the ability to manage independently even the smallest child with renal failure.

METHODS AND PATIENTS

Data was provided by the United Kingdom Transplant Support Service Authority from the national transplant database. All patients 18 years and under at the time of renal transplantation in Northern Ireland between the years 1984 and 1998 inclusive were included. Information was collected relating to primary diagnosis, donor and recipient age, waiting time on the transplant list, organ refusal, graft and patient survival, cause of graft loss and growth parameters post transplant.

RESULTS

From 1984-1998 a total of 77 cadaveric renal transplants have taken place in Northern Ireland in patients 18 years of age and under. The commonest primary diagnosis was reflux nephropathy in 31 cases (40.3%), eight cases were caused by hereditary nephropathy (10.4%) and seven by glomerulonephritis (9%). Five (6.5%) cases were caused by congenital renal hypoplasia or dysplasia and one (1.3%) by each of the following – infantile polycystic kidney, medullary cystic disease, Alports disease and cystinosis. 22 cases were classified in the national transplant database as other diagnosis and not

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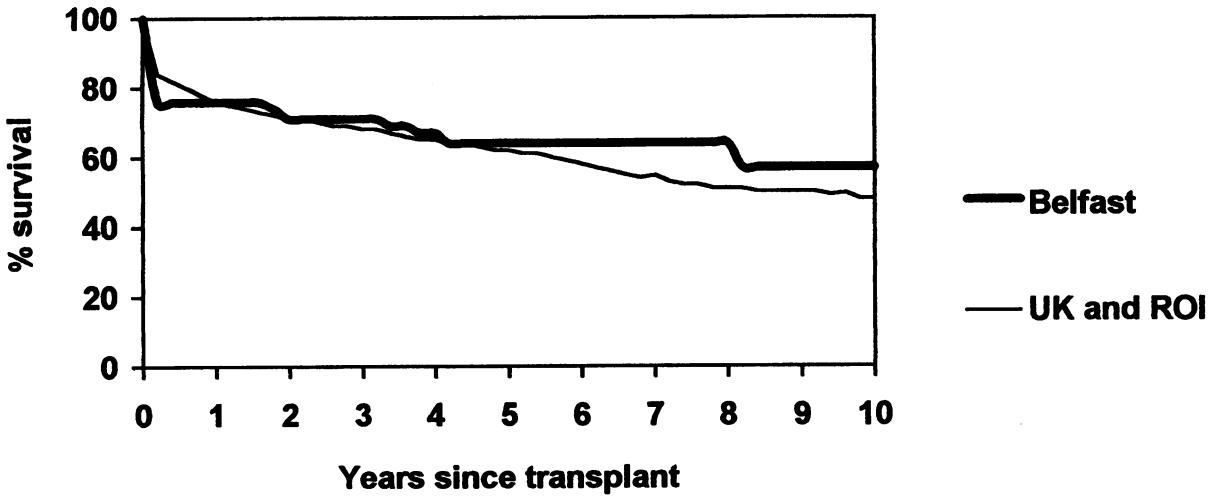

Fig 1. 10 year transplant survival plot for first cadaveric paediatric kidney grafts since 1984, Belfast v rest of UK and Republic of Ireland (ROI).

further specified. The five year graft survival was 64% (fig.1).

From 1984-1988 inclusive 15 donors (68% of donors for this 5 year period) to paediatric recipients were order then 18 years. In 1989-1993 10 donors (43% of donors for this 5 year period) and in 1994-1998 nine donors (28% of donors for this 5 year period) were adults. 23 donors in the period 1994-1998(72% of donors for this 5 year period) were 18 years or less with 17 (53%) in the 5-14 age group.

In the period 1984-1990 all recipients were older than 5 years of age. From 1990-1998 nine transplants took place in the age group 2-4 years, none have taken place in recipients less than 2 years of age.

In 1984-1988 twenty-two patients waited on the transplant waiting list for a median time of 87 days, in 1989-1993 twenty five waited for a median time of 182 days and from 1994-1998 thirty patients waited a median time of 316 days for transplant.

One hundred and seventeen offers of organs were refused from 1984-1998. The commonest reason in 66 cases (56%) was an inadequate tissue match. Eight offers (6.8%) were rejected because the recipient was unfit, and eight because of lack of resources; 18 (15.4%) were not used because of problems related to donor age, size or history. In four (3.4%) cases the ischaemic time was unfavourable, a further four had associated adverse clinical factors. One (0.8%) was rejected for an anatomical reason, a further eight for reasons unspecified in the National Database.

Of the 77 transplants seven failed in the first 7 days post transplant and an additional three during days 8 to 30 (13%). Two deaths occurred in the early postoperative period (mortality rate of 2.6%). The causes were fluid overload and ARDS (acute respiratory distress disorder).

Of the children currently attending the RBHSC transplant follow-up clinic the mean standard deviation score for height is -0.83, with a range of -2.3 to +1.4. Only two children have a standard deviation score of less than -2.

DISCUSSION

Interest in transplantation dates back for centuries but the earliest experiments that met with any success occurred in the first decade of the last century. Kidneys that functioned briefly are recorded after transplantation from one dog to another by Ullman in 1902. By the fourth and fifth decades of the 20th century attempts were being made to transplant a kidney from a cadaver to a live recipient, but invariably met with failure. A breakthrough occurred in 1954 in Boston when an identical twin donated a kidney to his sibling and the graft survived for 8 years, failing because of recurrence of the primary disease.[1]

In Belfast the first adult renal transplant which took place in 1962 between identical twins failed because of technical problems, but led to a successful haemodialysis and transplant programme for adults. A programme for children was inaugurated in 1980 with the appointment of a paediatric nephrologist and the introduction of a continuous peritoneal dialysis program using parent-operated automated cyclers. The service

is presently run by a multidisciplinary team led by 2 paediatric nephrologists (the second appointment being in 1995) supported by 3 renal nurse specialists, and a part time psychologist, dietician and social worker. All surgery is performed by renal transplant surgeons based at the Belfast City Hospital.

The United Kingdom Transplant Support Service Authority (UKTSSA) has recently published audit figures for renal transplants in the United Kingdom and Republic of Ireland for 1984-1993[2] and in this ten year period 1406 paediatric renal transplants (18 years and under) have taken place. Table I illustrates how Belfast compared with other centres on a numerical basis during this 10 year period.

In the 15 year period from 1984-1998 a total of 77 cadaveric renal transplants have taken place in Northern Ireland in patients under the age of 19 years. The 5 year graft survival of 64% compares favourably with nation-wide statistics (fig.1). 1990 was a particularly busy year (fig.2) when a total of 10 transplants took place supervised by a single paediatric nephrologist, with the active support of the adult nephrology team. The commonest primary diagnosis was reflux nephropathy, which explains the preoccupation of all paediatricians with the investigation of childhood urinary tract infections. There is the potential that some patients who present late in

TABLE I

Cadaveric kidney transplants in recipients aged 0-18 years at time of transplantation (1984-1993). (Population base ref. 14)

Hospital	*Number of Transplants*	*Population base (millions)*
Guys	238	9.13
Great Ormond Street/Royal Free	162	11.65
Manchester	132	4.0
Birmingham	117	5.49
Leeds	97	3.67
Dublin	83	4.5
Glasgow	79	5.1
Newcastle	65	3.03
Cardiff	58	2.16
Bristol	56	3.93
Belfast	47	1.59
Liverpool	26	3.06

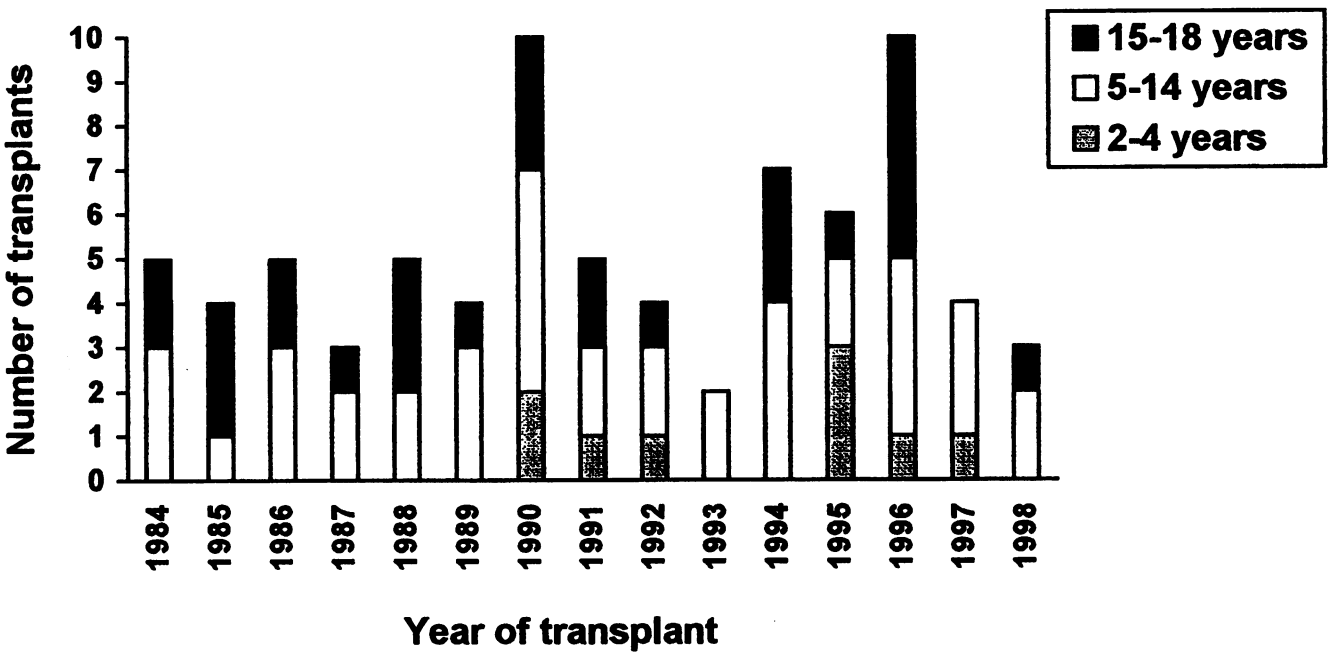

Fig 2. Paediatric cadaveric renal transplants in Belfast (1984-1998).

childhood with chronic pyelonephritis could be detected at an earlier phase by antenatal [3] and family screening [4,5] and early referral of children with proven urinary tract infections.[6,7] Table II lists the other commonest causes which are very similar to the range of conditions encountered nation-wide. The Northern Ireland figures are obviously much smaller, and the apparent predominance of chronic pyelonephritis is not significant.

TABLE II

Primary renal disease leading to transplantation in 77 patients in Northern Ireland (1983-1998), compared with percentage figures for UK/Republic of Ireland (1984-1993).

Primaryrenal disease	*Total*	*Percentage of total (77)*	*Percentage of total in UK/ Republic of Ireland (1406)*
Glomerulonephritis	7	9%	12%
Pyelonephritis, chronic	31	40.3%	28%
Polycystic kidneys, infantile	1	1.3%	2%
Medullary cystic disease	1	1.3%	3%
Hereditary nephropathy	8	10.4%	1%
Alports syndrome	1	1.3%	1%
Cystinosis	1	1.3%	3%
Congenital renal hypoplasia	2	2.6%	6%
Congenital renal dysplasia +/- urinary tract malfommation	3	3.9%	10%
Others	22	28.6%	34%

During the 15 year period the age range of the donors has been changing from a predominantly adult to a child population. This can be partly explained by the fact that in 1990 a new rule meant that a donated paediatric kidney was offered firstly to a paediatric patient. This change may also be partly explained by the increasing awareness of the medical profession and public alike of the need for organ donation, even when the potential donor is a dying child.

The age group of the recipient has also been changing during the 15 year period. Prior to 1990 all recipients were five years or older, but the 2-4 age group has seen an average of one transplant per year since then (figure 2). These nine transplants have become possible due to improving surgical techniques and because aggressive medical treatment of congenital nephrotic syndrome,[8] and end-stage renal failure in neonates has enabled survival to a size and weight compatible with transplantation. A major contribution to patient-survival is the introduction of intensive skilled nutritional support including the use of night-time tube feeding via gastrostomy, and peritoneal dialysis techniques in infants as small as 1000 grams. The Paediatric team while having reservations about the developmental outcome of babies treated for chronic renal impairment from infancy, has demonstrated the ability to dialyse and transplant these infants.

The median waiting times on the transplant list have gradually increased in each successive 5 year period, initially being about 3 months but by the late 1990's extending to about 11 months. This of course is not a problem unique to Northern Ireland. Despite national publicity campaigns organ demand continues to outstrip donation. Live donation is an alternative which has been underway for decades; locally a total of 5 such donations have taken place, 3 of which are still functioning.

Generally only a kidney with a haplotype tissue type match is considered and ideally a match on both DR loci is sought. Not every kidney offered therefore will be accepted, and on average 8 were turned down each year. Figure 3 shows that, as expected, the commonest reason by far is that a better match was required. Other factors to be considered include a prolonged ischaemic time (>24 hours) or adverse anatomical reasons e.g. in one case a tear in the renal vein meant that the operation would be technically difficult. It is unfortunate that 8 offers had to be declined because of lack of resources. In practice this usually meant the lack of a post-operative intensive-care bed or that key consultant nephrology or surgical staff were not available. This is a problem that is seen throughout the UK and Republic of Ireland where about 4% of offers are turned down for this reason.[2]

Of the 77 paediatric transplants in Belfast we have seen seven fail in the first 7 days post-

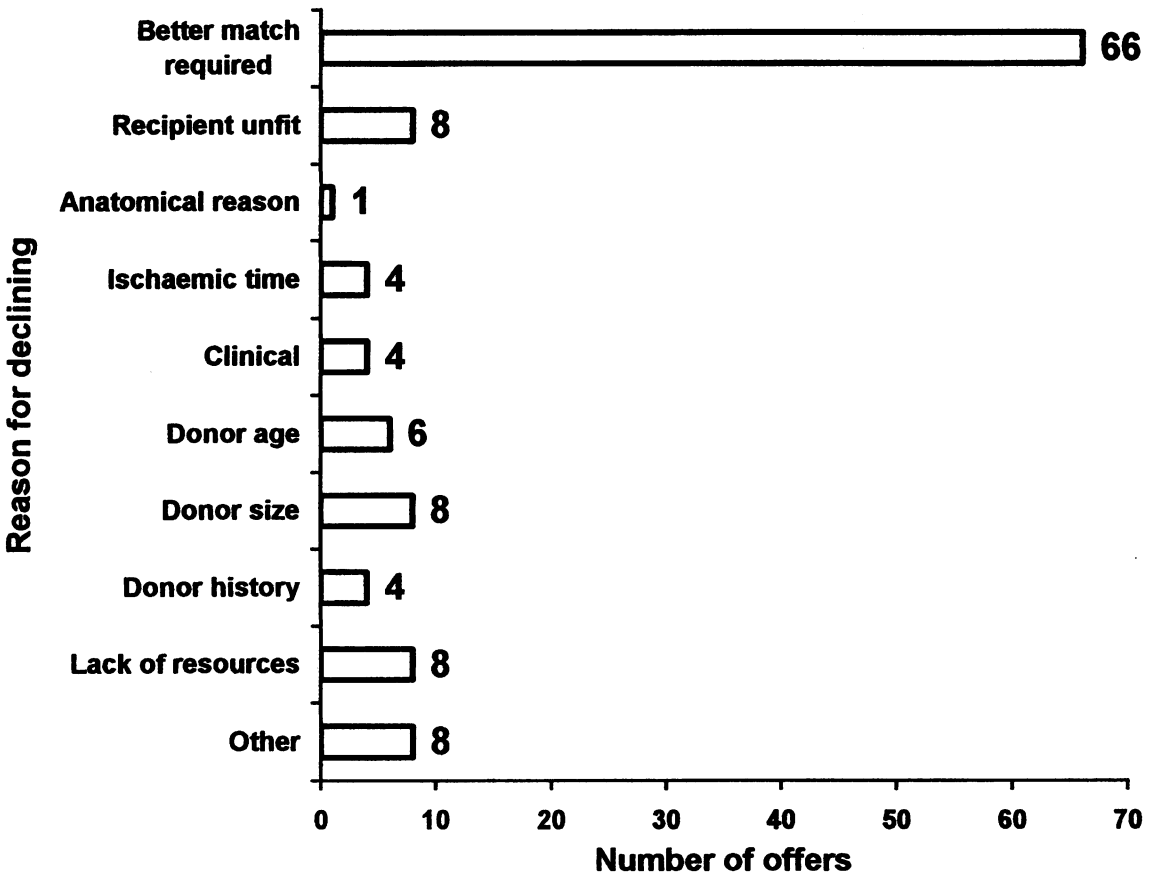

Fig 3. Reasons for declining paediatric kidney offers to Belfast (1984-1998).

transplant and an additional three in days 8 to 30, amounting to 13%. Guy's hospital for example has seen 45 fail in the first 30 days post transplant [2] accounting for 19% of the total (these statistics cover the period 1983-1994). The classifications of causes of graft failure shown in Table III are those employed by the UK Transplant Support Service. Initially a proportion of kidneys may be lost immediately following surgical placement due to an overwhelming immunological reaction. These are classified under the general title of hyperacute rejection. We believe this grouping fails to distinguish in our patients between severe immunological rejection, and early vascular thrombosis possibly caused by technical problems with the anastomosis. In 10% the primary cause of renal failure has recurred, usually glomerulonephritis. The apparent difference in the proportion of local patients suffering from rejection whilst on immunosuppression compared to nationwide figures, (Table III) is likely on review to result from a local anomaly in data reporting. The Belfast graft losses on immunosuppression are probably similar but hidden within the "other" category.

Two deaths, both occurring in the early postoperative period, represent a mortality rate of 2.6%. The causes of death were (a) fluid overload and (b) ARDS (Acute Respiratory Distress Syndrome.) In the UK and Republic of Ireland 48 deaths occurred in the 10 year period 1984-1993 giving a mortality rate of 3.4%, the 4 commonest causes of death being cardiac arrest (15%), fluid overload (13%), pulmonary infection (10%) and septicaemia (8%).[2] An ongoing audit of causes of early graft loss and death has led to refinement of transplant protocols in order to improve outcome.

Initially all children were immunosuppressed with prednisolone and azathioprine in combination until the mid 1980's. When cyclosporin became available it was an important milestone, which led to improved graft survival.[9] This drug works by inhibiting the transcription of interleukin 2 and thus early T cell activation. The use of cyclosporin became routine in our children despite initial dosage difficulties related to variable metabolism in childhood. Nephrotoxicity is avoided by careful blood level monitoring but

TABLE III

Cause of graft failure in Northern Ireland, (1984-1998), compared to graft failure in the UK/Republic of Ireland (1984-1993).

Cause of failure	*Northern Ireland*	*UK/ Republic of Ireland*
Hyperacute rejection	14%	2%
Rejection while on immunosuppressive drugs	29%	67%
Recurrent primary renal disease	10%	3%
Vascular or ureteric operative problems	5%	8%
Vascular thrombosis	19%	12%
Other	23%	8%

side-effects causing persistent and occasionally unacceptable problems are hirsutism and gum hypertrophy. More recently Tacrolimus, (a macrolide antibiotic) an agent with immunosuppressive activity approximately 100 times that of cyclosporin,[10] has become established as an efficacious drug in this field in which side-effects (e.g. nephrotoxicity and neurotoxicity) are reversible with dosage reduction.[11]

Of the children currently attending the RBHSC transplant follow-up clinic the mean standard deviation score for height is -0.83, with a range of -2.3 to +1.4. Only two children have a standard deviation score of less than -2, both of whom have been in chronic renal failure since infancy. This reflects careful attention to renal bone disease (using phosphate binders and vitamin D analogues), nutrition and the use of human growth hormone [12] in these children, and is one of the most dramatic improvements in this age group. Eradication of short stature as a result of chronic renal impairment and renal osteodystrophy is potentially achievable in all patients who can comply with modern treatment regimens.

CONCLUSION

Our figures demonstrate that in terms of short and long term graft survival and mortality Belfast is comparable to any similar centre nation-wide. Advances have been made during the 15 year period, most noticeably in the youngest children receiving transplantation. It is clear that a successful end stage renal replacement programme for children is achievable in a small geographical area with a limited population. There are advantages of an association with an adult unit, but the special needs of chronically ill children and demands for professional family support require the skills of a paediatric medical environment. Concerns for the future must focus on the ever-increasing waiting time and the shortage of donated organs, which are not problems restricted to Northern Ireland. Living related donation is part of the solution, and of course xenotransplantation may prove to be a controversial solution in the 21st century and is at present being evaluated.[13]

ACKNOWLEDGEMENT

The statistics in this paper were prepared by the UK transplant Support Service Authority from the National Transplant Database. The authors wish to acknowledge the role played by the adult nephrology service in providing help, advice and support that continue to benefit the paediatric dialysis and transplant programme. A particular debt of gratitude is owed to all the transplant surgeons, most recently Mr John Connolly.

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Multiple Sclerosis in Northern Ireland:

A historical and global perspective

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SUMMARY

The uneven worldwide distribution of multiple sclerosis has been of interest to epidemiologists, neurologists and statisticians for over a century, prevalence rates for the disease apparently being determined by variations in age, gender, geography, race and ethnic group. Northern Ireland has been recognised as an area of high MS prevalence since the truly seminal work of Allison and Millar almost 50 years ago.

The most recent study in Northern Ireland was undertaken in 1996 and involved the neighbouring districts of Coleraine, Ballymena, Ballymoney and Moyle (population, 151,000). Overall, 254 definite and probable cases were identified (prevalence: 168.2/100,000) with a further 34 suspected cases (overall prevalence: 190.7/100,000). Females predominated (ratio, 2.1: 1) and the average age at onset was 31.6 years. The highest age specific prevalence rate for females was in the 35-44 years old age group (519.6/100,000) and for males was in those aged 55-64 (292.3/100,000). The spectrum of disability was broad and 20% could be considered to have relatively "benign" disease. These figures sadly confirm that Northern Ireland has one of the highest and rising MS prevalence rates in the world and implies an enormous potential for societary costs.

MS EPIDEMIOLOGY – THE EARLY YEARS

Accumulated data over the last century indicates that multiple sclerosis (MS) is the commonest disabling neurological disease of young adults in developed countries. Although the earliest attempts to establish the frequency of MS involved the observation of the numbers of cases among hospital admissions with nervous diseases, in 1922 the study of the disease was taken a stage further by the reported distribution of MS in the United States based on diagnoses among army inductees in World War I.[1]

The first attempt to establish properly MS prevalence by identifying the total number of cases within a defined population was performed in Switzerland in 1918-22 and reported in 1926 (prevalence: 36.4/100,000).[2] The first such study in the British Isles was undertaken by an eminent Belfast neurologist, Sidney Allison, in Wales in 1929 (prevalence: 25.8/100,000).[3]

Although several hundred epidemiological surveys of MS have been undertaken worldwide, the credit for the first recognition that MS exhibited an uneven distribution must go to Charcot, who in 1868 commented that "even today I do not believe that disseminated sclerosis is known in England" and in 1877 continued to observe that although the disease was prevalent in France, it was little recognised in Germany and uncommon in England.[4,5] Although these observations are inapplicable today, other variations are now well established.

EVIDENCE FOR A LATITUDINAL GRADIENT?

The theory that the epidemiology of MS shows a latitudinal gradient in frequency probably originates from the demonstration in 1950 that MS death rates increased from south to north within North America.[6] Subsequent studies gradually developed the picture of a higher prevalence in temperate than in subtropical and

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tropical zones, with a suggestion of a decline in rates again towards the poles. Some of the most elegant supportive studies have come from Australia, where the prevalence declines gradually from tropical Queensland (12/100,000) in the north to Tasmania (76/100,000) in the south.[7,8]

Further evidence for geographic or environmental factors influencing the frequency of MS has come from migration studies. In South Africa, MS prevalence in immigrants from the UK and other European countries is about 36/100,000 population.[9] This rate is intermediate between those for the countries from which these people originated (50-100/100,000) and that for native born white South Africans (11/100,000). Further study of Europeans migrating to South Africa has also indicated that the risk of MS is related to the age of migration.[10] In the group migrating before age 15, the number developing the disease was only one-third of the number expected from rates in the European population generally.

The effects of latitude and changes in risk with migration are however only part of the picture. For example, in the US the significantly higher MS prevalence in the northern states has been shown to be better correlated with the extent of Scandinavian ancestry.[11] What is now clear is that what have previously been interpreted as geographical or environmental factors influencing disease prevalence are more likely to be racial and genetic. Generally, MS is most frequent in areas settled by individuals of predominantly Scandinavian descent.

CLUSTERS AND EPIDEMICS

Within these apparent trends along latitudinal gradients and across ethnic groups, the identification of apparent clusters and epidemics in, for example, the Faroes,[12] Iceland,[13] Florida,[14] Norway,[15] and Denmark[16] has caused much intense speculation regarding more specific possible aetiological factors, in particular, infectious agents. To date, despite intensive survey, no single infectious agent has been successfully incriminated.

POST-WAR SURVEYS IN GREAT BRITAIN

Since World War II there have been more than 30 epidemiological surveys in Great Britain (GB). The most intensively surveyed areas until recently have been the north-east of Scotland, Orkney and Shetland. Studies have involved numerators and denominators both large and small, used differing diagnostic criteria and employed varied epidemiological methods.

The Orkneys and Shetland have had the highest prevalence rates for MS in the world, prevalence in the former reaching a peak of 309/100,000 in 1974.[17] Interestingly, and in contrast to the pattern of earlier studies on these islands, both island groups have demonstrated a decline in MS prevalence in their most recent studies.[18,19] On the Scottish mainland, three studies have been conducted in the north-east, largely based on Grampian, the prevalence there reaching a peak of 178/100,000 in 1980.[20]

Such figures in Scotland, together with a perception that MS was much less common in the south of England, contributed to a belief that a north-south gradient for MS prevalence exists in GB. Over the past decade however there have been several well conducted studies in England and Wales which have challenged this hypothesis, with broadly similar prevalence rates for areas as far apart as Jersey (113/100,000),[21] Sussex (136/100,000),[22] North Cambridgeshire (118/100,000),[23] Glamorgan (120/100,000)[24] and Rochdale (122/100,000).[25] The absence of a latitudinal gradient within Scotland itself has also been confirmed by studies in south-east Scotland (prevalence: 187/100,000)[26] and Tayside (prevalence: 184/100,000)[27] which have found prevalence rates similar to those for Grampian, Shetland and Orkney.

THE HISTORY OF MS EPIDEMIOLOGY IN IRELAND

Northern Ireland has one of the most surveyed populations for MS in the world, previous studies having been undertaken in 1951, 1961 and 1987.[28-30] The original studies of Allison and Millar were among the most extensive ever completed, based as they were on the population of the province as a whole. They identified Northern Ireland as a high risk area for MS, observing prevalence rates of 51/100,000 in 1951 (population: 1,370,709) and 80 per 100,000 in 1961 (population: 1,484,775). More recently in 1987, a study of the contiguous Coleraine, Ballymoney and Moyle districts in the north-east of Northern Ireland (population: 86,500) produced a crude prevalence rate of 138/100,000.[30]

The 1951 study provided a template for all subsequent studies. All hospitals and doctors in the country were surveyed. A scheme of

classifying patients was established which is still widely applied. For this purpose patients were categorised as having "probable MS" (some physical disablement, usually a remitting quality in the history and on examination, physical signs explicable only by multiple lesions), "early MS" (patients showing few or no physical signs but having a recent history of remitting symptoms of the kind commonly associated with the onset of the disease) or "possible MS" (suggestive clinical findings but a progressive or static history and insufficient evidence of multiple lesions).

Remarkably, all 887 cases on the provisional register were individually assessed by Allison and Millar, the diagnosis being discarded in over 20%. Pains were also taken to establish an accurate incidence rate by personal questioning and checking statements with doctors, hospital records and relatives. The final overall incidence figure was 2.74/100,000. Allison and Millar's huge efforts were however undermined by at least two factors. Firstly, by the prevalence date replies had not been received from 25% of the doctors in Northern Ireland. Secondly, the incidence rate was calculated over a prolonged period and up to the prevalence date (1937-51) and may therefore have missed patients who had onset of disease during this period but who died before the survey was carried out, and also those who had onset during this period but had not yet been identified. One conclusion of the study also appears suspect. Although the authors state that there was no evidence to suggest that the disease was unevenly distributed, there is a considerable variation in prevalence rates across the region from 24/100,000 in Co. Londonderry to 63/100,000 in Co. Tyrone.

In the second study by Allison and Millar, 1,146 cases were identified in a population of 1,425,000. Again all of these patients were individually assessed. An unusually high proportion of "possible" cases were noted – 29% – rather more than the already high level seen in 1951 – 21%. However, even allowing for this increased recognition of "possible MS", the confidence limits for the 1961 prevalence figure (76-85/100,000) lie well above those from 1951 (47-55/100,000).

The 1987 study was the first in Northern Ireland to use the Poser criteria.[31] It was also the first to use the Kurtzke disability status scale [32] as a measure of neurological impairment in an MS population. The prevalence rate for probable disease by the Allison and Millar criteria was 104/100,000 and for definite/probable disease by Poser was 97/100,000.

Studies of MS prevalence elsewhere in Ireland have been less detailed, although one study reported in 1977 involved the whole population of the Republic of Ireland.[33] Covering almost three million people, it was subject to the problems of accurate case ascertainment inherent in a population of this size. Although many sources were used to identify cases and the existence of the study was advertised in the medical press, no data is provided by the authors on response rates to requests for information. Also patients who were identified to the researchers were not individually assessed, the opinion of the attending neurologist or physician being accepted. No diagnostic criteria were used, patients being designated as either probable or possible cases, and no measure of disability was applied. The overall prevalence rate for patients with probable or possible disease was 73/100,000. In a further study in the county of Wexford in 1984,[34] the criteria of McDonald and Halliday were used which make comparison with other surveys difficult. Although all patients were individually assessed, a remarkable 40% of this population were deemed to have benign disease, suggesting a bias in the case ascertainment against those with greater disability. It is also noteworthy that the quoted prevalence rate of 48.4/100,000 for clinically definite and progressive probable MS was actually less than that identified for the county 13 years earlier (54.5/100,000).[33]

CURRENT SITUATION IN NORTHERN IRELAND

In 1998 we first reported on a further prevalence study in Northern Ireland.[35] Our aims were to update the MS prevalence in the new era of magnetic resonance imaging and more sophisticated immunological investigation. A further purpose was to provide a database for immunological and genetic studies for which the relatively homogeneous conformation of this population is ideal.

METHODS

The survey populations were the neighbouring Ballymena, Coleraine, Ballymoney and Moyle districts, spanning the counties of Antrim and Derry. The total land area of 2,030km^2 lies between latitudes 54°7 N and 55°3 N. In the 1991

census, the population was 146,066, but by mid-year 1995 it had risen to an estimated 151,000 – Ballymena (57,500), Coleraine (54,100), Ballymoney (24,600), Moyle (14,800).

Primary sources for case identification were the records of the Northern Ireland Regional Neurology Service (NIRNS) at the Royal Victoria and City hospitals in Belfast and those held in outreach neurology clinics serving the study area at the Coleraine, Waveney, Moyle, Antrim and Mid-Ulster hospitals. Hospitals with inpatient diagnostic indices and computerised databases were further sources.

A postal survey of GPs in the area was performed. Those failing to respond were canvassed on a second and third occasion where necessary.

Local branches of the Multiple Sclerosis Society of Northern Ireland at Ballymena, Coleraine, Ballymoney, Antrim and Larne were approached for information. Another charity, Action MS, was also approached. The records of the MS Centre at the Dalriada Hospital in Ballycastle which provides a respite care facility were examined.

The hospital and/or GP records of all patients identified were studied. Potential MS patients were then invited for assessment. An invitation was not issued if felt by the GP to be inappropriate. Assessments occurred at a neurology clinic, in the patient's local health centre or own home and involved interview regarding date of onset, date of diagnosis, nature of the initial episode, subsequent clinical course and family history. Date of onset was obtained from the patient where possible, from the medical records if not. Date of diagnosis was obtained from the medical records.

Those satisfying the Poser criteria for clinically definite (CDMS), laboratory-supported definite (LSDMS), clinically probable (CPMS) or laboratory-supported probable (LSPMS) MS were accepted as prevalent cases. To enable comparison with previous studies a "suspected" group was included and the criteria of Allison and Millar were also employed.

A comparison of this study with the previous three in Northern Ireland was performed using the Allison and Millar criteria and calculating confidence intervals by a standard method.[36]

Patients were categorised as having relapsing-remitting (RRMS), secondary progressive (SPMS) or primary progressive (PPMS) MS. Those with an EDSS of ≤ 3.0, ≥ 10 years after onset were considered to have benign MS.

Patients were deemed prevalent if alive and resident in the study area on July 1st 1996. Addresses of patients were established as being within the study area using postcodes and maps obtained from HMSO and Ordnance Survey. Ethical approval was obtained from the Queen's University of Belfast Research Ethics Committee.

RESULTS

The provisional list of people with MS comprised 402 names. Many were identified by more than one source. Ninety-four of 97 (96.9%) GPs within the area responded positively to requests for information. Sources for the provisional cases and the proportion of the overall number notified were: GPs, 247 (61.4%); departmental records, NIRNS, 217 (54.0%); MS charities, 109 (27.1%); hospital database inpatient codings, 89 (22.1%); Dalriada MS Centre, 38 (9.5%).

Patients were excluded from the provisional register on the following grounds: residency outside the study area (47 cases); deceased (45 cases); not MS (22 cases). Therefore 288 patients remained alive and prevalent within the study area on 1st July 1996. The sources for these were: GPs, 230 (79.9%); departmental records, NIRNS, 158 (54.9%); MS charities, 74 (25.7%); hospital database inpatient codings, 69 (24.0%); Dalriada MS Centre, 33 (11.5%). Of the 288 prevalent patients, 116 (40.3%) were notified by a single source: GPs, 85 (29.5%); departmental records, NIRNS, 19 (6.6%); hospital database inpatient codings, 10 (3.5%); MS charities, 1 (0.3%); Dalriada MS Centre, 1 (0.3%).

Two hundred and fifty-one of the 288 patients (87.2%) were formally interviewed and examined. In a further eight cases (2.8%) an EDSS was calculated using information provided by the general practitioner or by other consultant neurologists during clinic attendance. The diagnostic classification of prevalent cases using the Poser criteria was as follows: CDMS – 185 (64.2%); LSDMS – 24 (8.3%); CPMS – 43 (14.9%); LSPMS – 2 (0.7%), and; suspected – 34 (11.8%). Applying the Allison and Millar criteria the classification was: probable MS – 186 (64.6%); early probable and latent MS – 60 (20.8%), and; possible – 42 (14.6%).

The prevalence rate based on all 288 patients is 190.7/100,000 (95% CI 168.7-212.7/100,000) whilst restricting to those with definite or probable disease by the Poser criteria gives a prevalence of 168.2/100,000 (95% CI 147.5-188.9/100,000).

The previously unsurveyed Ballymena population contained 110 patients [prevalence: 191.3/100,000 (95% CI 155.6-227.0/100,000)], 100 fulfilling the Poser criteria for definite or probable disease [prevalence: 173.9/100,000 (95% CI 139.9-208.0/100,000)].

There were 196 female and 92 male patients (ratio 2.1: 1). The mean age of prevalent patients was 49.3 (range 18-79, SD 13.3) years, the mean age for females and males being 48.3 (SD 13.4) and 51.5 (SD 13.0) years respectively. Mean age of onset was 31.6 (range 12-66, SD 10.1) years, the figures for females and males being 31.0 (SD 10.1) and 33.0 (SD 10.1) respectively. The age and sex specific prevalence rates are given in (Table 1). Both the peak age specific prevalence rate and modal age of prevalent female cases are in the 35-44 year age group. For males the peak prevalence rates are in the 45-54 and 55-64 year age groups whilst the modal age group for prevalent males is 45-54 years.

The homogeneity and stability of the population is emphasised by 90.9% of those with definite/probable disease being born either within the study area (184 patients) or elsewhere in Northern Ireland (47 patients). This figure reaches 95.1% upon exclusion of those cases whose place of birth was not ascertained, with just nine cases (3.5%) born elsewhere in the British Isles and three (1.2%) born overseas.

In those with definite or probable disease the mean interval between initial symptoms and diagnosis was 6.2 years. The mean duration of disease in definite/probable cases was 18.4 (range 0-52, SD 11.4) years. Using the technique of doubling the mean duration at prevalence day, the mean life expectancy was 36.8 years.[37]

The distribution of Kurtzke EDSS scores is shown in the figure. The mean EDSS score was 4.9 and the median 5.5. Clinical course from onset was established in 280 (97.2%) patients. Ninety-eight patients (35.0%) had RRMS, 36 (12.9%) had RR and benign disease, 111 (39.6%) had SPMS and 35 (12.5%) had PPMS. Of 180 patients undergoing an EDSS assessment and having disease duration of ≥10 years, 36 (20%) had a benign course.

Initial symptoms were established in 283 cases (98.3%). The commonest was sensory [95 (33.6%)] followed by motor [78 (27.6%)], brainstem/cerebellar [70 (24.7%)] and optic neuritis [57 (20.1%)]. Twenty-six (9.2%) had more than one of these symptoms initially and nine (3.2%) had another form of disturbance at

TABLE I

Prevalence of definite/probable MS in Coleraine, Ballymena, Ballymoney and Moyle per 100,000 by age and sex.

Age Group (years	*Male No.*	*Rate/10^5*	*Female No.*	*Rate/10^5*	*Total No.*	*Rate/10^5*
0-14	0	0	0	0	0	0
15-24	0	0	5	41.3	5	20.3
25-34	8	74.9	20	186.3	28	130.8
35-44	13	132.9	50	519.6	63	324.6
45-54	24	286.9	42	482.3	66	386.6
55-64	19	292.3	32	443.0	51	371.6
65-74	11	212.4	25	394.6	36	312.7
75+	2	68.3	3	56.0	5	60.4
TOTAL	77	104.1	177	229.9	254	168.2

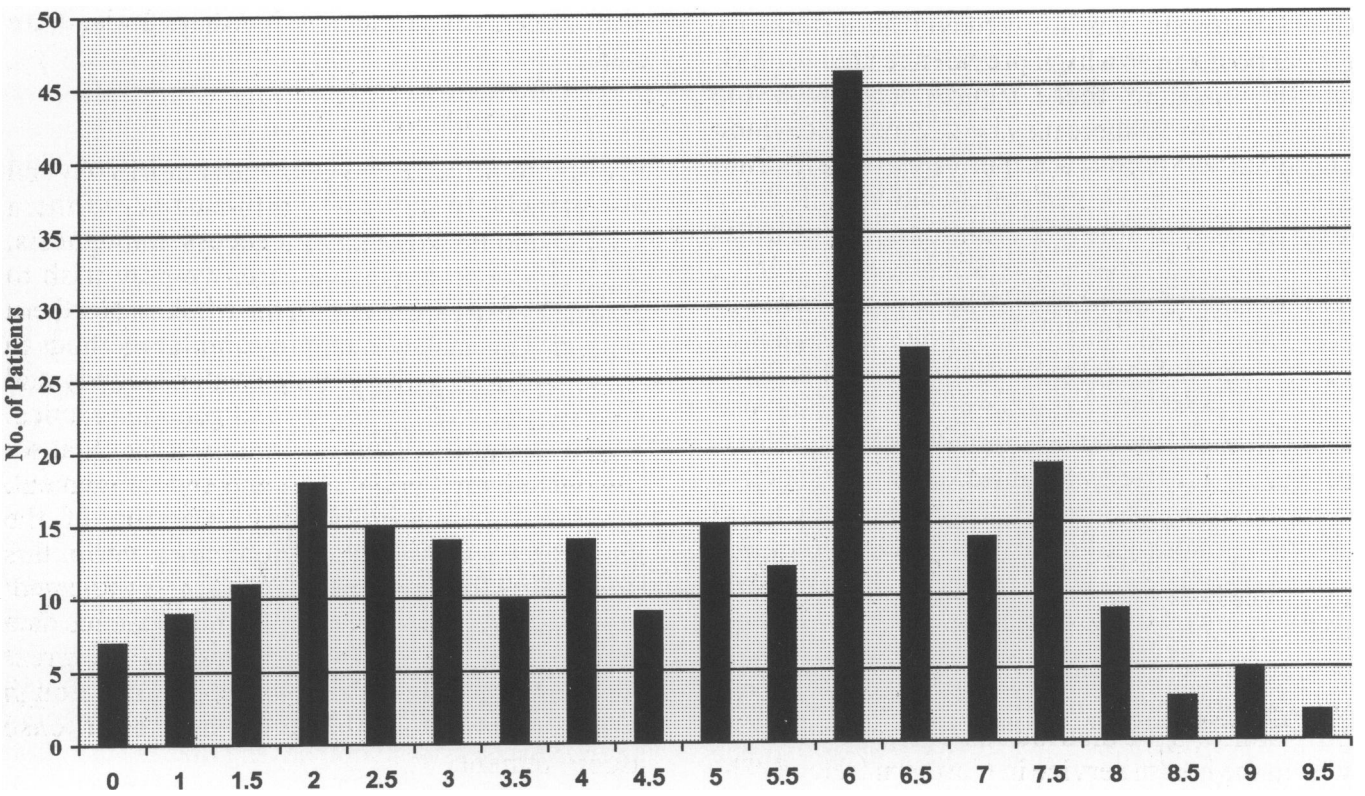

Fig. Kurtzke EDSS scores for prevalent patients.

onset (e.g. sphincter disturbance, sexual dysfunction). Sixty-five patients (22.6%) had a history of MS among first-, second- or third-degree relatives.

DISCUSSION

This study was the fourth completed in Northern Ireland in 50 years. We believe that, given the resources available, the population size in this study was optimal for accurate ascertainment of cases, not so small as to be subject to the quirks of clustering and not so large as to omit prevalent cases. The first two previous studies involved the entire population of the province [28, 29] and as such may be biased by incomplete ascertainment, while the third involved a rather smaller population.[30] The rising prevalence seen in the previous three has been emphasised.

The confidence intervals for the recent study lie entirely outside those of the previous studies, the differential being greater when restricting to those with probable or early probable and latent MS: 1951 – 41/100,000 (95%CI 37-44); 1961 – 57.100,000 (95% CI 53-61); 1987 – 104/100,000 (95% CI 85-128), 1996 – 163/100,000 (95% CI 144-185). This rising prevalence in serial studies, although not invariable,[24] has been demonstrated elsewhere[20] and attributed to several factors including prolonged survival of MS patients, improved recognition of cases, changes in survey methodology and the widening application of paraclinical tests in diagnosis. The prevalence rates for the Ballymena area, being similar to those for the more recently surveyed Coleraine, Ballymoney and Moyle districts, encourage our belief that the methods of case ascertainment have been thorough and evenly applied.

In the British Isles only Shetland, Orkney and Suffolk [38] have had higher prevalence rates. All of these involved significantly smaller populations with wide confidence limits and in Suffolk there was no neurological review. Other similarly populous areas studied in the British Isles (Sutton;[39] pop 169,600: Jersey & Guernsey,[21] pop 145,246) have had significantly lower prevalence rates. Although there is now little evidence for a latitudinal gradient within these islands, our figures, taken together with those in Scotland, appear to support the existence of a "step" between Northern Ireland/Scotland and England/Wales. This in turn may reflect the distinct profiles of the population bases, the genetic composition and ethnic origin being similar in Scotland and Northern Ireland.[40]

Overall, this study reinforced Northern Ireland's global position as a high prevalence area for MS. On the basis of these figures and, with the presumption that there may be an even distribution of the disease across Northern Ireland, we could extrapolate that almost 3,000 individuals have definite or probable MS and there are a further 400 suspected cases in the region as a whole. A comparison of *standardised* prevalence rates for probable and definite MS in the UK, that is prevalence calculated on the basis of the 1961 census population of Northern Ireland,[29] is shown in Table II. The list is limited to those studies providing sufficient information for such a comparison to be made.

In light of the new and costly disease modifying therapies becoming available for the disease [42-43] and the standards being established for the management of many of its symptoms, these figures have major implications for health care provision and the distribution of resources to and within the health service in Northern Ireland. The long and unacceptable delay identified in our recent study between onset of symptoms and diagnosis of MS (6.2yrs) partially reflects the long waiting lists for clinical assessment and prolonged waiting times for supportive investigations. Again, given that the newer disease-modifying agents may be at their most effective early in the course of the disease, the imperatives for adequate funding and provision of neurological services in Northern Ireland are clear.

FUTURE STUDY

In order to broaden the awareness of MS beyond the intensively surveyed north-east of Northern Ireland and improve patient access to diagnosis, treatment and supportive care, we now wish to establish an MS database for the whole of Northern Ireland. This task will employ similar methods to those outlined in the 1996 prevalence study and will involve every hospital and general practice. The recent study detailed here indicates that we can depend on their support and encouragement. In addition, continuing investigation of the immunogenetic predisposing factors within this stable and homogeneous population is indicated; there remains a need for updated prevalence data in the Republic of Ireland, based on current diagnostic criteria and employing more thorough and now well established means of case ascertainment.

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TABLE II

Standardised prevalence rates (SPR) for probable and definite MS in the UK (based on 1961 Northern Ireland census population)

Survey	*Male Population*	*SPR/10⁵*	*Female Population*	*SPR/10⁵*
N. Ireland 1996[35]	74,000	100	77,000	226
Tayside 1996[27]	190,715	85	204,885	236
Jersey 1991[21]	40,620	46	43,462	140
Guernsey 1991[21]	29,836	37	31,328	98
Sussex 1991[22]	289,129	58	307,214	142
S. Cambs 1990[41]	143,252	66	152,816	171
Rochdale 1989[25]	98,978	75	104,365	156
SE Wales 1985[37]	191,302	73	203,044	142
Sutton 1985[39]	81,518	64	89,483	137

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Biliary complications associated with laparoscopic cholecystectomy – an analysis of common misconceptions

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SUMMARY

Background

Several views are expressed by surgeons on biliary complications following laparoscopic cholecystectomy as follow: most are caused by trainees; complications occur in the presence of difficult anatomy/pathology; injuries occur more proximally than at open cholecystectomy; most injuries are recognised immediately and most can be managed non-operatively. The aim of our study was to determine if these views are substantiated in clinical practice.

Methods

The mode of presentation, management and outcome of thirty-two patients referred to a hepatobiliary unit over a seven year period were analysed.

Results

In 72% of cases the initial operator was a consultant. Five of the 32 complications (16%) occurred in the presence of difficult anatomy/pathology. Two patients had proximal biliary tree injuries, the only mortalities (two) occurring in this group. Only 41% of injuries were detected immediately; 87% required surgical intervention, hepaticojejunostomy being the most common procedure performed (75%).

Conclusion

Our study shows that the majority of bile duct injuries are not caused by trainees, do not occur because of unusual anatomy/pathology, do not occur in the proximal biliary tree and are not recognised at the time of operation. Most injuries ultimately require major reconstructive surgery for definitive management.

INTRODUCTION

Since the advent of laparoscopic cholecystectomy there have been a large number of publications discussing the problem of biliary complications, in particular the problem of bile duct injuries.[1-10] Despite this, there are a number of views that are often expressed on the subject have no support in the literature. These include the following:

- That after the initial 'learning curve' the incidence of biliary injuries is approximately the same as in the 'open' era[2]
- That the majority are caused by trainee surgeons[11, 12]
- That injuries usually occur in the presence of unusual anatomy or difficult pathology[3]
- That biliary injuries are generally higher than those that occur with open cholecystectomy[13]
- That injuries are often recognised at the time of surgery[4, 14]
- That most complications are easily managed, and that most can be managed non operatively[15]

Based on our experience we felt that these are probable misconceptions; therefore we reviewed

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this series of patients referred to a specialist hepatobiliary unit.

PATIENTS AND METHODS

Northern Ireland is a well defined geographical area with a relatively stable population of 1.6 million. Over a seven-year period from 1992, thirty two patients were referred for management of biliary complications arising from laparoscopic cholecystectomy. In one case the initial laparoscopic cholecystectomy had been performed outside Northern Ireland. There were 5 male and 27 female patients with a median age of 58 years. Seven patients were referred at the time of initial surgery, nineteen were referred 'early' (within six weeks of initial surgery) and a further six were referred 'late' (after six weeks). Injuries were classified according to the method described by Strasberg *et al*[1] (summarised in Table 1). Eight patients had Type A injuries. In three of these a cystic duct leak occurred as a direct consequence of an unsuspected common bile duct stone. One patient had an injury to the segment V duct in the gallbladder bed and the remainder of the Type A injuries were due to cystic duct necrosis or to laceration with a clip. There was one Type B injury with the common bile duct partly occluded by a clip. Three patients had Type C injuries, one due to a transected right posterior sectoral duct and two due to a transected accessory duct. There were nine patients with Type D injuries, all with lacerations to the common bile or hepatic ducts. Ten patients were referred with Type E2 injuries. One of these occurred following conversion to an open procedure for dense adhesions. Eight of the E2 injuries were 'classical' laparoscopic injuries.[8] One patient could not be included in this classification. She was referred three years after initial surgery with recurrent episodes of pain and jaundice due to stones in the cystic duct remnant and the common bile duct for which she had undergone repeated ERCP. At operation she was found still to have the distal portion of the gallbladder in-situ. Incomplete excision of the gallbladder causing these problems has previously been described.[16]

Where biliary reconstruction was required this was carried out using an 80 cm Roux-en-Y loop anastomosed to the bile duct confluence, with the anastomotic circumference increased by extending the opening along the horizontal portion of the left hepatic duct. The anastomotic technique used was that described by Blumgart.[17] These patients are all under long-term follow-up with regular measurement of liver enzymes.

RESULTS

Type A Injuries – Leak from minor duct (e.g. cystic duct stump) – 8 patients

None were recognised at the time of initial surgery. All presented in the early postoperative period with bile peritonitis and, in four cases, jaundice as well. Two were managed by ERCP and stone extraction with percutaneous drainage. One had ERCP following laparotomy and placement of drains. The rest had suture repair of the injury. All are alive and asymptomatic with normal liver function tests after follow-up ranging from 1 to 64 months.

Type B Injury – Occlusion of part of biliary tree by a clip – 1 patient

This patient was managed by ERCP and stenting. The stent was removed after six months and the patient remains asymptomatic at one year with normal liver function tests.

Type C Injuries – Leak from accessory duct – 3 patients

One patient had a transected right posterior sectoral duct which was recognised at the time of initial surgery. An immediate hepatobiliary referral was made and a primary repair carried out over a T-tube. The patient was asymptomatic with normal liver function after 30 months follow-up. The other two patients had leaks from accessory ducts and both presented in the early postoperative period with generalised biliary peritonitis. One patient initially underwent laparotomy at which time oversewing was carried out, and the patient was subsequently referred because of a continuing bile leak. This was managed by ERCP, sphincterotomy, percutaneous drainage and drainage of a pleural effusion. The patient settled and had normal liver function tests after 3 months follow-up. The other patient initially underwent ERCP with stenting and percutaneous drain insertion; however eventually a laparotomy was required with the insertion of a large bore drain for management of a bile collection.

Type D Injuries – Lateral injury to major bile ducts – 9 patients

Seven patients had the injury recognised at the time of initial surgery. One patient had a Mirizzi Syndrome and a tear occurred in the common hepatic duct due to excessive traction on the gallbladder fundus. This was referred immediately

TABLE I
STRASBERG CLASSIFICATION OF BILIARY INJURIES

A	Leak from Minor Duct (in continuity with CBD)	8	25%
B	Occlusion of Part of Biliary Tree	1	3.1%
C	Leak from Duct (not in continuity with CBD)	3	9.4%
D	Lateral Injury to Extra Hepatic Duct	9	28.1%
E_1	Circumferential Injury >2cm from bifurcation	0	0%
E_2	<2cm from bifurcation	10	31.2%
E_3	at bifurcation	0	0%
E_4	involving right and left ducts	0	0%
E_5	involving other hepatic ducts	0	0%

and the patient had a primary hepaticojejunostomy carried out with no late complications. In the remaining six a primary sutured repair had been carried out with or without a T-tube. Two of these required no further treatment and were asymptomatic with normal liver function after six years and three months respectively. The remaining four developed strictures. One of these had an end to side hepaticojejunostomy performed in the same unit, before presenting later to this unit with cholangitis due to recurrent stricturing at the site of the anastomosis. This was treated by revision hepaticojejunostomy with revision of the entero-enterostomy to lengthen the Roux limb. This patient remained well with normal liver function after 4 years. Two patients presented with Bismuth type II strictures, one early and one late. These were treated by hepaticojejunostomy and both were asymptomatic with normal liver function after 4 and 5 years. One further patient developed a stricture but was not referred until 10 months after the injury by which stage he had developed a Bismuth type IV stricture and cirrhosis. Prior to referral, various inappropriate management options had been attempted, including endoscopic and percutaneous balloon dilatation. A hepaticojejunostomy was performed but the patient died in the postoperative period secondary to DIC and liver failure.

Two further patients with type D injuries presented in the early postoperative period with biliary peritonitis. One developed a late stricture requiring hepaticojejunostomy and was asymptomatic with normal liver function after 5 years follow-up. The other was referred early with a small puncture wound to the common hepatic duct. A sutured repair was carried out with no complications at 7 months.

Type E Injuries – Circumferential injury to major bile ducts – 10 patients

Of these, 5 were recognised at the time of surgery – one occurring after open conversion for dense adhesions. Three of these were referred immediately at the time of initial surgery and had a hepaticojejunostomy performed as a primary repair. All were well with normal liver function tests after between one and six months follow-up. Two had a sutured repair over a T-tube. One of these was referred early with a Bismuth type II stricture, had a hepaticojejunostomy and was well after 11 months follow-up. The other developed a Bismuth type II stricture after 2 years requiring a hepaticojejunostomy.

The remaining 5 patients with type E2 injuries presented in the early postoperative period with obstructive jaundice. All were referred early, one having had a laparotomy and T-tube insertion prior to referral and another having had a hepaticojejunostomy prior to referral. This patient developed a dehiscence of the anastomosis within a few days and was referred with biliary peritonitis. At the time of referral the patient was requiring ventilation, inotropic circulatory support and dialysis. A revision hepaticojejunostomy was performed to the left and right hepatic ducts. There was no further bile leak or deterioration in liver function, but the patient developed progressive multi-system organ failure and died. Hepaticojejunostomies were carried out on the remaining four patients and all were well with normal liver function at follow up ranging from 9 months to 6 years.

DISCUSSION

The aim of this paper was to examine some commonly expressed views on laparoscopic cholecystectomy to determine if they are supported by our data. These will be examined in turn.

Complications are no more common than in open cholecystectomy:

Our data do not directly address this issue. However, because of the static nature of the population in Northern Ireland and the fact that there are rarely any referrals in to or out of the region, it is possible to form a strong impression. A previous paper from the same region reported 30 patients referred over a 21 year period during the era of open cholecystectomy.[18] Our paper reports 32 patients referred over a 7 year period. Whilst the number of cholecystectomies performed may have increased since the advent of laparoscopic cholecystectomy, it is very unlikely that this can explain the apparent increase in referrals and much more likely that there has been a real and significant increase in the incidence of biliary complications.

The majority of complications are caused by trainee surgeons:

In this series the initial operator was a consultant in 23 cases (72%). Clearly, even if the procedure is carried out by a trained surgeon, the risk of complications persists.

Complications mostly occur in the presence of difficult pathology or anatomy:

It is difficult to precisely quantify these issues. However referring surgeons were asked why they thought the complication had occurred. Only one cited an anatomical variation as the cause and only five described difficult pathology (e.g significant inflammation). A further three complications were due to unsuspected common bile duct stones. The vast majority of complications (84%) arose, therefore, in the absence of any unusually difficult anatomy or pathology.

Biliary injuries occur more proximally in the biliary tree than at open cholecystectomy:

In this series there were no patients who had received type D or E injuries at or proximal to the bile duct confluence, although two patients later developed E4 type injuries. One presented very late after persistent inappropriate attempts at management by stenting, and one patient had already undergone hepaticojejunostomy prior to referral. Thus, in our experience there is nothing to suggest that bile duct injuries are occurring at a higher level than in the open era. There were, however, no patients in our series with associated vascular injuries. Other authors have noted a significant number of cases with concomitant arterial injury and have felt that this may contribute to more proximal biliary injury.[19]

Most complications are recognised at the time of surgery:

In this series 13 patients (41%) had their injury recognised at the time of initial surgery. Of the 19 patients with the more serious type D and E injuries, seven patients (78%) with type D injuries, but only five patients (50%) with type E injuries had them recognised immediately. Overall these data indicate that the majority of complications do not become apparent until the post-operative period.

Most complications are easily managed non-operatively:

In this series only four patients (13%) were managed without open surgery. Of 18 patients who had a laparotomy prior to referral, 10 (56%) required a further procedure. Five patients with type D injuries (56%) and all patients with type E injuries required a hepaticojejunostomy. Two patients required revision of a previous hepaticojejunostomy. The two deaths in the series resulted from inappropriate early management and a delay in referral.

One of these deaths further illustrates the hazards of attempting a definitive repair in a patient acutely ill in the early postoperative period when a period of external biliary drainage would have been more appropriate. Presumably some patients, particularly those with a localised bile leak were managed locally by ERCP and stenting, with or without percutaneous drainage, and our percentage of patients requiring open surgical management may be falsely high. Nonetheless, these data indicate that the assumption that most complications are easily managed non-operatively is false.

Based on our experience and informal discussion with the surgeons concerned, it would appear that many of these complications were avoidable, given that eight of the injuries were 'classical'. A careful review of the anatomy prior to dividing any duct is an essential step of laparoscopic cholecystectomy. Earlier conversion to open surgery in the face of difficult dissection, unexpected findings or suspected biliary injury would probably have prevented or minimised many of the complications discussed. This is despite the fact that one bile duct injury in this series occurred after conversion.

It is therefore important to remember that even after conversion, the factor making the procedure risky or difficult may still be present and the surgeon must maintain a high level of caution and safety. We could not recommend a 'no-conversion policy' as advocated by some.[20] The role of routine cholangiography remains unclear and there are no appropriate prospective randomised trials of its effectiveness, although one recent retrospective study suggested that it did significantly reduce the risk of injury.[21] Only one patient in our series had a cholangiogram and this did not prevent a major injury from occurring. It is possible that cholangiography may have allowed earlier identification of biliary injuries, and may have prevented the three complications in this series that occurred due to unsuspected common bile duct stones.

In conclusion, an analysis of our experience has proved useful in addressing a number of common misconceptions regarding the occurrence of biliary complications following laparoscopic cholecystectomy. In addition we have shown that, with prompt referral, a successful outcome can be obtained for the majority of patients. Delay in referral and persistent attempts at inappropriate management can be catastrophic.

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Proximal femoral fracture in Northern Ireland between 1985-1997 – trends and future projections

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SUMMARY

The aims of this study were to identify changing trends with time of the incidence of proximal femoral fracture and to enable future number of hip fractures to be projected. Hospital theatre records in Northern Ireland were surveyed in 1985, 1991, 1994 and 1997 to establish the number of surgical procedures for proximal femoral fracture. The age and sex specific rates for males and females aged 50+ years were calculated. Analysis of age and sex specific incidence rates was undertaken using linear regression and Poisson regression.

A 1.6% increase per annum (95% CI 1.0 – 2.2) was noted in males and females from 1985 to 1997. Projected increases in rates of proximal femoral fracture were calculated using population projection for 2001, 2006, 2011 and 2016. Modelling (a) assuming the age standardised rates in 1997 remain static and continue predicted a 55% fracture increase in males and a 29% increase in females by 2016, (b) assuming the secular increases continued predicted a 93% fracture increase in males and a 67% increase in females and (c) assuming further linear growth on a log-scale predicted a fracture increase in males of 135% and 99% in females.

The number of proximal femoral fractures in Northern Ireland is increasing faster than that anticipated due to demographic changes alone, supporting a secular increase which was evident throughout the period of time studied, in contrast to that reported from other regions in the United Kingdom.

INTRODUCTION

Proximal femoral fracture is a common injury in elderly people with a current mortality at six months in females of 16% and in males of 43% in Northern Ireland.[1] There is also significant morbidity with 83% of those who previously lived at home returning home after four months and 7% requiring long term nursing care.[2] The clinical resources required for acute care are considerable with utilization of 25%[3] of acute orthopaedic beds, with additional need for rehabilitation and long term community care support. The cost has been calculated at £12,000 per fracture.[4]

While the resource implication of increasing numbers of proximal femoral fractures as a result of demographic increase in the number of elderly people is recognised[5], the incidence of proximal femoral fracture appears to be increasing more rapidly than that attributable to demographic

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ageing of the population alone.[6-11] The rise in age specific incidence of proximal femoral fracture has been reported to be levelling off in England and Wales[12], Minnesota[13] and Australia.[14] Considerable regional differences in age-standardised hip fracture rates exist with the highest rates in North Europe.[15] The explanation of such differences between regions and trends with time remains unresolved, with dietary, environmental, skeletal structure[16] and cohort effects[10] as possible contributory factors. Comparative information within the United Kingdom is limited.

Many United Kingdom studies have used Hospital Activity Analysis derived data to determine changes in incidence. Inaccuracies in coded records have been reported from a number of countries[17] and thus may not accurately capture and reflect the true incidence of hip fracture. They have been previously shown in Northern Ireland to incorrectly code 6% and fail to code 8% of cases.[18] An alternative data source was therefore considered in Northern Ireland involving theatre procedure records of proximal femoral fracture fixation. Subjects managed conservatively will not be captured, but over 95% of subjects with proximal femoral fracture receive surgical as opposed to conservative management, and non-operative management has remained at less than 5% over the time period studied.[2,18] Utilising theatre record books in Northern Ireland was, therefore, more likely to reduce coding errors and more accurately identify proximal femoral fracture subjects than Hospital Activity Analysis returns. The relatively small and stable geographical population of 1.6 million people in Northern Ireland also assists in accurate identification of proximal femoral fracture numbers with surgical treatment carried out in a defined small number of acute hospital locations.

A study was therefore undertaken to gather information from theatre record books to establish the age specific incidence of proximal femoral fracture, identify changing trends with time of the incidence of proximal femoral fracture, and to enable future projections of proximal femoral rates to assist in planning and provision of health care.

METHODS

A survey of all theatre records of hospitals in Northern Ireland undertaking operative management of proximal femoral fracture in 1985, 1991, 1994 and 1997 was carried out. The ten hospitals providing operative treatment were individually visited and data recorded directly from theatre registers (RAW, DS) and entered on to a database. Details of age, sex, operative procedures and date of surgery of proximal femoral fracture were obtained.

The population of Northern Ireland at the different sampling times and population projections for 2001, 2006, 2011 and 2016 were obtained from the Office of the Registrar General in Northern Ireland.[5] This allowed the age and sex specific rates to be calculated in five year bands for 50-90+ years of age. Analysis of age and sex specific incidence rates was undertaken using linear regression and poisson regression to identify changes between the sampling points.

RESULTS

The age-specific rates of proximal femoral fracture for males and females are recorded for the years 1985, 1991, 1994 and 1997 (Table I). This reveals a 1.6% increase per annum (95% CI 1.0 – 2.2) in both sexes. The increase per annum was similar in both sexes. The rate of increase is greater with increasing age and this trend was noted within both, males and females (Figure 1).

The projected increases in rates of proximal femoral fracture were calculated using the age 50+ years population projections for 2001 (males 214,000, females 261,000), 2006 (males 233,000, females 275,000), 2011 (males 254,000, females 297,000) and 2016 (males 277,000, females 323,000). This was firstly modelled assuming the age standardised rates present in 1997 remained static, secondly assuming the continuing secular increases within each age and sex sub-group at time points 1985, 1991, 1994 and 1997, and thirdly based on exponential growth (i.e. linear growth on a log scale, or equivalently, a constant percentage increase per annum). (Table II).

The first projection equated to a 55% increase in males (348 → 540) and a 29% increase in fractures in females (1275 → 1642) from the year 1997 to 2016. (Figure 2).

The second projection equated to an increase in fractures of 93% (348 → 670) in males and in females of 67% (1275 → 2130) from the years 1997 to 2106.

The third projection equated to an increase in males of 135% (348 → 820) and in females of 99% (1275 → 2540) from the years 1997 to 2016.

TABLE 1

Annual incidence rates for fractures of the proximal femur by age group over the period 1985-1997

Age Group (years)	*Males (rate/100,000)*				*Females (rate/100,000)*			
	1985	1991	1994	1997	1985	1991	1994	1997
50-54	26	29	17	28	55	43	30	39
55-59	23	46	28	49	97	88	71	47
60-64	37	53	47	56	101	97	134	80
65-69	99	88	59	133	168	185	170	196
70-74	190	173	151	202	382	387	393	414
75-79	243	242	386	412	741	833	833	912
80-84	662	610	803	643	1247	1419	1666	1527
85-89	1207	1207	1386	1298	2175	2278	2541	2607
90+	1930	1576	1878	2101	2623	3292	3381	4714
Total Fracture No.	230	257	292	348	870	1037	1182	1275

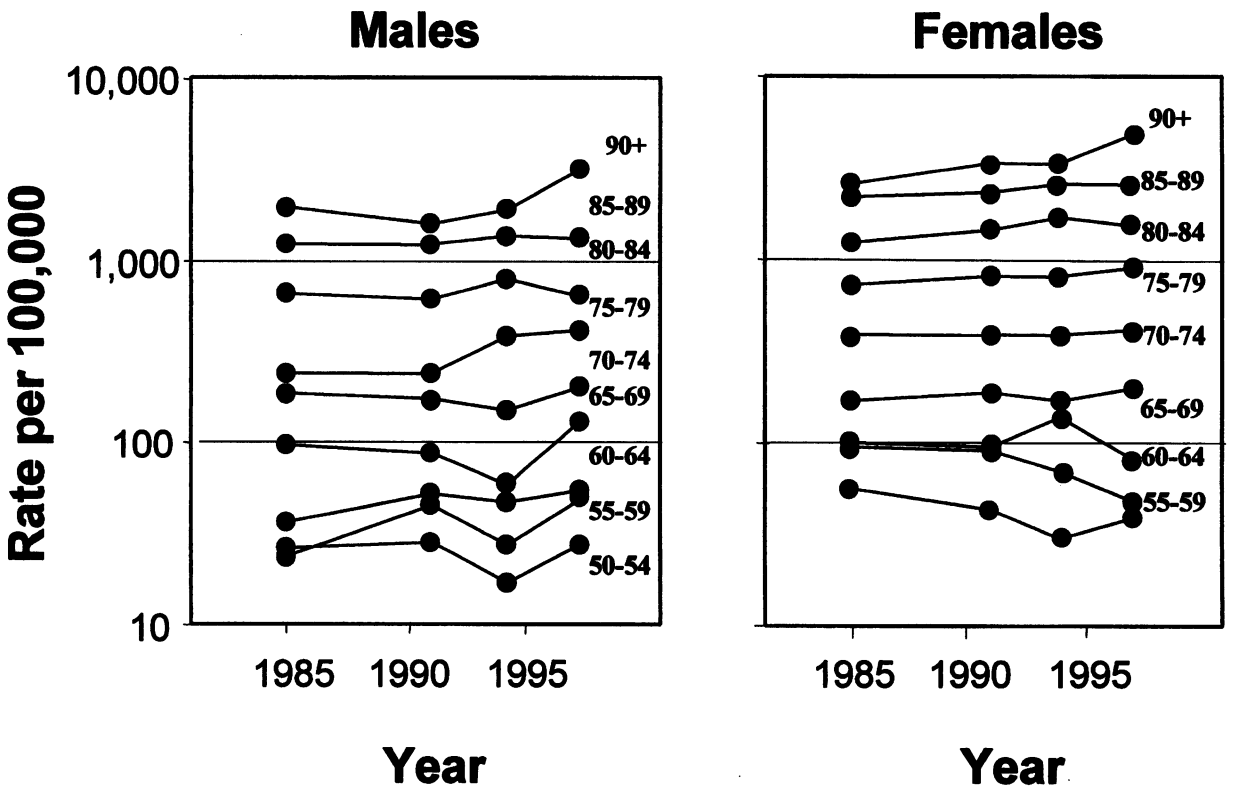

Fig 1. Trends in age specific fracture rates from 1985-1997 for males and females aged 50+ years.

TABLE 2

Projected increase in number of hip fractures in Northern Ireland in males and females age 50+ years from 2001 to 2016 using a) age-specific rates in 1997, b) linear projection, c) exponential growth rate.

	MALES			*FEMALES*			*TOTAL MALES AND FEMALES*		
	a Projected from age-specific rates in 1997	*b Projected from linear growth model*	*c Projected from exponential growth model*	*a Projected from age-specific rates in 1997*	*b Projected from linear growth model*	*c Projected from exponential growth model*	*a Projected from age-specific rates in 1997*	*b Projected linear growth model*	*c Projected from exponential growth model*
2001	365	370	380	1339	1410	1450	1704	1780	1830
2006	437	480	510	1440	1640	1740	1877	2120	2250
2011	470	550	620	1539	1870	2090	2009	2420	2710
2016	540	670	820	1642	2130	2540	2182	2800	3360

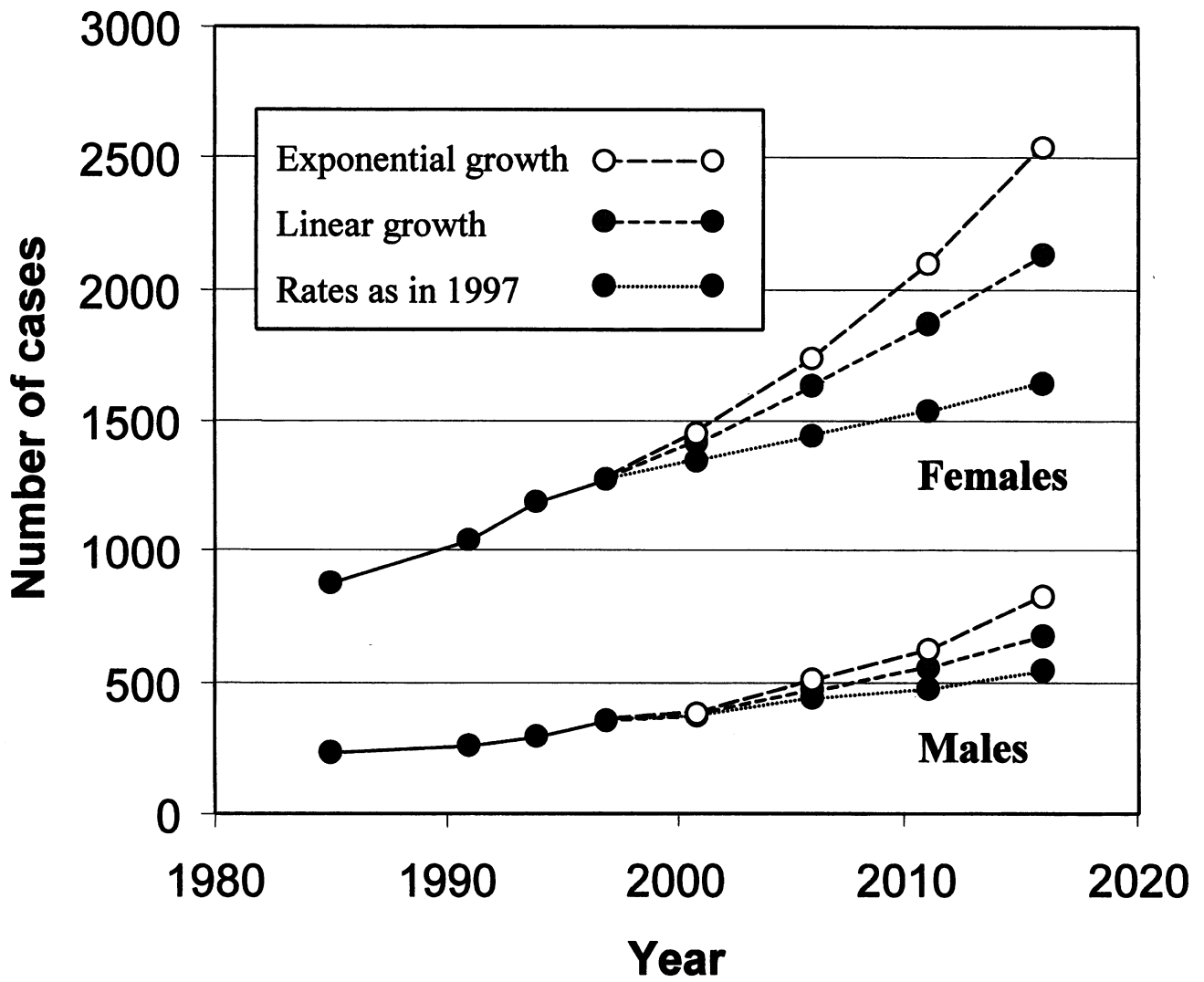

Fig 2. Projected increase in number of hip fractures in Northern Ireland in males and females age 50+ years from 2001 to 2016 using three assumptions

DISCUSSION

This analysis confirms that there is an increase in the proximal femoral fracture rate in Northern Ireland from 1985 to 1997 that exceeds that expected from demographic ageing of the population alone. This secular increase of 1.6% per annum occurred in both sexes and is greater in the older age groups studied but is equivalent in males and females. This is similar to the pattern reported from Finland.[19] This may be due to a cohort effect but the data available is insufficient to allow more detailed analysis or to confirm that there was a significant reduction in hip fracture incidence in younger women age 50 to 64 years (Figure 1). Across the time period studied there is evidence that the secular increase of 1.6% remains constant, and it is thus more likely that the incorporation of a secular increase of 1.6% per annum will accurately predict the future number of proximal femoral fractures.Assuming the absence of a further secular increase after 1997 and adopting 1997 age-standardised rates this would nonetheless result in significant increase in fractures of 55% in males and 29% in females by the year 2016. The higher increase in anticipated proximal femoral fractures in males than females has also been reported from Sweden.[20]

The health costs of the projected increase in proximal femoral fractures are significant. The current cost in Northern Ireland for 1623 fractures in 1997 was £19.5 million assuming the cost of £12,000 per fracture,[3] which is predicted to rise to the equivalent of £33.6 million in 2016 to treat the 2800 fractures projected. There is therefore a pressing need to elucidate the causes of the current secular increase and to clarify our understanding of possible environmental, nutritional behavioural and genetic influences. Similarly possible causes of the absence of a levelling off of age-specific incidences of proximal femoral fracture in Northern Ireland in comparison to that reported for England and Wales[12] merits further study.

In summary the number of proximal femoral fractures in Northern Ireland is increasing faster than that anticipated due to demographic change alone, supporting a secular increase which was evident throughout the time period studied, in marked contrast to that reported for some other regions in the United Kingdom.

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Periprosthetic femoral fractures in Northern Ireland

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SUMMARY

Twenty-five patients with periprosthetic femoral fractures were admitted to the Ulster Hospital between August 1998 and May 2000. Average age was 77 years (range, 42-96 years) with a female to male ratio of 2:1.

Twenty-four of the fractures occurred following primary joint arthroplasty on average 7.6 years from insertion of the primary prosthesis. One patient sustained an intraoperative fracture during revision surgery. In the majority (80%), the periprosthetic femoral fracture was associated with a traumatic event.

On average, two days elapsed from the time of injury until admission to our unit. Time from admission to surgery was on average 4 days. All patients were treated by open fracture fixation. Duration of stay in the fracture unit was on average 20 days.

Prior to their fracture 92% of patients were living at home and 84% were mobile either unaided or with the use of a stick. At most recent review, 72% are back living at home and 60% are mobile either unaided or with the use of a stick.

We emphasise that there is the likelihood of an increase in periprosthetic femoral fractures due to the increasing number of primary arthroplasties being performed on a more active, ageing population. Preventative measures and cost implications are also discussed.

INTRODUCTION

Fractures of the femoral shaft after total hip replacement are increasingly common, and present a complex management problem.[1] Incidence varies from 1% after primary hip arthroplasty to 4% after revision surgery.[2]

Periprosthetic femoral fractures may occur intraoperatively or in the postoperative period and many predisposing factors have been identified.[3] Patients are often elderly and frail thus adding to the difficulties faced by the orthopaedic surgeon when dealing with this complex injury.

Management may be conservative including such measures as skeletal traction and cast bracing. However in the majority of cases surgical intervention is required to achieve stable fracture fixation and to avoid the complications of prolonged bed rest.

Due to the complex nature of these fractures, they therefore place a greater demand on medical, nursing and rehabilitation resources and with the ever increasing number of primary hip arthroplasties coupled with the ageing population, prevention of these fractures should be the key aim of the orthopaedic surgeon.

We present an audit of the management of periprosthetic femoral fractures in our unit and discuss the impact that the ageing population will have on the provision of services for this group of patients.

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PATIENTS AND METHODS

We reviewed the charts and radiographs of 25 patients with periprosthetic femoral fractures treated in our unit between August 1998 and May 2000. Age, gender, side, type of primary prosthesis and date of insertion, primary diagnosis, event leading to fracture, date of injury, referring hospital, time delay to admission to fracture unit, presence of pain prior to fracture, mobility and living circumstances were recorded for each patient. Preoperatively, the femoral fractures were classified according to Johanssen *et al*,[4] into three types (Type I–fractures proximal to the tip of the prosthesis, Type II–fractures through the tip, and, Type III–fractures distal to the prosthesis). The presence of radiolucent lines surrounding the femoral and acetabular components was noted. These were classified into zones according to Gruen [5] for the femoral component and Charnley-DeLee [6] for the acetabular component. ASA grading, intraoperative blood transfusion requirements and operating time were also recorded.

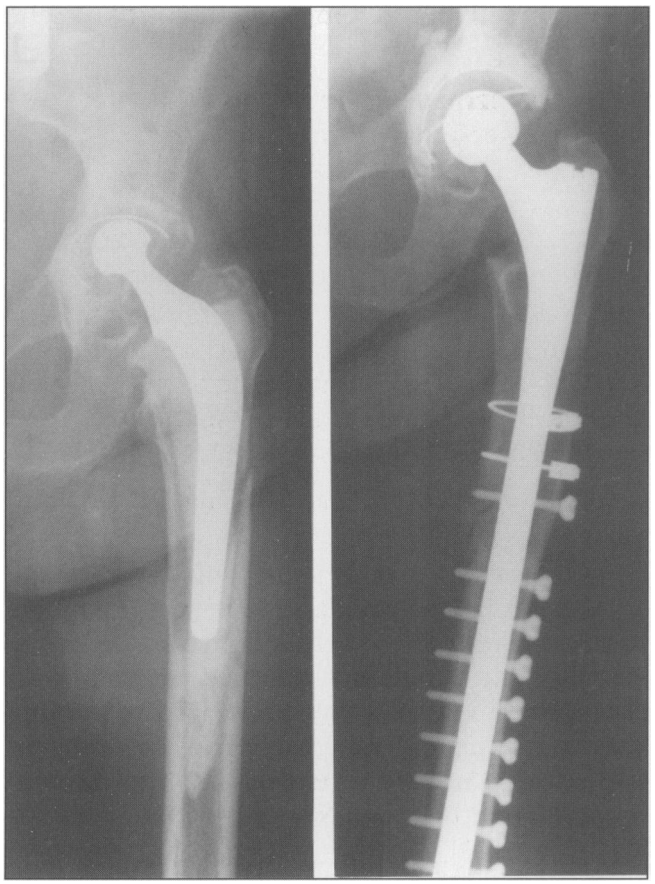

Fig 1. Radiograph of left femur demonstrating – type I periprosthetic femoral fracture around a loose stem with extensive osteolysis on the medial aspect of the distal stem (left); fracture stabilisation using a Kent hip prosthesis replacing the femoral and acetabular components (right).

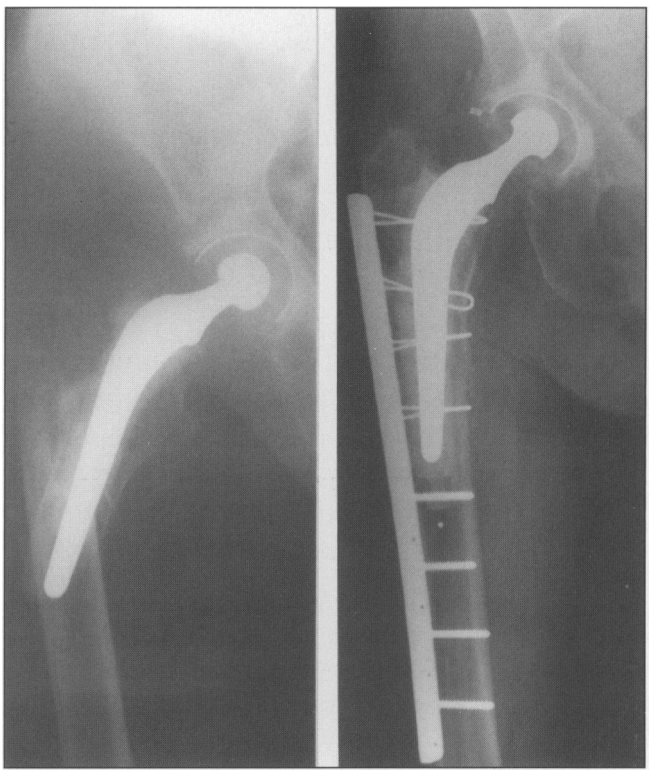

Fig 2. Radiograph of right femur demonstrating – type II periprosthetic femoral fracture at the tip of the stem (left); fracture fixation using a plate supplemented with cerclage wires (right).

All operations were performed by the senior author (JGB). Fractures associated with a loose prosthesis, confirmed peroperatively, were treated using a distal-locking long-stemmed Kent prosthesis (Biomet Merck Ltd, Bridgend, UK) with or without acetabular replacement using an elite plus flanged LPW cup (Figure 1). Fractures associated with a fixed prosthesis were managed using a cable ready plate (Zimmer, Inc., Indiana, USA) and cerclage wiring (Figure 2). Intravenous antibiotics (cephamandole 1 g) were given at induction and at 8 and 16 hours postoperatively. Enoxaparin (40 mg daily) was used for antithrombotic prophylaxis. All patients spent the first 24 hours in the high dependency unit and patients were immobilised until their wound was dry.

Complications (early and late), duration of stay and placement on discharge from the fracture unit was noted for each patient. Home circumstances, mobility and the presence of hip or other joint pain at latest review was also recorded.

RESULTS

Of the 25 cases reviewed (8 males, 17 females), there were twenty-four postoperative periprosthetic femoral fractures and one intraoperative periprosthetic femoral fracture. Average age was 77 years (range, 42-96 years). The right side was affected on 13 occasions and the left on twelve.

The types of primary prostheses were as follows: Charnley [17], Custom [2], Austin-Moore [2], Howse [2], Exeter [1] and one uncemented Porous-Coated-Anatomic prosthesis. Time from insertion of the primary prosthesis to fracture was 7.6 years on average (range, 3 months to 20 years).

Of the 24 postoperative fractures, 20 fractures were associated with a fall. The remaining four fractures were atraumatic in nature (two occurred whilst walking, one resulted from a twisting injury and one occurred whilst turning in bed). Five of these patients were referred via our own casualty department, with the remainder being referred from ten different hospitals distributed throughout the province (Table I). Average time from fracture to admission to our unit was two days (range, 0-eight days). Fourteen patients were ASA grade II, 10 were grade III and 1 grade IV. Four Type I, 19 Type II and 2 Type III fractures were identified.

Time from admission to theatre ranged from 0 to 13 days (average, 4 days). In most cases, patients were delayed because of medical complications, most commonly cardiac or respiratory in origin.

Table I

Distribution of referring hospitals

Referring Hospital	*Number of patients*
Ulster Hospital Dundonald	5
Lagan Valley Hospital	3
Antrim Area Hospital	3
Craigavon Area Hospital	3
Daisy Hill Hospital	3
Coleraine Hospital	2
Erne Hospital	1
Altnagelvin Hospital	1
Musgrave Park Hospital	1
Royal Victoria Hospital	1
Whiteabbey Hospital	1

Fourteen patients required a long-stemmed Kent prosthesis (eight of these patients also required revision of their acetabular component due to the presence of loosening). Ten patients required cable-ready plating and in one case fracture fixation was achieved by means of two cerclage wires. Average operating time was 115 minutes (range, 56-168 minutes) and the volume of blood transfused intraoperatively was on average 450 mls (range, 0-1250 mls).

In the early postoperative period, three patients developed urinary tract infections and one patient had a superficial wound infection. All cases were successfully treated with antibiotic therapy.

Prior to sustaining their fracture, twenty-three patients were living in their own home, one patient was living in a residential home and one was resident in a nursing home (Table II). Twelve patients were mobile without aids, nine patients required a stick whilst walking, three patients required the use of a zimmer and one patient was wheelchair bound (Table III). All patients with a loose prosthesis had hip pain prior to their fracture.

Table II

Home circumstances pre-fracture and at latest review

Home circumstances prior to fracture	*Home circumstances at latest review*
23 Own home	18 Own home
1 Nursing home	4 Nursing home
1 Residential home	2 Rehabilitation units
	1 Residential home

Duration of stay was on average 20 days (range, 8-49 days). On discharge, eighteen of the patients were transferred back to the initial referring hospital, three patients returned to their own home, two patients were discharged to nursing homes, one patient was discharged to a relative and one patient returned to residential accommodation.

Currently, 18 patients are living in their own home, 4 patients are in a nursing home, two patients are still in rehabilitation units (both patients are < 4 weeks following surgery) and one patient is in residential accommodation. At present, five patients are mobile without the use of aids, 10 patients require the use of a stick, eight

Table III

Mobility pre-fracture and at latest review

12 without aids	5 without aids
6 one stick	10 one stick
3 two sticks	8 zimmer
3 zimmer	1 two helpers
1 wheelchair bound	1 wheelchair bound

patients require the use if a zimmer frame, one patient requires two carers to transfer and one patient has remained wheelchair bound.

Late complications include one dislocation at six weeks (managed by closed reduction), two cases of fracture non-union following cable ready plating requiring further surgery, and two patients with persistent ipsilateral hip pain.

DISCUSSION

Periprosthetic fractures of the femur after hip replacement are a serious complication that can prove difficult to treat. Although previously considered uncommon, the incidence of this complication has increased in recent years.[3,7] This increase is due in part to the greater number of primary and revision hip arthroplasties being performed on an increasingly active ageing population.[7]

Periprosthetic fractures of the femur can occur intraoperatively and postoperatively. The incidence of both intraoperative and postoperative femoral fractures associated with primary joint replacement has been reported to be less than 1%.[4,8] Revision surgery is however associated with a greater risk of both intraoperative and postoperative fracture (6.3-17.6%).[3,7] In order to prevent periprosthetic femoral fractures it is important to know which factors increase the risk of this complication. Many factors are well recognised in the pathogenesis of periprosthetic femoral fractures,[3] some of which are preventable whilst others are not. Trauma, osteoporosis (primary and secondary), osteopenia, revision arthroplasty, loose prostheses, cortical perforation and the use of uncemented implants are but a few of the factors that have been identified.[3,7]

The primary goals in treating periprosthetic femoral fractures are to achieve union of the fracture and to create a stable arthroplasty in order to obtain early mobility. Although, many patients with periprosthetic femoral fractures are frail and elderly, operative intervention is often the best, if not the only option. The use of traction and casting, although less invasive, does not remove the risks of pressure sores, deep venous thromboses and other complications associated with prolonged immobility.

Surgical options include open reduction and internal fixation using plates and screws, revision of the femoral component to a long-stemmed prosthesis (Kent hip prosthesis) and revision arthroplasty (both components replaced). These procedures may be supplemented by additional fixation, most commonly using cerclage wires.

Hospitalisation costs are significant for periprosthetic femoral fractures for several reasons. Firstly, patients are often in hospital for long periods (average of 20 days in our study). This does not include the time spent in the referring hospital, both before and after surgery. Secondly, the prostheses are expensive due to their complexity (£2000 per Kent hip prosthesis, £1000 per cable ready system). Thirdly, patients usually require high dependency care or even intensive care at an average cost of £1012 per day, and finally, patients often require a significant input from the rehabilitation team (average cost £134 per day). As a result, the cost per patient is often in excess of ten thousand pounds. However, non-operative treatments, such as traction, may be just as, if not more expensive due to the fact that patients can require a period of in-patient treatment of up to four months. Furthermore, even if fracture healing is achieved, the patient may still require operative intervention for a loose prosthesis. Aside from the financial cost, operative treatment often allows the patient to become mobile earlier and to return to their pre-fracture quality of life. In our series, at latest review, 18 of the 23 patient's resident at home before their fracture were back to living in their own home environment. Also, patients with pain arising from a loose prosthesis are often relieved of their symptoms.

We acknowledge that the follow up period of this study is short (average, 2 months). However, since we are dealing in general with an elderly population with a reduced life expectancy, short-term outcome measures are more important. Regaining independence and relief of pain in the early postoperative setting contribute to enhancing the patient's quality of life.

In conclusion, periprosthetic femoral fractures are becoming increasingly common. With over 2000 primary arthroplasties being performed in Northern Ireland each year, coupled with an ageing, more active population, we predict that the incidence of periprosthetic femoral fractures will increase steadily.

Prevention, through improving surgical technique, early detection of loose prostheses and early revision arthroplasty with routine outcome review, should be the primary approach to this problem.

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Drugs for dementia: the first year

An audit of prescribing practice

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SUMMARY

In March 1998 the Department of Health and Social Services issued prescribing guidelines for the use of drugs for dementia. A criterion based audit of 202 consecutive cases was undertaken over one year which showed that the prescribing guidelines in general were being followed. A small number of patients, 3, were prescribed the drugs outside the guidelines and most failures, 10, were due to poor recording of data in the clinical record. Despite the recommendation of the DHSS no agreed shared care protocols have been implemented but this does not seem to have affected access to these drugs.

As a result of this audit changes have been made with regard to documentation of patient assessments and suggestions made to review Clinical Resource Efficiency Support Team (CREST) guidelines.

INTRODUCTION

Dementia is an organic syndrome characterised by a progressive decline in intellect, behaviour and personality in which there is no clouding of consciousness. It is estimated that 3.2% of people aged 70 - 79 and 10.8% of those aged 80 - 89 years have dementia of the Alzheimer's type (DAT).[1] The condition is usually irreversible and until recently there have been no drugs developed which have had a significant effect on any of the aspects of the condition. In DAT, loss of cholinergic neurones in the nucleus basalis and loss of choline acetyl transferase in the hippocampus and neocortex are the main pathological and biochemical changes.[2,3,4] Research into drugs for DAT has mainly been directed at combating this cholinergic deficit by reducing its breakdown through inhibiting acetylcholinesterase. By the end of 1994 several double blind clinical trials suggested that tacrine, a centrally active non-competitive reversible acetylcholinesterase inhibitor, when prescribed for DAT may improve cognitive impairment.[5,6,7,8] In 1996 evidence was published showing improvement in cognition with donepezil hydrochloride, a piperidine based cholinesterase inhibitor.[9,10] In April 1997, both tacrine and donepezil were licensed for use in DAT. In March 1998, regional guidelines for the use of Drugs for Dementia (DFD) were published by the Clinical Resource Efficiency Support Team (CREST) on behalf of the Department of Health and Social Services (DHSS), Northern Ireland.[11]

The Antrim/Ballymena Psychiatry of Old Age (POA) team uses a multidisciplinary consultant led approach in which social workers, community psychiatric nurses and doctors have a role in the assessment and management of patients. The team, in anticipation of the CREST guidelines of which they had prior knowledge through one of the authors (SAC) extended its service in January 1998 to provide a "Memory Clinic" to which General Practitioners (GP) could refer patients over 65 for assessment of early cognitive impairment. Although suitability for DFD was a prime consideration, it was intended that any patient could be assessed whatever the cause of their impairment. Assessment could be undertaken

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by any team member and protocols were established for data collection, cognitive assessment, prescribing and review which were necessary to ensure adherence to the CREST guidelines. All patients were seen by the consultant at the first appointment to verify the accuracy of data collected and establish the diagnosis. It was required that for all referrals to the memory clinic a physical examination and necessary investigations (e.g. ECG, FBP, U&E etc.) would be performed by the referring GP.

After the first year of DFD use it was decided to perform a criterion based audit of the prescribing practice of the Antrim/Ballymena POA team. The audit objectives were to see if all patients with DAT had been assessed for DFD, if drugs were prescribed in accordance with CREST guidelines and to identify any failures, why they occurred and how they could be overcome. The opportunity was taken to establish a database for future audit and research on this patient population.

METHODS

All patients seen by the Antrim/Ballymena POA team in the period January 1 1998 to December 31 1998 were identified using the hospital patient administration system and the patient record retrieved for audit. The inclusion criteria for audit were that DFD were recommended or prescribed during the audit period or that the patient had a diagnosis of DAT or any variant either in words or using the ICD.10 codes F00.0, F00. 1, F00.2 and F00.9 (pre-senile, late onset, mixed and unspecified Alzheimer's disease respectively).

There were no exclusion criteria.

Patient's notes that satisfied the inclusion criteria were audited. The audit criteria were based on the regional guidelines issued by CREST in March 1998. These, in essence, recommended that a diagnosis using ICD. 10 criteria for DAT should be made by a specialist (in old age psychiatry, elderly care medicine or neurology), and that the disease should be mild to moderate as measured by a Mini Mental State Examination (MMSE) score of 10 to 26.[12] There should also be a shared care arrangement in which the GP would prescribe as advised by the specialist and monitor side effects, and the specialist would keep the patient under review to assess ongoing need for treatment. However, despite attempts to initiate formal shared care agreements locally no agreement has been reached. At present the authors of this paper are not aware of any shared care agreement being implemented anywhere in Northern Ireland so it was decided to acknowledge that all cases would be an audit failure as regards this criterion.

Demographic details, diagnosis, assessment, follow up arrangements and whether or not DFD were recommended or prescribed were recorded from the notes. Reasons for not starting or for discontinuation of DFD were also recorded.

An audit success was that any patient diagnosed with DAT was assessed for suitability for DFD and any patient with mild to moderate DAT (MMSE 10 to 26) was recommended for DFD with follow up by the specialist according to the CREST guidelines.

Audit failures were those patients who received DFD without a diagnosis of DAT, who were not assessed in accordance with the CREST guidelines or if the CREST guidelines were satisfied but the patient was not considered for DFD.

RESULTS

There were 509 patients seen during the year and it was possible to obtain the notes of 505. The inclusion criteria for audit were satisfied in 202 cases. The results of the audit are summarised in the Table.

199 of the audited patient notes contained a diagnosis of DAT, the remaining three cases having a diagnosis of multi-infarct dementia (2) and organic amnesia (1). All three patients had been prescribed DFD.

In the 199 DAT cases, 100 patients were recommended for DFD. Of these 98 satisfied the audit criteria and two did not, having a MMSE <10. These two had been started on DFD for management of severe behaviour disturbance that had failed to respond to all conventional treatments. In all but four cases DFD were initiated by the POA team, the others being started by a GP, a neurologist, a geriatrician and a cardiologist. In 14 patients DFD were discontinued because of continued cognitive decline (1), deteriorating mental state i.e. irritability, aggression, delusions and agitation (7), bradycardia (1), gastrointestinal (GI) side effects i.e. nausea or diarrhoea (4) and one patient because of a cerebrovascular accident. Of the 99 DAT patients not on DFD 50 had a MMSE < 10, 19 had no MMSE recorded and 30

TABLE

Summary of audit results

Audit failures	7	CREST criteria met but DFD not offered
18	5	no MMSE recorded
	3	diagnosis other than DAT but offered DFD
	2	MMSE less than 10 but offered DFD
	1	wrong diagnosis
Audit successes	98	CREST criteria met; DFD offered and used
184	50	CREST criteria failed and refused DFD
	22	CREST criteria met, DFD offered but not used
	14	MMSE impossible to record (documented)

had a MMSE score of 10-26. In the 19 cases where no MMSE were recorded 11 were too mentally impaired to test, one patient was too physically ill and two patients refused testing: they were considered valid exceptions. In five cases no reason was given for a MMSE not being recorded.

Of the 30 DAT patients who had an MMSE of 10-26, five patients had deteriorated cognitively after initial assessment which had taken place several months before the memory clinic started and when reassessed during the audit period had dropped below the lower limit of 10 on the MMSE. Three had become physically ill and two patients had died. Although DFD had been recommended by the POA team three patients refused or were non-compliant with treatment. Three further patients did not receive DFD despite specialist recommendation because either the GP refused to prescribe or the family refused to dispense. In another four cases investigation results were pending before DFD recommendation. DFD were not recommended in two patients due to cardiovascular conduction defects. These 22 were considered valid exceptions. In seven cases no reason was given for non-prescription of DFD and one patient was wrongly diagnosed.

Nearly all the patients had been prescribed donepezil as rivastigmine, another acetyl-cholinesterase inhibitor, was only licensed for use in May 1998, halfway through the audit period.

Follow-up of the 100 patients commenced on DFD occurred in 99 cases; the remaining patient moved away from the area and had been referred to another POA consultant.

In summary, there were 148 audit successes, 18 audit failures and 36 valid exceptions.

DISCUSSION

Although CREST guidelines suggest that various specialists may recommend treatment with DFD the burden is falling particularly on consultants in POA both in Northern Ireland and Great Britain.[13] In this study DFD were initiated by doctors other than old age psychiatrists in only four of the 100 cases. If a consultant in another specialty recommends and a GP initiates treatment, patients usually will be referred to POA teams for follow up, assessment of psychiatric or behavioural problems or for access to domiciliary services. So although DFD may be initiated outside POA teams at some point most patients will become known to the local team. It is probable therefore that most people residing in Antrim and Ballymena who received DFD during 1998 were seen by this POA service. The outcome of this prescribing audit is probably a fair reflection of what is actually happening to the total population receiving DFD and lessons learned can be applied to any specialist prescribing DFD.

Most patients diagnosed with DAT were assessed for DFD, and if prescribed, the CREST guidelines

were generally adhered to and follow-up was universal. However, there were 18 audit failures, a rate of 9%. In three of these patients there was a failure in prescribing i.e. DFD were prescribed for a diagnosis other than DAT. A specialist not recommended by CREST prescribed for one patient with multi-infarct dementia and a neurologist and a psychiatrist prescribed for organic amnesia and multi-infarct dementia respectively.

In 13 patients there was a failure in the POA team's assessment. No MMSE had been recorded in five cases; in seven cases, although the patients met the CREST guidelines, DFD were not considered and no reason given. One patient had been wrongly diagnosed. The patients in these 13 cases had not been assessed in the memory clinic but rather on domiciliary visits or in other psychiatric clinics. It is possible that patients were referred for other reasons e.g. depression or behaviour disturbance and priority given to this and the possibility of treatment of dementia overlooked.

In the two cases of DFD use in DAT with a MMSE less than 10 the indication was for treatment of severe behaviour disturbance which had not responded to conventional treatments i.e. neuroleptics, antidepressives and anticonvulsants. There is evidence that DFD can improve the behaviour disturbances associated with DAT [14, 15] and in these cases families were involved in the decision to use DFD and were aware of the licence restrictions. There was a dramatic improvement in one patient who was able to return to her previous home having been considered for an on-going care hospital bed prior to prescription of DFD.

A small number of patients (3) who agreed to the use of DFD were refused the drugs by the family or the patient's GP. These patients had expressed clear views about treatment and the team felt that the patients' views were valid and competent. Subsequent family discussions and letters to the GPs involved did not change the situation. This is a worrying aspect of service delivery and one that is impossible for the specialist to deal with as family, on whom the patient depends, refuse to fill prescriptions or administer the drugs. Although not a concern of this audit it is an ethical and practical problem which specialists need to be aware of and which requires further debate.

The failure of any grouping to produce a shared care agreement needs to be considered. Although no agreements exist, in reality GPs and specialists are working together to provide a service. If no difficulties are being experienced perhaps there is no need to provide such agreements and the CREST guidelines should therefore be reviewed. CREST should also consider including in the guidelines indications for DFD use in severe behaviour disturbance when conventional treatment measures have failed.

As most audit failures occurred during the assessment process protocols should ensure that anyone with a diagnosis of dementia has a recorded MMSE, that the type of dementia is specified and that a statement is recorded for those with DAT as to whether or not they are suitable for DFD.

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Review

Non-small cell lung cancer and CHART (Continuous Hyperfractionated Accelerated Radiotherapy) – where do we stand?

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SUMMARY

This paper reviews the use of hyperfractionated and/or accelerated radiation therapy in the curative treatment of non-small cell lung cancer, and explains the scientific rationale behind the development of these regimes. The indications, practicalities and economics of introducing them routinely are addressed. Novel radiotherapy techniques are further discussed in the context of current developments and on-going clinical trials.

INTRODUCTION

The estimated average incidence of non-small cell lung cancer in Northern Ireland is over 750 new cases per year.[1] Up to 20% of patients may be suitable for a surgical approach – of those who do have resection (estimated at less than 10% in Northern Ireland), fewer than half will be long term survivors. Tumour-related reasons for inoperability include local invasion and spread to mediastinal lymph nodes. Over the last 3 years, an annual average of 450 patients with lung cancer were referred to the Northern Ireland Centre for Clinical Oncology (NICCO). In 1994, 331 new lung cancer patients received radiotherapy treatment. Extrapolating from fractionation statistics, about 280 patients were treated for NSCLC, of which 38 received radical radiotherapy. This is in keeping with a recognised figure (~10%) for the proportion of patients referred for radiotherapy who have stage I/II disease and are suitable for small volume radical radiotherapy. Standard radical radiotherapy involves treating a planned volume once daily, five days per week, for up to 6 weeks. In the 30-40% who have unresectable locally advanced disease confined to the thorax, survival is of the order of 40% at one year and 15-20% at two years. Failure rates and patterns have been well documented, and indicate an intra-thoracic failure rate of up to 48%, depending on stage, histology and radiation dose delivered.[2] Up to three-quarters of these failed with distant metastases, therefore the role of systemic chemotherapy continues to be widely studied. Nonetheless, many die of uncontrolled intra-thoracic disease and methods of improving the radiotherapy technique which might improve survival, need to be pursued. In recent years non-standard fractionation schedules have been studied in clinical trials for different disease sites. In 1997 a large multicentre prospective randomised controlled trial was reported in the Lancet describing a highly significant survival advantage for locally advanced NSCLC using CHART.[3] This regime involves using smaller fraction sizes, three times per day for a continuous 12 day period. There are obvious practical and economic implications if this were to be made routinely available. The potential health gain in this common disease cannot be ignored.

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BACKGROUND

The concept and advantage of fractionating radiotherapy was recognised clinically within the first 25 years after the discovery of x-rays by Roentgen in 1895. It was Regaud in France, who reported in 1927 that a ram could be sterilised and the scrotal skin spared if x-rays were delivered in several smaller daily doses rather than one large dose.[4] This astute observation, although fundamentally not applicable to treating a tumour located deep to normal tissue, opened the door to many fractionation experiments in subsequent years.[5]

It was in the 1940s that experimental radiobiology studying mammalian cells in culture, began its evolution, and very soon the clinical and laboratory efforts became clearly complementary. By the 1970s, the concepts of normal tissue tolerance and tumour cell kinetics were becoming much better understood. Attempts were made to develop mathematical models to help explain the phenomena of different tissues responding in different ways. If this could be done, then extrapolation might be able to suggest how to improve further the therapeutic index – in other words, how to gain better tumour control without causing further significant damage to the normal tissues unavoidably encompassed within the treatment field.[6,7] This is precisely the way in which a better understanding has been achieved, thus leading to the phase III clinical trials which are described later.[8,9] Understanding the effects of radiation at a molecular level may provide further information on which to develop and optimise clinical radiotherapy.[10]

Although not perfect, it is the linear-quadratic model on which much has been based to date. This model is derived from experimental cell survival curves worked and their shape or 'curviness', as shown in Figure 1. At a lower dose (D1), more damage occurs in acute reacting tissues such as skin or mucosa. As the dose (per fraction) increases (D2), there is a higher probability of damage to late reacting tissues such as spinal cord, lung or kidney. Reproductive capacity of a cell determines its radiobiological survival, partially determined by its ability to repair sub-lethal or potentially lethal damage which has been caused by radiation. In vitro half-time repair of normal tissues has been observed to be between 0.5-2.0 hours. When more than one fraction per day is given, the optimum rest period in order to

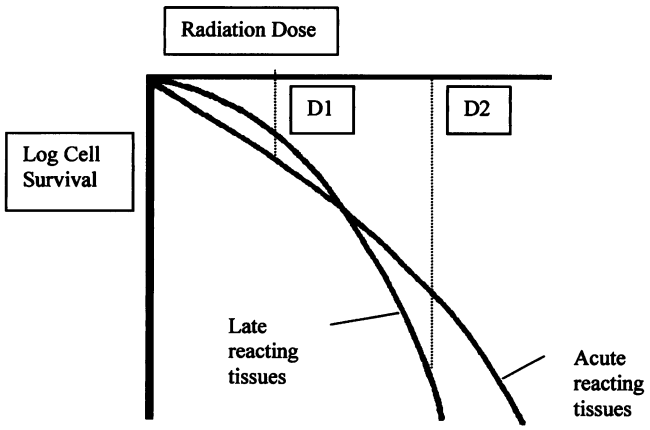

Fig 1. Cell survival curves for acute and late responding responding tissues.

allow maximum normal tissue repair between fractions, has been calculated to be 3-8 hours. The theory of what shares a tissue's cell survival curve involves the 'hit' theory of radiation on DNA, and whether a single-stranded break (SSB) or a double-stranded break (DSB) has occurred. As the number of SSBs increases, the likelihood of that cell not surviving increases linearly, (represented by α). As the number of DSBs increases, the likelihood of that cell failing to replicate increases exponentially, (represented by β). From these parameters, a formula can be derived to closely represent the experimental observations. An α/β ratio can thus also be derived, and for acute reacting tissues such as skin and mucosa it is well represented by a high value of 10, whereas for late reacting tissues such as lung or central nervous system, it is better represented by a low value of around 3. Tumour cells resemble acute responding tissues, and have a high α/β ratio. It has been observed that it is the *dose per fraction* which is the key determinant of late morbidity, whereas the overall treatment time is important for acute morbidity and effect on tumour. It would seem that certain tissues (eg. spinal cord), have a better capability of repair at lower doses per fraction.

The other aspect of radiobiology which is important to the understanding of the rationale behind the design of current fractionation trials, is tumour cell kinetics.[11] Although it can take often months for a tumour to clinically double in size, flow cytometry studies using bromodeoxyuridine to label cells have shown that the real or potential doubling time (Tpot) is of the order of 7 days, (2.3-5 days for lung tumours). The reason for this discrepancy is that

90% of the growing tumour cells are shed, apoptose, differentiate, or simply do not survive, and this is known as the 'cell loss factor'. It is particularly high in squamous cell carcinomas. When a dose of radiation is given, many cells will be killed, but as a result there will be re-vascularisation and re- oxygenation of the remaining cells, allowing improved nutrition and thus survival of a proportion of cells which would otherwise not have survived. The result of this, and other factors, is rapid tumour cell repopulation. Taking these main radiobiological considerations into account, fractionation schemes have been developed – low doses per fraction reduce late normal tissue damage, and shorter overall treatment time achieves maximum tumour kill allowing less tumour cell repopulation during treatment.[12, 13]

In conventional fractionation, doses of 2 Gray are delivered once each day, five days per week. Overall treatment times are normally around six weeks. In *hyperfractionation*, smaller doses per fraction are delivered two or three times per day, leaving the overall treatment time unchanged. This approach theoretically allows the total tumour dose to be escalated without increasing late morbidity, thereby improving the therapeutic index. In a recent review of hyperfractionated radiotherapy in human tumours, it was consistently demonstrated to be more effective in terms of responses than was conventional radiotherapy. However the methodology used to collate the information in this review has been critisized.[14] In *accelerated radiotherapy*, treatment is delivered in a shorter overall time, leaving the fraction size unchanged. The theory behind this is to reduce the amount of tumour cell repopulation during the treatment course. Several different strategies may be employed:

1. A straightforward short intensive course – total dose must be reduced because of otherwise significantly increased acute tissue toxicity.
2. Split-course technique – a rest period is introduced between the second and fourth week of treatment which allows acute normal tissue regeneration to occur so that total dose does not need to be reduced.
3. Concomitant boost technique – the second phase or small volume is given concurrently rather than sequentially.
4. Escalating dose – the total weekly dose is increased each week. It is thought that the regeneration of normal mucosa is stimulated early in the treatment course and might therefore be able to tolerate higher doses as the course is delivered.

By combining hyperfractionation and accelerated radiotherapy, continuous hyperfractionated accelerated radiotherapy or CHART was developed, represented diagrammatically in Figure 2, in order to maximise the potential gain.[15] This technique uses smaller multiple fractions per day and therefore a lower overall total dose. The acute tissue injury occurs only after the course is completed, and can therefore be allowed to heal and regenerate without the problem of having to complete treatment.

The Radiation Therapy Oncology Group (RTOG) published a preliminary report of a prospective randomised study of various irradiation doses and fractionation schedules in the treatment of inoperable carcinoma of the lung, in 1980.[16] Radiological complete response (CR) rate was 10-25%, and 2-year survival only 12%. From this, the exploration of novel radiotherapy schedules has mushroomed, in a determined effort to find the optimum scheduling. Laboratory studies have played a huge part in painstakingly and scientifically providing the basis of clinical studies.

METHODS

The literature was reviewed using Medline, and authoritative texts reviewed. A search was conducted for all papers and specifically all clinical trials in hyperfractionated or accelerated radiotherapy. Fewer than 15 review articles

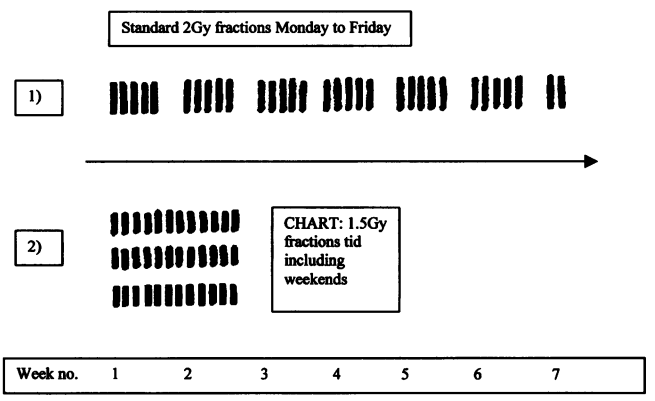

Fig 2. Diagramatic representation of standard and CHART radiotherapy fractionation schedules.

relating primarily to fractionation of radical radiotherapy for NSCLC since 1985 were identified. In these, the role of combined chemo-radiation is discussed prominently.

The practical questions of staffing, and changes required in any radiotherapy department considering introducing these techniques, is not adequately addressed, although any additional cost of multiple daily fractions, has been analysed in detail recently.[17] Information was also obtained from the Radiotherapy Department at NICCO, from the Northern Ireland Cancer Registry at Royal Victoria Hospital, and from the Belfast City Hospital.

CLINICAL TRIALS IN NON-SMALL CELL LUNG CANCER

It has been shown that improving local control is a prerequisite for improving overall survival.[18] An RTOG pilot study in 1985 studied 120 patients who were treated with 1.2Gy fractions twice per day, to total doses ranging form 50.4Gy up to 74.4Gy.[19] There was a 13% complete response rate (CR) and a 33% partial response rate (PR), although the severe late complication rate was 10% with doses greater than 60Gy. Median survival overall was 7.2 months, compatible with other studies giving standard radiation. In 1990, an RTOG randomised phase I/II trial of 848 patients, compared total doses ranging from 60Gy up to 79.2Gy over 5-6½ weeks, given again in 1.2Gy fractions twice per day.[20] Although sub-group analysis must be regarded with some caution, the authors noted that in good performance status patients with stage III disease, a significant survival benefit was seen as the dose was escalated to 69.6Gy, but not thereafter (2-year survival of 29% in favourable stage III). There was no increase in acute or late tissue toxicity.

Regarding predominantly accelerated radiotherapy for NSCLC, a study in 1986 reported 17 patients who were treated with 1.8-2Gy fractions, twice per day to a total dose of 66Gy in less than four weeks.[21] There was a 40% CR, but all experienced oesophagitis, and 24% had severe complications. In another small study, only 12 patients were reported, and four of these had small cell lung carcinoma.[22] The main interest here was in describing a novel three-times per day fractionation schedule which achieved the aim of accelerating treatment but not altering normal staffing levels. Out of only eight patients with NSCLC given 1.1 Gy twice daily, there were six patients (75%) who achieved a complete response (CR) at the primary site of disease, although not all of these patients had a CR at the nodal site as well.

On the basis of the results of the RTOG randomised phase I/II study, a phase III randomised trial was conducted, and this included 452 patients with inoperable intra-thoracic disease (stage II-IIIB).[23] Standard radiotherapy was compared to hyperfractionated radiotherapy and also to induction chemotherapy followed by standard radiotherapy. In the combined chemo-radiation arm the median survival was 13.8 months, and was statistically better than the standard or the hyperfractionated radiotherapy arms (median survivals of 11.4 and 12.3 months respectively). However, a recent up-date has suggested that this benefit was confined to histologies other than squamous cell carcinoma.[24]

Since the early seventies, the RTOG has conducted a number of prospective trials in an attempt to clarify the role of radiation in NSCLC.[25,26] In 1988 an RTOG pilot study looked at 56 patients who were given 75Gy in 28 fractions over five-and-a-half weeks.[27] Daily dose to the mediastinum was 1.8Gy and 2.68Gy to gross tumour. Out of 44 patients who received the prescribed dose, there was a 72.7% response rate with 17 CRs and 15 PRs. Follow-up ranged from 1-3 years; at the time of reporting, there were nine patients alive and disease-free and five who died of intercurrent illness. Twenty-four had died of known tumour.

The concomitant boost technique was tested in an RTOG phase I/II trial in 1993.[28] Three hundred and fifty-five patients were entered, and the total dose was escalated from 63Gy in 5 weeks (45Gy plus 18Gy boost) up to 70.2Gy in 5.5 weeks (50.4Gy plus 19.8Gy boost). The final 114 patients received 70.2Gy in 5 weeks. Severe acute toxicity occurred in 2-3% of patients, and late morbidity was up to 9% overall. Two year survival rates ranged from 16% in the earlier patients to 21% in the later patients. At a similar stage, a phase I/II trial involving 37 patients was reported.[29] They were treated with 2Gy fractions twice per day to a total dose of 50Gy in 4 weeks. There was no increase in acute or late morbidity and 3-year survival was 10%. An RTOG phase I/II study of 59 patients with T3/T4 NSCLC, treated with the concomitant boost technique was reported in 1995.[30] Treatment was given on 5 days per week,

2.68Gy per fraction to the primary tumour over 5.5 weeks. Total dose was 75Gy in 28 fractions. Median survival was 10 months and only 3 patients had severe late complications. It was concluded that this was a feasible technique with acceptable late toxicity and comparable survival rates to the best reported in the literature using either hyperfractionated radiotherapy or combined chemo-radiation.

A prospective trial of split course versus conventional radiotherapy was reported in 1995.[31] Two hundred and seventy-three consecutive NSCLC patients were randomised, and all were staged, treated and followed up by a single physician in an attempt to maintain uniformity. No difference in survival was found between the two arms, median survivals being 11.6 and 10.9 months respectively. The split course arm was associated with less morbidity.

A pilot study of accelerated hyperfractionated thoracic radiation therapy (AHTRT) for unresectable stage III NSCLC was reported in 1993.[32] The main endpoint was toxicity. Twenty-one patients were treated with 60Gy in 40 fractions giving 1.5Gy twice daily with a 2-week break midway through treatment. The median survival was 10.8 months. The 1 and 2-year survival rates were 48% and 29% respectively. Three year survival was 14%. Because of these encouraging results, a further study has since been initiated comparing standard radiotherapy against AHTRT +/- chemotherapy.

In 1990, a phase I/II trial of continuous hyperfractionated accelerated radiotherapy, or CHART, was reported.[33] Sixty-two patients with locally advanced NSCLC received 50.4Gy escalated up to 54Gy, given in 1.5Gy fractions three times per day on 12 consecutive days. Oesophagitis was the only notable complication but was not severe, and 42% went into radiological CR. The 2-year survival was 34%. As a result of these findings, a phase III randomised controlled clinical trial was conducted.[3] Five hundred and sixty-three patients were entered, and randomly allocated in a 3:2 ratio for CHART or conventional radiotherapy (60Gy in 30 fractions over 6 weeks). Patients with stages IA-IIIB lung cancer and good performance status were included. Two-year survival was improved from 20% to 29% (p=0.004, see figure 1) and subgroup analysis indicated that the largest benefit for the accelerated regime occurred in the 82% of patients who had squamous cell carcinoma. In this subgroup, 2-year survival increased from 19% to 33%. Overall, there were no significant differences in acute or late morbidity. As a follow-on from this, CHARTWEL (CHART weekend-less) is being piloted with a view to maintaining the radiobiological advantage whilst producing less interference with normal working patterns.

ECONOMIC AND STAFFING IMPLICATIONS

The cost of treating with a course of radiotherapy has not generally been a significant part of overall analyses before, but then recommending routine out-of hours radiotherapy treatments has not until now, been a prominent issue.[34] It has been argued however, that sub-optimal radiotherapy is more costly in the long run.[35] CHART was used in 10 UK centres during the 2 major trials for both bronchus and for head and neck cancer. The cost of CHART versus conventional radiotherapy was compared,[17] and CHART was not suprisingly found to be more expensive. However, for NSCLC, the difference was calculated to be £698 per patient (less if a hostel ward is available, which is the case at NICCO). If CHARTWEL proves to be as effective as CHART, then not only would the cost be reduced further, but the important issue of staff working times would not be as significant. It is also acknowledged that these costs relate only to treatment, and not to the longer term gain of disease-free or overall survival which in turn reduces the need for palliative and supportive care facilities.

Out of 280 NSCLC patients who had radiotherapy in 1994, at NICCO approximately 40 had radical radiotherapy, and 240 palliative radiotherapy. It can only be estimated how many out of the 240 would have had locally advanced disease, and of those, how many might have been suitable for CHART. Given that only 5% of patients referred for CHART were suitable for inclusion in the randomised trial,[36] then perhaps 12-15 patients from this cohort might have been suitable for entry. Allowing for an increase in the number of referrals over the last few years, it is projected that a total of 60-70 patients per year might be offered an accelerated radiotherapy regime. Additionaal total funding could therefore be estimated to be £40,000-£45,000 per year. In contrast, the expenditure on new chemotherapy drugs in the UK is estimated to be up to £18,000 per patient treated.[37]

OTHER ASPECTS OF RADIATION THERAPY DEVELOPMENT

The place of more intensive fractionation schedules has been evaluated in a number of other situations. The most promising is in head and neck cancers, although the smaller incidence and obvious heterogeneity create inherent difficulties in showing statistical differences in overall or disease-free survival. There have been encouraging results indicating trends towards better local control for more advanced disease (T3/T4).[38, 39] There is equivocal evidence at present in oesophageal carcinoma,[40, 41] bladder transitional cell carcinoma, prostate cancer and malignant gliomas.

Another main area of development in radiation oncology, is the use of conformal radiotherapy (CFRT). Rather than using rectangular fields and lead shielding to modify the shape of the beam, multi-leaf collimators (MLCs) have been developed which enable a more finely shaped beam to be delivered.[42] Three dimensional treatment planning is being used and assessed in many centres throughout the United States and Europe.[43, 44] Preliminary results for lung cancer indicate a 2-year cause-specific survival of 90% for stage I/II and 53% for stage IIIA/B.[45] With improvement in technology and lower costs, there is considerable anticipation.[46] In addition, Intensity Modulated Radiation Therapy (IMRT) is a yet further advance in the ability to deliver more precisely shaped dose distributions, and is created by varying the intensity of the beam across the treatment field. The first patient was treated using this technology in Houston, Texas, in March 1994, and by July 1997, more than 500 patients had been treated using IMRT at 14 institutions.

However, no technology nor combination of other treatment parameters can make up for geographically missing microscopic tumour, so it is therefore vital that imaging and other aids to defining tumour volume and therefore target volume continue to be actively explored.[47] The logic behind physically reducing the amount of normal tissue in the treatment volume is self evident, and dose responses have indeed been shown for locally advanced NSCLC.[48] The ability to dose escalate without increasing normal tissue damage using a conformal approach is undoubtedly exciting, however the benefits will need to be demonstrated by prospective randomised controlled trials before it should be recommended for routine use in the UK. The first of these trials by the Medical Research Council (MRC) in prostate cancer, is already underway.

The idea of optimising radiotherapy either by fractionation schedules, beam shaping, or both, is now the focus of many studies. The selection of patients most likely to benefit from these techniques is crucial, and it may be that using specific assays to determine clonogen doubling time, patients could be more accurately selected for CHART (short Tpot) or concomitant boost accelerated radiotherapy (longer Tpot).[49, 50] Other ways to enhance the tumour kill effect of radiation are with the use of radiosensitisers such as misonidazole,[51] or the concurrent breathing of carbogen and nicotinamide,[52] but these techniques remain experimental. Intraluminal brachytherapy (or radiation delivered from a source, rather than external beams) is also of interest, but as yet has no defined place in the radical treatment of NSCLC.

An interesting concept that is currently under investigation, is bio-effective dosimetry.[53] This has potential to produce treatment plans based on biological effect, rather than absorbed dose, to any given point. Although there is a long way to go before this could be introduced to clinical departments, it is one of the many ways in which the planning and delivery of radiation may be yet further advanced.

CHEMOTHERAPY FOR NON-SMALL CELL LUNG CANCER

The place of systemic chemotherapy in NSCLC has been widely investigated, and there is now evidence that a modest survival advantage can be achieved.[54] Many investigators are therefore looking at chemo-radiotherapy combinations, using platinum-based chemotherapy and intensive fractionation,[55] however there are still reasonable concerns about toxicity.[56] Similarly, with increasing evidence of benefit for combined treatment in unresectable oesophageal carcinoma,[57] the possibility of enhancing local control even further with intensified radiotherapy needs to be investigated. Indeed, the ultimate search for a combination of optimised radiotherapy and the most effective systemic chemotherapy in unresectable tumours, provides considerable material for on-going and future clinical trials.

CONCLUSIONS

While results of surgical resection for early tumours are good this disease has a poor prognosis controlling intra-thoracic tumour in this common disease should be a priority in cancer research and management. Of many possible ways, and combinations of ways, to approach this problem, CHART has shown a statistically significant benefit in a large multi-centre randomised controlled trial. However, adopting this technique into routine clinical practice requires more resources and careful patient selection.[58] Two years on after publication, only a few UK Centres find themselves able to offer CHART to selected patients, and the reasons for this are clearly outlined in a recent editorial.[59] The bottom line includes difficulties in changing departmental working hours, and lack of financial support. There is no real doubt that it ought to be made available; however the practicalities of its introduction as an available standard, should not be underestimated.

Novel and developing radiation therapy must be incorporated as an intregal part of modern cancer management. It is essential that participation in national clinical trials is encouraged, that radiotherapy techniques are optimised, and that combined modality approaches are able to be fully supported.

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Renal replacement therapy in Ireland – the Belfast experience

Based on the 2nd J Creery Ferguson Memorial Lecture of the Royal College of Physicians of Ireland on the occasion of the bicentenary of the Royal Victoria Hospital – 7th March 1997

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"Science is like a web, growing by interactions which reach out in time and space".[1] Such interactions between individuals working in science and medicine have contributed to the jigsaw of knowledge, and these human linkages were as powerful then in their effect as the Internet may become one day.

Dr John Creery Ferguson provides a good example of the interactions and links between Belfast and Dublin. Born in Tandragee in 1802, he was the son of Dr Thomas Ferguson who later practised in Dublin.[2] After graduating in Arts in Dublin University in 1823, John Creery Ferguson studied medicine in Edinburgh where he graduated in 1825. Fellow graduates were Stokes and Corrigan. He then studied in Paris with Kergaradec and Laennec. Kergaradec had already used the stethoscope to auscultate the human pregnant abdomen, and soon after his return to Dublin in 1827 Ferguson heard the human fetal heart, the first to do so in the British Isles. In 1827 he was granted the license and, in 1829 the Fellowship of the King and Queen's College of Physicians. He was appointed Professor of Medicine in the Queen's College, Belfast in 1846 and spent the remainder of his life there. He was the first President of the Ulster Medical Society in 1862. He died in 1865.

Until the end of the second world war, the hospital ward was the kingdom of a senior doctor. In the larger teaching hospitals working alongside the pre-eminent consultant was often a younger colleague, already well qualified, who shared the use of beds, outpatient departments and laboratory facilities, if there were any. The practical work of patient care was done to a large extent by junior doctors in training, differing in experience and skill. Patient care not requiring medically trained personnel was carried out by nursing staff at varying levels of proficiency.

As a student trained during the war, when newly qualified doctors very soon went off to the Forces, I revelled in being a resident pupil. It fell to us to write the clinical history of the newly admitted patients. Proficiency in taking blood samples, giving injections, performing lumbar punctures, aspirating pleural effusions and collections of fluid elsewhere in the body, and the administration of anaesthesia for minor procedures was acquired while a student. The increased confidence in approaching patients is sometimes derided as the "bedside manner", but at its best it is a real social skill to be acquired, which greatly eases contact between patients and doctors. We had the task of testing routine early morning admission urine samples. In the Royal Victoria Hospital students carried out blood sugar and blood urea estimations. It is awesome to remember that decisions on the treatment of patients were actually based on the tests we carried out in the side ward. The flame photometer was still an esoteric research tool, body fluid electrolytes were not yet measured for clinical purposes.

By the early 1950's in Belfast some special areas of expertise had already been recognised, within medicine – cardiology, mental diseases, neurology and dermatology; in surgery – orthopaedics, otorhinolaryngology and ophthalmic surgery. At the end of the war even neurosurgery was carried out by a general surgeon, Mr Barney Purce. Urology had begun to develop, but in this field Dublin was more advanced than Belfast. A supporter of these developments was Professor John Henry Biggart, Dean of the Faculty of

Medicine in the Queen's University from 1943 until 1970. His lectures were always interesting and stimulating; with his personal magnetism they have remained in my memory. His message was that a sound understanding of pathology was not only the key to understanding human diseases, but also the foundation of training for the aspiring clinician. Remembering this dictum, many of us made our way to the Institute of Pathology.

This was the scene in which early attempts at organ replacement occurred. Replacement of renal function was the earliest and still is, by far, the most widely used form of organ replacement therapy. Before the war the physiology of the kidneys and diseases of the urinary tract were poorly understood. Although it was appreciated that renal tubular function controls to a large extent the acid base equilibrium in the body, urine was regarded mainly as a means of excretion of excess water and electrolytes. Nothing at all was known about the important endocrine function of the kidneys.

Effective treatment of kidney failure dates from the invention during World War II of the first workable artificial kidney by Dr Willem Kolffk (Fig. 1) in Klampen, a small town in occupied Holland. He demonstrated that when the kidneys have failed, the waste products of metabolism could be removed from the bloodstream, and that clinical improvement rapidly followed. Moreover, repeated treatment enabled many patients whose kidneys had failed acutely to be kept alive long enough for kidney function to recover. The idea of removing toxic substances from the bloodstream was not new, but Kolff devised the first practical equipment for this purpose, and the first evidence that acute renal failure need not be irreversible.

During Kolff's treatment the patient's blood was passed from a cannula placed in the radial artery into a long tube of cellophane wound around a supporting horizontal drum. The drum rotated on a spindle so that the blood-filled tubing was repeatedly bathed in a tank containing dialysis fluid. The cleansed blood was then returned to the patient through another cannula inserted into an adjacent large vein on the same limb, the process being repeated until the biochemical abnormalities were considerably ameliorated. The blood was prevented from clotting by repeated injections of heparin into the blood circuit. Kolff reported his work in 1944,[3] and subsequently gave artificial

Fig 1. Willen Kolff and the author, 1966.

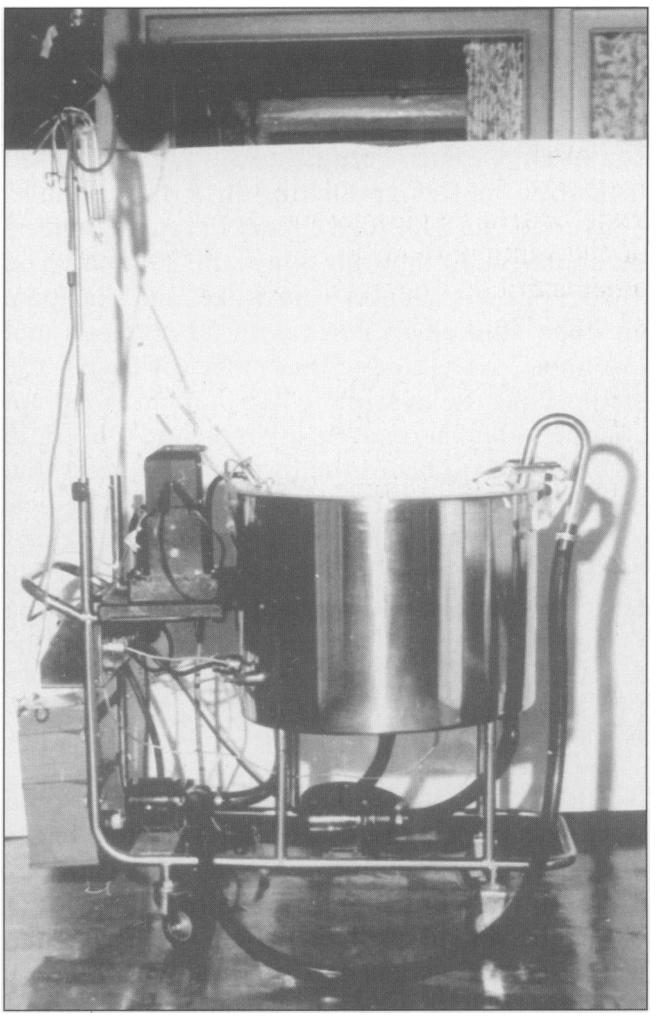

Fig 2. Kolff's "Twin Coil" artificial kidney, in use in Belfast 1959-1970.

kidneys to Hammersmith Hospital in London, Mount Sinai Hospital in New York and the Royal Victoria Hospital in Montreal, all of which reported successful treatments. Sadly, the kidney he gave to Amsterdam was never used. These reports, as well as leading to the setting up of new artificial kidney units over the world, stimulated great interest in the human kidney, its function and its diseases. Kolff went on to devise an improved twin coil artificial kidney, where a very large surface area was provided, the stream of blood issuing from the patient being divided into two, to supply two tubes (Fig. 2). This design could be manufactured sterile and ready for use – the first disposable artificial kidney. In all coil dialysers (several modifications appeared later) the dialysis fluid is pumped around the blood filled dialysis tube, instead of the tubing being rotated in a stationary bath of fluid. The coil is supported in a container, the fluid is pumped through the coil and splashes back into the bath to be re-circulated. About the mid 1960's Kolff's team with the commercial support of the Dow Corning Company jointly developed the capillary kidney. In this blood is pumped through enormous numbers of capillary tubes spun of dialysis membrane, around which the fluid is pumped. Although intended to be a disposable kidney, in some centres it is cleaned and re-used for treatment of the same patient. Kolff went on to work on other artificial organs. By 1966 he had produced an artificial heart.

My experience as a house surgeon in 1947, with Mr Cecil Woodside (Fig. 3) in the Royal Victoria Hospital, proved to be the foundation of my career in renal medicine. Woodside had achieved international recognition for his work on stone disease, and was to have been awarded a medal at the International Congress of Urology in Barcelona in 1939, which was cancelled because of the outbreak of war. There were always patients in his wards undergoing investigation and surgery for renal stones. He urged me to consider a career based on research into causation of stone disease. However paediatrics had always attracted me, and after a post as house physician in the Royal Belfast Hospital for Sick Children, I went to Professor Biggart's department to work for the degree of MD. This achieved, I went to see the Professor of Paediatrics hoping to be accepted as a trainee in his specialty. His immediate answer was "No!" I was a woman and married, there were plenty of young men aiming for his specialty.

Fig 3. Cecil J A Woodside, FRCS (1897-1955): Senior Surgeon, Royal Victoria Hospital, and first Chairman of the Northern Ireland Hospitals' Authority.

I was bitterly disappointed as I had won the Gold Medal in Diseases of Childhood in the final MB examination and two postgraduate scholarships in the subject. My husband suggested that I should learn about biochemistry, but the Professor of Biochemistry would accept me only on condition that I was prepared to work as a research student for a PhD. Three years later, now with the degrees of both MD and PhD, I seemed little better equipped for the hospital job rat race.

Mr Woodside, maintaining his interest in me, had a good suggestion – Dr Graham Bull who had recently come to Belfast as the first full-time Professor of Medicine (Fig. 4), might have a place for me. Quite reasonably, after hearing my story, Professor Bull said that while there was a post as lecturer in medicine available, I had not worked in clinical medicine for nearly five years, and was not a suitable candidate. However, he suggested that I might be a suitable candidate for a personal grant from the MRC, if I could produce a research topic. Bull was just about to set up a laboratory for the Department of Medicine, and I suppose saw me as someone with laboratory experience who could help choose new apparatus and organise it. He said "Go and bash the books in the library and come back with a detailed

Fig 4. Professor (later Sir) Graham McG Bull, MD, FRCP (1918-1987): first full-time professor of Medicine, The Queen's University of Belfast.

project". Amazingly this resulted in a personal grant from the MRC which supported me for five years.

In 1948 Graham Bull had arrived at Hammersmith Hospital in London from Cape Town. The team there, including Malcolm Milne, Russell Fraser, Joe Yucas and Jan Borst began to use Kolff's rotating drum kidney. By Bull's accounts dialysis treatment with the original model was a formidable task. It took several hours to prepare the apparatus, and six hours for the treatment. The patient often developed rigors and even convulsions. In the hope of avoiding its use, he and his colleagues developed the so-called "conservative treatment".[4] This was based on careful control of fluid and electrolyte balance, provision of calories as pure carbohydrate and fat to spare breakdown of body tissues with its resultant production of nitrogen and potassium. The regimen later became famous as the Bull-Borst diet. In theory the treatment could be used anywhere and doubtless saved many lives world-wide. Many patients with acute renal failure recovered their kidney function within a week or 10 days, and conservative management was sufficient to save them, but for those with more severe kidney failure, it was not sufficient. Moreover the diet of glucose or lactose and oil further increased the patients' nausea, and they developed sore mouths. They became very thirsty, but if they were totally anuric fluid intake had to be restricted to 400 mls daily. Cardiac arrest from a high potassium level was a serious risk.

One day in 1958, Professor Bull called me to his room. He had with him Mr John Megaw (Fig. 5) Consultant Surgeon at the Belfast City Hospital. Mr Megaw saw specialisation in urology beckoning, but was hesitant about giving up general surgery – in fact he never did so. The event which led to his visit was a patient we had just treated in the Royal Belfast Hospital for Sick Children. He was a boy seriously injured in a road accident who developed acute renal failure. Conservative treatment appeared to be insufficient, and he was transferred to Hammersmith Hospital in the belief that without artificial kidney treatment he would die. Ironically, he began to produce urine during the journey to the Hammersmith. This event led to questions being asked in the Stormont Parliament, followed by a statement urging that Northern Ireland should have an artificial kidney. Megaw saw this as an opportunity to enhance the image of the Belfast City Hospital, hence his visit to Bull. Until Megaw's momentous visit to him in 1958, Bull had maintained that most patients with acute renal failure would recover with conservative treatment, and that the population of Northern Ireland was not big enough to justify an artificial kidney. Megaw wanted to set up an artificial kidney unit at the Belfast City Hospital and was looking for someone with suitable training. Bull knew that I desperately wanted a post which gave more contact with patients – I already ran a special clinic for patients with kidney stones. I had never seen an artificial kidney and he knew this, but silenced my objections, explaining to Megaw how my training and experience suited me for the project.

Some weeks later, with Megaw and John Storey (head of the firm which supplied hospital equipment to the Northern Ireland Hospitals Authority), I set off on visits to see the two models of artificial kidney then available. In Leeds General Infirmary Dr Frank Parsons

Fig 5. John Megaw, FRCS (1913-1971): Senior Surgeon, Belfast City Hospital, whose plan it was that an artificial kidney service should be situated there.

demonstrated his rotating drum kidney. He reiterated the problems described by Bull, and I became more and more disenchanted with the whole idea. We then visited the RAF Renal Unit at Halton, headed by Dr Ralph Jackson (later Air Vice-Marshall Sir Ralph Jackson) who showed us the twin coil kidney. This appeared to be much simpler in use and very efficient. Jackson assured me that my laboratory background was a good preparation. What I needed was a suitable isolation room, the twin coil artificial kidney, and a technician to assist me in preparing the equipment and weighing out chemicals. He could arrange for me to stay for a short period in Halton to see how it was set up and used. He advised that I should wait until our equipment arrived, and I had had time to do mock set-ups before the visit.

The twin coil artificial kidney was ordered and plans were made to remodel Ward 9 in the main block of the Belfast City Hospital to include a two-bed renal unit. A technician, Maurice Bingham, was recruited from the biochemistry laboratory. The artificial kidney arrived in early June 1959, but Ward 9 was not yet ready and we were given a small storeroom in which to store it.

It happened that a refresher course was being held in the City Hospital two days later. Mr Megaw insisted that I should set up the artificial kidney and demonstrate it to the general practitioners. I had seen a twin coil kidney once – Maurice Bingham had never seen one. We read the accompanying booklet and proceeded to set it up, using red ink to mimic the blood circuit. Mr Megaw and the assembled family doctors seemed suitably impressed.

Meanwhile Dr Haskel Eliahou from Israel, who was just finishing a year's attachment to Professor Bull's ward, came to ask me to let him see the new kidney in action before he returned home. We persuaded Mr Richard Welbourn, Senior Lecturer in Surgery, to ligate the ureters of a dog, which after 48 hours became profoundly uraemic. The first haemodialysis in Northern Ireland was carried out in the animal theatre in the Department of Surgery. We managed to treat the dog with a short dialysis, enough to demonstrate a considerable reduction in the blood urea concentration. Dr Eliahou returned to Israel where he set up the Renal Unit in Tel Aviv, and later became a world expert in the treatment of acute renal failure.

I was now ready to visit Halton and see how dialysis should be carried out. However, the following week an elderly man was admitted in uraemia due to prostatism. He was semi-comatose with a blood urea of over 600 mg/100 ml. Megaw demanded that I should treat him by dialysis. Maurice and I set up the twin coil kidney in Ava 2 theatre in the children's department of the Belfast City Hospital and Eileen Martin, the technician in the Department of Medicine Laboratory, weighed out three sets of chemicals to make up three batches of dialysis fluid. On 22nd June 1959, in fear and trepidation we treated our first patient. Unfortunately after immediate improvement he died within a week of a stroke.

From then on we were in business. Still without our accommodation, our headquarters a storeroom, we became a travelling dialysis service. The hospital van took us and our equipment to the patient, most frequently in the Royal Victoria Hospital. We dialysed patients there and in other Belfast hospitals many times. There were always problems, plugs did not fit and there were difficulties with the water supply. Our second patient recovered from post-natal renal failure after 36 days of virtual anuria. When I last saw her, more than 20 years later, she had

normal renal function. She had undergone another successful uneventful pregnancy. Another early patient who developed acute renal failure following an incompatible blood transfusion presented a problem in treatment. It was necessary to cross-match about 250 units of blood in order to find the 15 units of compatible blood needed to prime the dialyser for her several treatments. She too made a long-term complete recovery – and so I never got to Halton to see how haemodialysis should be done.

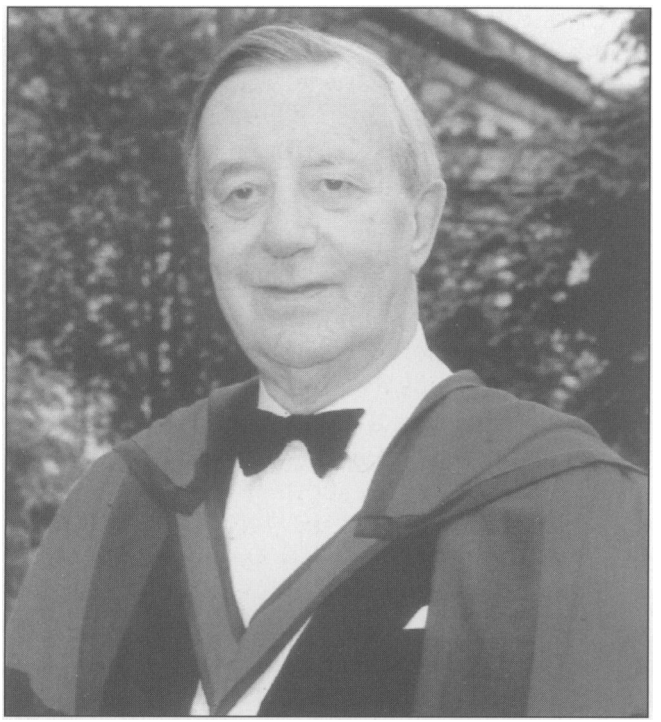

Fig 6. Anthony Walsh, FRCS (1922-1997): dialysis surgeon and later first transplant surgeon at Jervis Street Hospital, Dublin.

At this point during a family holiday we spent a night in Dublin. I learned that Jervis Street Hospital had recently obtained an artificial kidney, which was operated by a Dr Joe Woodcock. They had done their first haemodialysis in 1958, and were now at about the same stage as ourselves. A few months later the Dublin urologist, Anthony Walsh (Fig. 6) arranged a meeting with Billy O'Dwyer (Fig. 7) the physician of the Jervis Street team. Late that Saturday night Tony Walsh was called in to insert cannulae for a two year old girl with undiagnosed renal failure. I remember that she was as white as a sheet and that her bladder was empty. It was difficult to maintain her blood pressure during dialysis, despite much transfusion, and we thought she might not survive. However, she recovered after several more

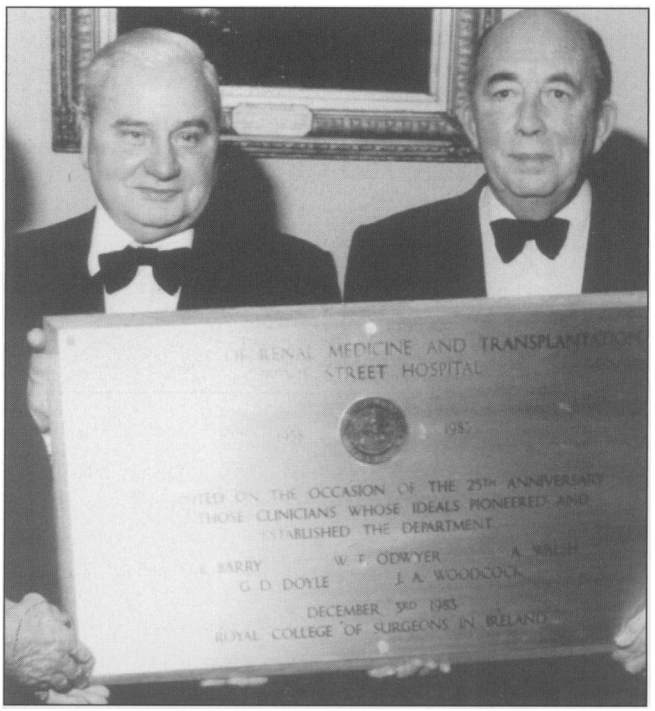

Fig 7. William O'Dwyer, MD, FRCPI (1916-1997), consultant physician, Joseph Woodcock, Woodcock, FRCPI (1918-1997): who collaborated with Anthony Walsh at Jervis Street Hospital, Dublin, in setting up the haemodialysis and renal transplantation service there.

treatments over the next ten days. For all three of us it was a first encounter with the acute haemolytic uraemic syndrome which recently had been described. That episode was the beginning of life-long friendships with Billy, Tony and their wives. In 1961 when the birth of my youngest child was imminent, I was still working single-handed. Billy telephoned from Dublin to say he and their team would hold themselves on call should dialysis be needed, while I had maternity leave. Maternity leave was three weeks beginning on the day on which my son was born.

In 1960 we moved into the new two-bed dialysis unit in the Belfast City Hospital. That year Maurice Bingham emigrated and was replaced by Jack Lyness. In 1963 Staff Nurse Kay Maguire (Fig. 8) joined the team and led the nursing developments until her untimely death in 1987. We continued to provide a travelling service when needed, in the RVH Respiratory Intensive Care Unit, in the Mater Hospital's single small room which served for all patients needing intensive care, in the Ulster Hospital, the Craigavon Hospital intensive care unit and even as far as Altnagelvin.

Fig 8. Kathleen (Kay) Maguire, SRN (1935-1987): first staff nurse, later Senior Nursing Officer, Renal Unit, Belfast City Hospital.

By 1964 there were plans for the BCH Tower Block, which was to include a haemodialysis unit. A sketch plan was drawn with the enthusiastic help of Paddy Semple, one of the two architects responsible for the tower block. In 1965 it became clear that some provision for the growing need of the renal unit would be essential long before the most optimistic estimate for the opening of the tower block. Space was not available in the main block and the solution was a new building behind the Ava Hospital. Following the successful treatment of our second chronic haemodialysis patient by renal transplantation in 1965 in St Mary's Hospital in London, we were determined to develop a service for the treatment of chronic renal failure which would include transplantation. We had established Kiil kidney dialysis (more economical in disposable items and did not require priming blood) for four patients with chronic renal failure in 1965, improvising the facilities we lacked. A new patient could be accepted only when an existing one was transferred to London for a transplant. The design of "Renal 1", with differential pressure ventilation allowed good quality reverse barrier nursing, to protect patients from hospital borne infection. This was then thought essential for transplantation as there was then a very high death rate from sepsis of immunosuppressed patients. Death from sepsis was indeed very rare in our subsequent transplant programme. Haemodialysis could be provided in each room, including the transplant suite. A large theatre was equipped for simultaneous dialysis of two chronic renal failure patients.

Until 1968 the medical staff consisted of myself alone. From time to time Professor Bull's British Council Research Fellows came to gain practical experience in the management of renal failure. From 1962 onwards a succession of British Council Fellows, all from overseas, came to Belfast for the specific purpose of studying the management of renal failure in the Renal Unit. Some stayed long enough to qualify for a PhD. Most returned to their home countries to set up renal services. In 1968, when the first phase of Renal 1 was opened, Dr Soyannwo from Nigeria and Dr Dimtrios Oreopolus from Greece were working in the unit, and both graduated PhD. Oreopolus went to Canada where he later earned world renown for his work on continuous ambulatory peritoneal dialysis (CAPD).[6]

From the early 1970's, haemodialysis was used for the treatment of more and more patients suffering from chronic renal failure. Almost as soon as it opened, the six places for regular dialysis in Renal 1 were insufficient. A new wing was planned to contain 10 haemodialysis beds and ancillary rooms, and opened in 1972. The 30 patients for which Renal 2 was planned soon proved insufficient, and this unit has been reorganised many times to provide treatment for more and more patients. With improved dialysis equipment leading to shorter dialysis time, and use of preparation rooms no longer needed, eventually 178 patients were treated in Renal 2, 55% three times and 45% twice weekly. Renal 1 and Renal 2 were replaced by a new 40-bed unit, the Belfast City Hospital Dialysis Unit, in 1998.

In the late 1960's access to the patient's bloodstream by Scribner's semi-permanent shunt was superseded by the Bresco-Cimino subcutaneous arteriovenous fistula. This technique was brought to Belfast by a young Dublin urological registrar, Sean Hansom, to whom we continue to be grateful. During the late 1970's systems of pumps were devised permitting dialysis by a single needle instead of two, which causes less discomfort to the patient, and sometimes enables the use of a less than ideal AV fistula. The Northern Ireland Kidney Research Fund provided for the special equipment needed in 1978.

This fund had been set up in 1971 by Mrs Josie Kerr and her husband Walter, with the help of other patients, their families and friends. Their devoted work has been of immense help over the years. Most of the present staff of the Nephrology Unit, including Dr James Douglas and Dr Ciaran Doherty, were Northern Ireland Kidney Research

Fund Fellows. Many nephrologists trained in the same way emigrated to posts on the other side of the Atlantic and Europe. Mrs Kerr was later awarded the MBE.

It was known from the end of the 19th century that the peritoneal membrane was semi-permeable, permitting the passage of water and electrolytes from the peritoneal cavity into the bloodstream. From the 1920's experiments in animals and human beings showed that the peritoneal membrane could be used for removal of some substances by dialysis. Peritoneal dialysis can be carried out without special equipment other than a suitable plastic cannula and a modified Y-piece transfusion set, using sterile dialysis fluid. This simple method was used from the early 1960's for treatment of acute renal failure, but was less satisfactory than haemodialysis mainly because of the high risk of peritonitis.

In 1977 Popovich and Nolph in the USA showed that very effective control of uraemia was achieved by continuous peritoneal dialysis, the fluid being changed only four times in the 24 hours.[5] The patient continued with normal activity, but the method had the disadvantage of a high incidence of peritoneal infection. Oreopolus, now in Toronto, introduced several improvements which led to world-wide acceptance of this method of treatment of chronic renal failure.[6] The important change was the substitution of plastic bags instead of bottles to contain the dialysis fluid. After the fluid has run in, the bag is rolled up and carried around in an unobtrusive bag at the waist, until needed to collect the spent fluid. It is not detached from the permanent flexible cannula during "dwell time". This CAPD method of self-dialysis can be taught to patients of moderate intelligence in one or two weeks. The high rate of peritoneal infection has fallen to acceptable levels with improvements both in technique and in dialysis sets. Automation can be used for self-treatment allowing reasonable hours of sleep during the night. However, some patients may later require haemodialysis because of failure of the peritoneal membrane to continue to filter efficiently. The use of CAPD has become widespread especially for children and older individuals. In Northern Ireland after a rapid increase over the past decade, the number of CAPD patients seems to have stabilised at about 20% of the total dialysis population although overall the numbers of patients on dialysis treatment continue to increase.

As long ago as 1902, Ullman had demonstrated in Vienna that a kidney transplanted from its normal site to the neck would produce urine, even a kidney taken from another animal or another species. Carrell and others repeated this experiment but found that urine production ceased after a few days. Attempts by Voronoy in the Ukraine about 1933 to transplant cadaver kidneys in the human were unsuccessful. In 1935 a young research worker, George Davis Snell, having chosen mouse genetics as his research subject, joined the Jackson Laboratory at Bar Harbour, Maine. The work at the Jackson Laboratory was centred on transplantable tumours in mice, and it was known that resistance in mice to foreign strains of tumours were genetically determined. Snell created and maintained large numbers of inbred mouse strains and their cogenic lines for his research. Lacking a name to describe these postulated genetic factors he called them "histocompatibility genes" on the suggestion of his neighbour across the hall. Using his inbred mice he was able to define lines which differed from a standard inbred strain by a single histocompatibility gene, by the introduction of a foreign but closely linked gene.[9] About the same time Peter Gorer, working in Guy's Hospital in London, devised a serological method of identifying antigenic differences between strains, publishing his classic paper "The genetic and antigenetic basis of tumour transplantation" as early as 1937.[7] Gorer went to work in the Jackson Laboratory in 1946. It turned out that Gorer by serology and Snell by inbred mouse linkage had identified the same locus, H-2. H-2 in the mouse turned out to be the analogue of HLA in the human.

During this time, Billinghan, Medawar and Brent in London were studying skin transplantation in rabbits. In 1944 Medawar published his experiments on skin autografts and homografts.[8] Later in a joint study with Snell they demonstrated that a graft of skin made to an unborn mouse would survive. This experiment led to the concepts of immunological tolerance and enhancement. This was the basis of work on the potential for tolerance and enhancement to contribute to human transplantation, discussed at many meetings of the British Transplantation Society in the 1970's.

Snell continued to work with H-2, identifying new alleles, and it became apparent that H-2 in the mouse was a model of great importance in human transplantation. His last area of research

was the identification of alloantigens on lymphocytes using the chromium labelled cytotoxic test. He continued to work at the Jackson Laboratory for the rest of his life. In 1980, aged 76, he shared the Nobel Prize with Barju Benacerrag and Jean Dausset, for the discovery of the major histocompatibility complex. Sadly, Peter Gorer died early, and did not share in the greatest accolade.

Meantime attempts to transplant kidneys in humans in Boston failed, as did attempts by Küss in Paris using steroid in the earliest attempts at immunosuppression. However it was shown in Boston that in animals skin could be transplanted between litter mates, the transplant not being "recognised" as foreign tissue. This led to the first successful human kidney transplant carried out in 1954 in Boston, by Murray and Merrill between identical twins. Over the next decade transplantation between identical twins was carried out in several centres in Europe and America without evidence of rejection, though some failed for technical reasons. An identical twin transplant carried out in Belfast in 1962 was a technical failure.

Few patients reaching end stage kidney failure have a twin able and willing to provide a kidney. Transplantation between less closely related individuals invariably failed from rejection. Whole body irradiation prevented massive infiltration of the graft with lymphocytes and other inflammatory cells but the patients died from uncontrollable sepsis associated with bone marrow suppression. Attempts to use drugs for immunosuppression were made in animal models. Mercaptopurine was found to prolong graft survival in dogs but was very toxic. Burroughs Wellcome in the New Jersey Laboratories produced a derivative of mercaptopurine, azathioprine, which proved a good immunosuppressive and much less toxic when used for dog kidney grafts by Roy Calne and others in Boston. In 1962 Calne and Murray used azathioprine successfully when a kidney taken from a patient dying during an openheart operation was transplanted into an unrelated individual. In 1962 Goodwin in Boston reported successful treatment of several rejection episodes with steroid in a mother-to-child transplant, though the child finally died from sepsis. Azathioprine combined with steroid became generally accepted as the main immunosuppression for transplantation for over two decades. Both are still in use in combination with other drugs. In 1976 cyclosporin A, a fungal metabolise was found to be a potent immunosuppressive; others have followed, but there is, as yet, no perfect immunosuppressive. Immunosuppression is a huge topic in itself.

The Belfast transplant programme began in 1968 after the opening of Renal 1. This provided a suitable environment. Dr Joseph McEvoy was appointed second nephrologist; and Mr Stewart Clarke and Mr Joseph Kennedy were appointed each to give two consultant sessions to provide continuous cover for harvesting and transplantation of cadaver kidneys. Dr John Alexander (Fig. 9) and Dr Cecil Hewitt volunteered to provide anaesthesia. Joseph Kennedy and John Alexander continued to take part in the transplant programme until retirement in 1996. Other consultants and trainees have contributed while the service has continued to develop, including Mr Gordon Loughridge, Mr Richard Donaldson, Dr James Douglas and Dr

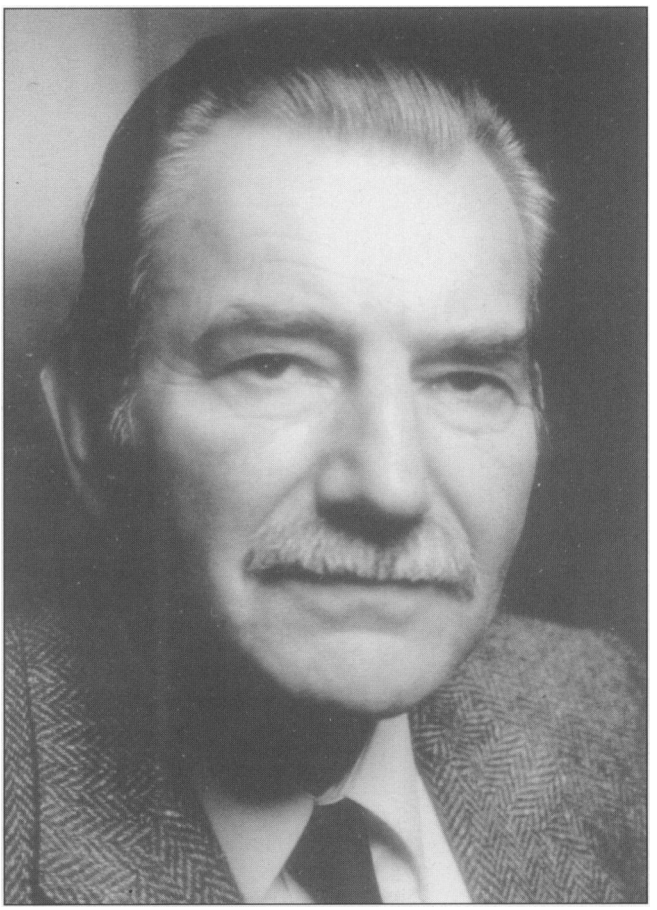

Fig 9. John Alexander, MA, FRCPI, FFARCI, DA (1930–) consultant anaesthetist at the Belfast City Hospital, one of two anaesthetists who formed the first anaesthetist rota for renal transplantation from 1958.

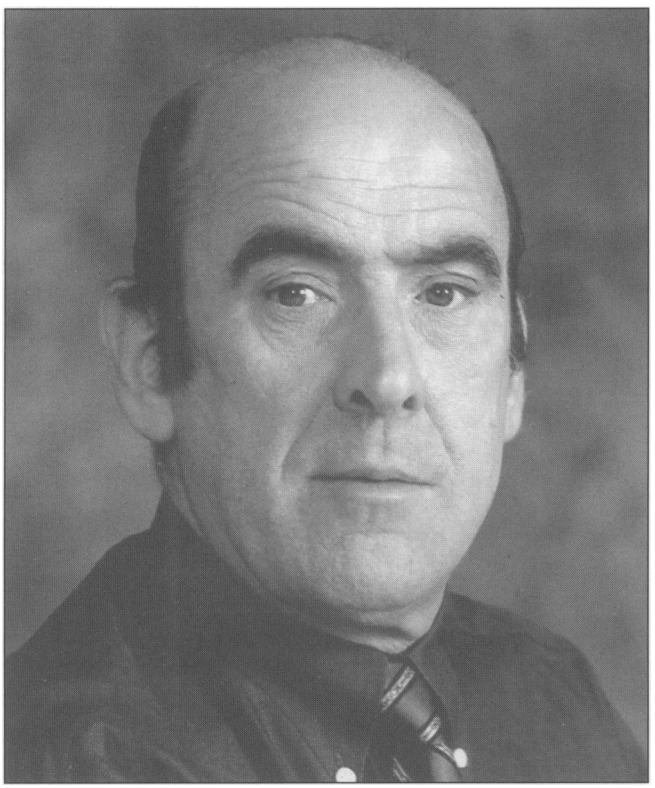

Fig 10. Derek Middleton, BSc, PhD (1946-): Tissue Typing Scientist associated with renal transplantation since 1968.

Ciaran Doherty. Dr Sam Nelson set up the Tissue Typing Service in 1968, later developed by Professor Derek Middletorto gain an international reputation.

The programme was carefully planned, using cadaver kidneys as the main source of grafts. The role of each member of staff was agreed, and each step of the procedure for the removal of cadaver kidneys, their insertion into the recipient, the drugs for immunosuppression and the post-operative care written down to form the "Belfast Recipe for Transplantation".[9] During the early years all the grafts came from cadavers, later occasional living related donors were used. A significant difference from other centres was the sparing use of corticosteroids. We used much lower doses of steroid, for induction, anti-rejection treatment if needed and long-term maintenance therapy.

The first transplant was carried out on 22nd November 1968. Initially successful it was lost three months later from irreversible rejection. Thereafter we achieved a one year first cadaver graft survival of 80% which was much above the 50% or even less than recorded in many units.

Fig 11. The team responsible for renal replacement therapy for Northern Ireland, with the author.
Back row: Derek Middleton, James Sandford, John Connolly, Robert Kernoghan, Ciaran Doherty, Peter MacNamee, Henry Brown, Peter Maxwell.
Front row: Claire Hill, Peter Garrett, William Nelson, James Douglas, Mary McGeown, Joanne Martin, Maurice Savage, Mary O'Connor.

Our results continued to top the figures collected by the UK Transplant Service until usage of cyclosporin A became general.

By 31st December 1996, 924 transplants had been carried out for 800 patients. Sixty-four came from living donors and 860 from cadavers. The one year first cadaver graft survival continues to hover about 80%, despite many much older and otherwise disadvantaged recipients. I am particularly proud of the long term transplant results; 56% of grafts transplanted more than 10 years ago continue to function.[10]

The hope that xenotransplantation may provide organs for transplantation is soundly based on the progress already made to produce transgenic pigs. Certainly progress is being made but there is much to be done before xenotransplantation becomes a clinical tool. It may soon be possible to suppress the initial hyperacute rejection of the transgenic organ, but we do not know whether the kidney's numerous functions will translate unchanged across the species barrier. There is anxiety about pig viral infections proving lethal in humans. Some have expressed ethical concern. I believe that xenotransplantation will become a clinical reality, but that the time may be more distant than some enthusiasts hope.

The future in Belfast is in the hands of the present capable team (Fig. 11). We are happy to welcome a new surgical member of the team, Mr John Connolly, whose brief includes vascular access surgery as well as retrieval of organs and transplantation. The future looks bright for Dublin's renal services. The Beaumont Hospital team has just published an innovative technique on the successful use of kidneys from tiny children for *en bloc* transplantation into adults.[11] Dublin teams have already successfully embarked on liver and heart transplantation. Long may the friendship and co-operation continue between Belfast and Dublin, based firmly on our common interests over the years.

ACKNOWLEDGEMENTS

Besides the help of many already mentioned, I gratefully acknowledge the help of the staff of the Robert Gray Regional Respiratory Intensive Care Unit at the Royal Victoria Hospital, and those of many other intensive care units throughout Northern Ireland, who have facilitated the provision of organs for transplantation. We are well aware of the great increase in their own workload which this imposes. I must again thank the members of the Northern Ireland Kidney Research Fund for their great support over nearly 30 years.

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Case Report

Airway management in a patient with a nail-gun injury to the floor of the mouth

G T Dobson

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It is uncommon for patients to present with a traumatic penetrating injury to the floor of the mouth with the object still in situ. This type of case presents an anaesthetic challenge in terms of airway management since both the presence of the object and the trauma of the injury have the potential to cause airway compromise. This report details the management of such a case.

CASE REPORT A 26 year-old man was admitted to hospital complaining of blurred vision and facial pain. He had been using a high-pressure air-driven nailing gun when an accidental discharge caused a penetrating injury below the mandible. Initial examination in Accident and Emergency showed an entry wound only and otherwise he was alert and orientated with a normal Glasgow Coma Scale and a patent airway. Radiographs showed the nail to be lying lateral to the body of the right side of the mandible, passing via the maxillary sinus into the right orbit (Figs. 1 and 2). Ophthalmological assessment showed decreased visual acuity in the right eye due to injury to the posterior pole of the retina and a traumatic optic nerve injury. The patient was scheduled for removal of the nail under general anaesthesia.

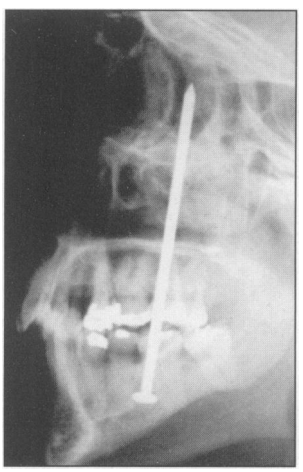

Fig 1.

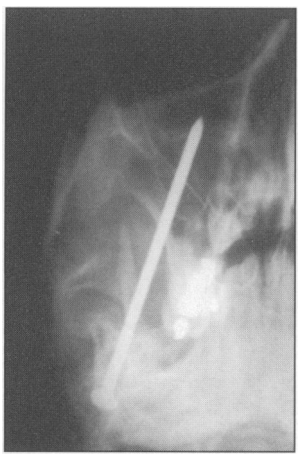

Fig 2.

The patient was a smoker of 20 cigarettes per day and there was nothing else of note at preoperative anaesthetic assessment. On examination, there were no signs of upper airway obstruction and the puncture wound was visible with no bruising or swelling of the area. There was no mouth opening (effectively nailed-closed) and otherwise external anatomy was normal. Patency was markedly reduced in the right nostril and normal in the left, he had normal neck movements and had full dentition with no gaps to allow oropharyngeal inspection. The patient was able to speak and move his tongue freely and intraoral injury was thought to be minimal. There was no CSF rhinorrhoea or otorrhoea. After discussion regarding the need for further investigations, the surgical team decided that a CT scan or angiogram was unnecessary.

Following consideration of the anaesthetic options, a fibreoptic-guided nasal intubation with sedation before induction of anaesthesia was planned. The patient received a full explanation, gave consent and 2 hours after ranitidine 50 mg intravenously, the patient was transferred to theatre approximately 10 hours post-injury. Standard monitoring was established and after fentanyl 100 mcg and glycopyrrolate 200 mcg intravenously, a propofol infusion was commenced at 1 mg/kg/hour and titrated to provide light sedation, with the patient able to

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obey commands. With the patient supine, a trans-tracheal block was performed using 4 mls of 2% lignocaine via a 22 g cannula and oxygen administered via the right nostril. The left nasal passage was prepared with oxymetazoline drops and then serially dilated with nasopharyggeal airways smeared with lignocaine gel. A 7.0 mm cuffed 'Portex' polar preformed northfacing endotracheal tube was passed over a lubricated 5.5 mm Olympus fibreoptic bronchoscope and this was inserted into the left nostril with the view displayed on a monitor. The intranasal, posterior pharyngeal and oral spaces were normal and easily visualised. After suction to remove oropharyngeal secretions, the glottis was easily visualised and the bronchoscope passed through the vocal cords into the trachea with minimal coughing. With the carina in constant view, the tracheal tube was rail-roaded over the lubricated bronchoscope and tracheal placement was confirmed visually, by auscultation and by capnography. With the tracheal tube secured, anaesthesia was induced with propofol 80 mg, the patient was paralysed with atracurium 35 mg and ventilated to normocapnia. SpO_2 did not fall

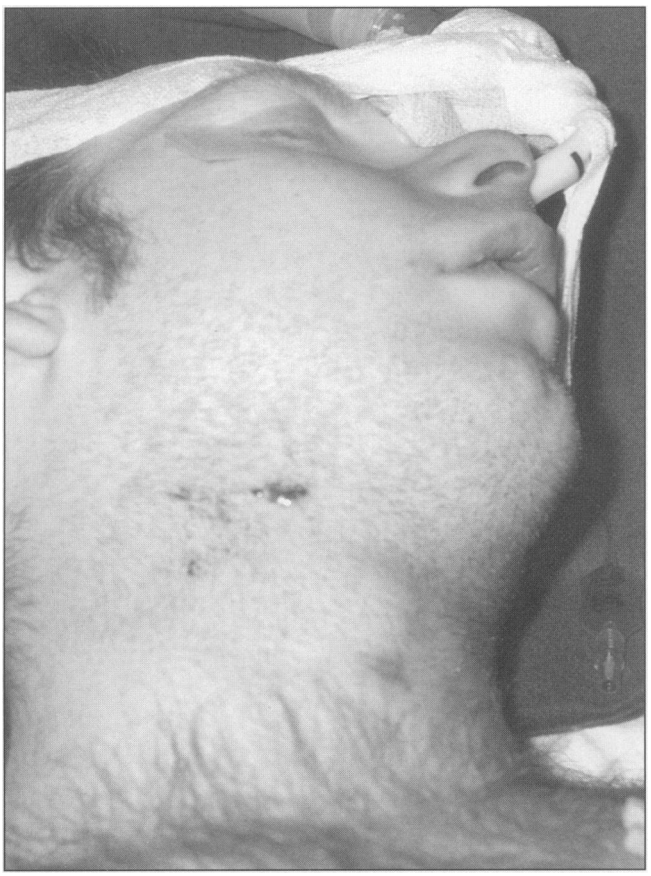

Fig 3.

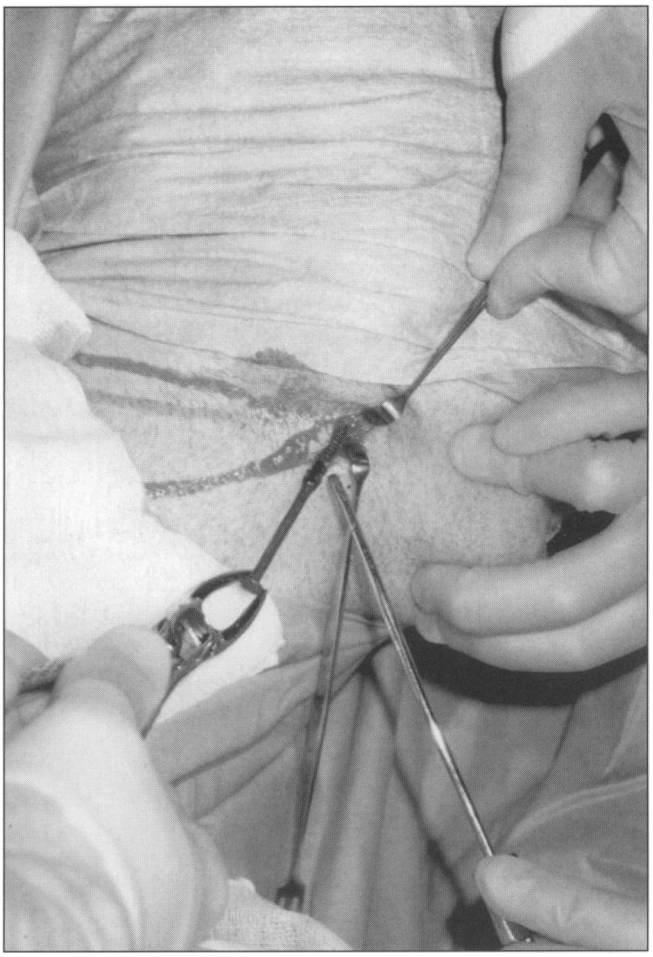

Fig 4.

below 95% at any stage of the procedure. The nail was removed by the maxillofacial surgeon without any significant haemorrhage (Figs. 3 and 4). At this point a full intraoral inspection was possible and mouth opening was normal. After confirming the absence of glottic oedema, the patient was extubated uneventfully and was discharged the next day. He had no recall of the fibreoptic intubation.

At ophthalmological review, visual acuity was decreased in the right eye with an afferent pupillary defect and optic nerve pallor consistent with a diagnosis of traumatic optic neuropathy. Otherwise, the patient made an uneventful recovery.

DISCUSSION

This patient presented with several anaesthetic problems:-

1. He was unable to open his mouth.
2. There was a foreign body in situ that could cause further damage with movement.

3. An intraoral, cerebral or vascular injury had not been excluded radiologically.
4. There was a risk of pulmonary aspiration, despite fasting.

Consultation of the ASA Difficult Airway Algorithm[1] suggests that in cases of a predicted difficult airway, a surgical airway should be considered. The patient presented without airway compromise, was fully conscious and able to protect his own airway. Thus, awake tracheostomy under local anaesthetic was deemed unnecessary, although the operating surgeon was skilled in this technique and equipment for trans-tracheal jet ventilation was in theatre should the need arise. The second decision to make is whether intubation should be attempted with the patient awake or following induction of general anaesthesia. Although it could have been possible to maintain the airway with head tilt and/or a nasopharyngeal airway, induction of general anaesthesia either by the intravenous or inhalational route was felt to be contraindicated due to the high risk of airway obstruction and hypoxaemia.

In this case, an awake intubation was thought to be the safest and most appropriate option. Options for this included blind nasal, retrograde and fibreoptic-guided intubation. Since a retrograde technique requires some mouth opening, and with the potential for anatomical distortion and the full extent of the injury being uncertain, blind nasal and retrograde techniques were considered unsuitable and therefore a fibreoptic technique was chosen. Fibreoptic-guided intubation is useful in the management of the difficult airway and has a high success rate when performed electively. Difficulties arise from uncooperative patients and from secretions and bleeding in the airway. This patient was co-operative and sedated appropriately and the airway seemed to be free from contamination with blood. In this case, the decision was made to sedate the patient and this was felt to be justified for a number of reasons. When sedation is given using drugs that can be titrated to effect and that are reversible, the conditions for both patient and operator are improved, allowing more patient co-operation, providing anterograde amnesia and decreasing the coughing associated with intubation. In comparison with other awake intubation options, fibreoptic-guided intubation is less invasive and the anatomy can be assessed during the intubation attempt.

In a review of the literature, there are two similar case reports describing impalement via the floor of the mouth. Bullingham and colleagues [2] describe a 22 year-old man impaled on an iron railing fence spike, and Ng and Lo [3] describe a 23 year-old man impaled with a bamboo skewer. Although both cases were associated with a more traumatic injury, the decision-making process and choice of airway management technique were similar to the case described above. Of note, due to extensive airway oedema, the patient described by Ng and Lo received an elective tracheostomy at the end of surgery.

In retrospect, the management of the case described could have been improved in some areas. In a comprehensive review looking at airway management following penetrating neck trauma, Shearer and colleagues [4] refer to a study by Herrin and colleagues [5] that recommends careful evaluation of the airway using physical and X ray examination prior to anaesthesia. Ng and Lo [3] also suggest that a CT scan is useful in airway evaluation in these cases. Due to the metallic nature of the foreign body in this case, the value of a CT scan would have been questionable owing to artefact production, but an angiogram may have been useful to exclude a vascular injury. A trans-tracheal injection of local anaesthetic was chosen for laryngotracheal anaesthesia. Although this technique is safe, complications can include haematoma formation, surgical emphysema and it may increase pulmonary aspiration risk should vomiting or regurgitation occur. Also, should the need for cricothyroid puncture have arisen, any anatomical distortion could have made this difficult. A 'spray-as-you-go' technique may have been a better choice.

In summary, this and the other cases described illustrate that, after careful airway evaluation, awake fibreoptic-guided nasal intubation is a safe technique for managing patients who present with an impalement injury to the floor of the mouth.

ACKNOWLEDGEMENTS

Thanks to Dr M Reid, Consultant in Anaesthesia and Intensive care, and Dr C Renfrew, Consultant Anaesthetist for their advice and assistance with the preparation of this case report. All of the photographs are published with the consent of the patient.

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Case Report

Curative surgery following failure of vancomycin therapy: A case report of methicillin resistant staphylococcal endocarditis on a native mitral valve

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Accepted 1 August 2000

Infective endocarditis is a life-threatening illness. Staphylococcus aureus is a common cause of endocarditis with an increasing number of cases caused by methicillin resistant *s. aureus.*

CASE REPORT A 66-year-old male with early gastric carcinoma underwent distal gastrectomy with retrocolic Roux-en-y gastrojejunostomy. He had no significant prior cardiac history. His initial post-operative course was uncomplicated but delayed gastric emptying due to obstruction at the anastamosis led to elective central line insertion for total parenteral nutrition on the eighth post-operative day.

After the indwelling central catheter had been present for 10 days, the patient deteriorated. He became pyrexial with a temperature of 40°C, tachycardic, with leucocytosis of 24.7 x 10^9/l (normal 4-10) and he had microscopic haematuria. Blood cultures were taken and the central line was removed empirically. Urine culture was positive for pseudomonas and this was initially presumed to be the source of sepsis.

Pyrexia continued despite intravenous antibiotics. After 72 hours the first blood culture confirmed bacteraemia with methicillin resistant staphylococcus aureus (MRSA) and at 96 hours the central line tip also cultured MRSA. These isolates were sensitive to vancomycin which was subsequently given intravenously (therapeutic levels were maintained with a dose of 1.2-1.5 g once daily). Pyrexia persisted but there was no cardiac failure or documentation of a new murmur. Six days after presentation the patient coincidentally developed chest pain and congestive failure. A cardiology consultation was requested. At this point a new mitral regurgitant murmur was detected. The diagnosis of endocarditis was established on both transthoracic and transoesophageal echocardiogram which confirmed mild mitral regurgitation and showed multiple anterior leaflet vegetations (see figures la and lb). Repeat blood cultures remained positive for MRSA, C-reactive protein was 154 mg/1 (normal 0-10); ESR was 115 mm/hour and the white cell count was 17.42 x 10^9/l.

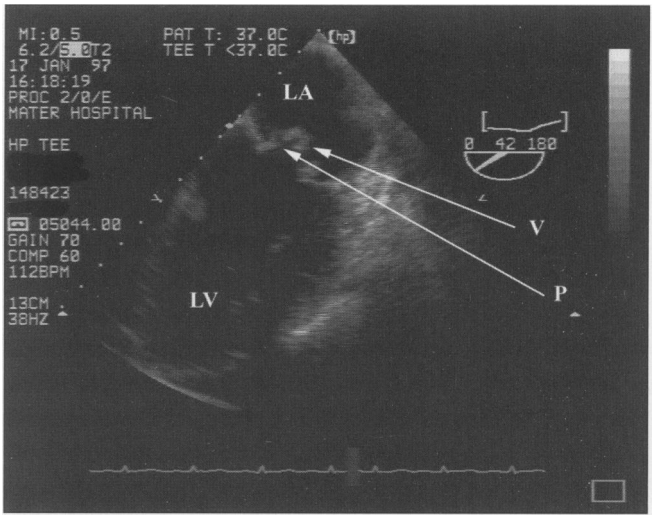

Figure 1a. Transoesophageal image showing a large vegetation (V) attached to the anterior leaflet of the mitral valve, prolapsing into the left atrium (LA) at end systole. The relatively echolucent area (P) represents a perforation in the anterior leaflet. LV represents the left ventricle.

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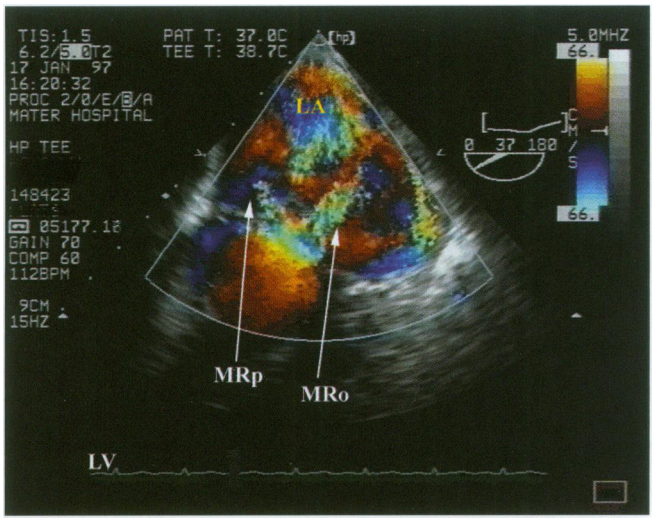

Figure 1b. With colour Doppler applied, there is severe mitral regurgitation filling the left atrium. At mitral valve level there are two distinct regurgitant jets, one through the valve orifice (MRo) and the other through the anterior leaflet perforation (MRp).

After maximal therapy with vancomycin and fusidic acid (500 mg 8 hourly IV) there was little improvement. Repeat transoesophageal echocardiography revealed progressive valve destruction, there was severe mitral regurgitation and anterior leaflet perforation. The patient was transferred to a tertiary referral centre with a cardiac surgical unit. Prior to cardiac surgery he had received a total of 44 days of intravenous vancomycin. The initial fusidic acid therapy was later changed to rifampicin. This was initially given orally (300 mg t.i.d. for 2 weeks) and then administered intravenously (600 mg daily) in the peri-operative period. Despite the aggressive antimicrobial therapy the inflammatory indices remained grossly elevated. The patient underwent mitral valve replacement with a St. Judes medical prosthesis on the 57th day after initial gastric surgery.

Figure 2. H & E stain (original magnification 10x). The surface of the valve cusp shows clumps of dark staining bacteria. The top right hand of the picture shows an inflammatory exudate. The valve cusp is hyalinised and there is an area of necrosis.

Histopathology of the excised valve revealed large colonies of gram positive cocci with necrosis of the valve substance and confirmation of the leaflet perforation which had been diagnosed echocardiographically (see figure 2). Antibiotics were stopped post-operatively on day 5. The patient subsequently made a full recovery and has had no recurrence of his gastric malignancy to date.

DISCUSSION

Staphylococcal endocarditis has long been recognised as an aggressive and rapidly progressive disease. Over the past 10 years, there has been a consistent rise in the incidence of this illness in line with both community-acquired and hospital-acquired *s. aureus* bacteraemia. Indeed *s. aureus* (and increasingly MRSA) is now one of the most common infective agents in hospital-acquired native valve endocarditis.[1] This condition is known to carry both a high morbidity and mortality. It should always be considered in the differential diagnosis for ill patients with persistent fever, and repeatedly positive blood cultures for coagulase-positive staphylococci. This is particularly the case in the presence of established risk factors for bacteraemia such as central venous line, peripheral venous line and arterio-venous fistula.

Features that occur more commonly in staphylococcal infection include persistent fever beyond seven days (but this may also reflect complications), haematuria, embolic events, neurological involvement and pronounced elevation of ESR and C-reactive protein (often >150).[2] Echocardiographic data should be obtained early with transoesophageal imaging being mandatory in a suspicious case not confirmed by transthoracic views. The Duke criteria have been reported to have a negative predictive value of 98% and should be applied to assist the diagnosis.[3]

The clinical course in this case was consistent with a typical *s. aureus* endocarditis. The large, friable and mobile vegetations were obvious on both transthoracic and transoesophageal

echocardiography. The early and progressive valve dysfunction, with persistence of the organism at histopathology, confirms the destructive and virulent nature of this infection. Active infection continued despite prolonged use of therapeutic agents to which the organism was sensitive.

Empirical treatment for methicillin sensitive bacteria is a semi-synthetic penicillin for 4-6 weeks plus gentamicin in the initial 5-7 days of therapy. When methicillin resistance is suspected or confirmed, intravenous vancomycin remains the current treatment of choice. Additional rifampicin and/or gentamicin have not been shown to improve cure rates, although adjuvant therapy is always recommended.[4,5] However, with the gradual emergence of vancomycin resistance in MRSA over the last year, management of similar infections may become increasingly difficult. Isolates of glycopeptide intermediate *s. aureus* (GISA) which do not respond to vancomycin or teicoplanin in vivo have now been isolated in both the United States and Japan. This bacterium has been demonstrated to have an abnormally high minimal inhibitory concentration (MIC) of vancomycin which is probably due to an increase in extracellular material. The most likely explanation is that the methicillin resistant organisms have undergone cellular modification as a result of prolonged exposure to vancomycin.[6,7] The authors suggest that quantitative assessment of MIC for glycopeptide resistance, infection control and active surveillance becomes mandatory. Combination therapy with ampicillin/sulbactam and arbekacin has effectively treated the organism in a case of pneumonia.

The timing of surgical intervention in endocarditis has been controversial and in individual cases remains a difficult decision. At present the American Heart Association advise consultation with a cardiac surgeon as soon as a diagnosis of aortic or mitral valve endocarditis is made. Present indications for surgery include acute valvular regurgitation with heart failure, fungal endocarditis, annular or aortic abscess, valve dysfunction with persistent infection despite appropriate treatment, recurrent emboli, mobile vegetations >10 mm, early mitral infection amenable to repair and persistent pyrexia with leucocytosis despite negative blood cultures. Pre-operative LV ejection fraction of >50% is associated with better survival.[8]

Surgical options abound, including homograft in active infection,[9] early radical surgery with mechanical prosthesis in staphylococcal infection,[10] and valve replacement after the acute infection has settled. A highly co-ordinated approach with early involvement of a cardiologist, a cardiac surgeon and a bacteriologist is essential to optimise the outcome of MRSA endocarditis. With best current management, native valve staphylococcal endocarditis has been reported to carry a mortality of almost 50% in some series.

The severe nature of this disease places even greater emphasis on the need for prevention and early detection. Any site of bacterial access should be kept fastidiously aseptic, particularly central venous cannulae. The diagnosis of infective endocarditis should be both considered and established early, as opposed to being one of exclusion. As drug resistance increasingly limits chemotherapeutic options, more aggressive surgical strategies may become necessary. The role of surgery may have to be redefined and early routine intervention adopted, if antibiotic resistance evolves more rapidly than drug development.

ACKNOWLEDGEMENT

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Case Reports

Conservative management of major liver trauma

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Management of major liver trauma remains a significant challenge. Conservative management has traditionally been recommended for minor (type I - II) blunt liver injuries but penetrating and major blunt liver injuries (type III - V) have generally been managed by surgical exploration.[1] However, more recently, the conservative approach has been adopted for the management of type III - V injuries.[2-8] We describe two patients with major liver injuries managed conservatively but with a different clinical course in each case.

CASE 1 A 48-year-old man was admitted after a fall of approximately 25 feet from scaffolding. Although haemodynamically stable, he was markedly cyanosed and tachypnoeic. There was surgical emphysema with decreased air entry on the right side of the chest. A needle thoracostomy followed by intercostal drainage was performed and his air entry improved. An abdominal CT scan revealed extensive laceration of the right lobe of liver, extending from the capsular surface

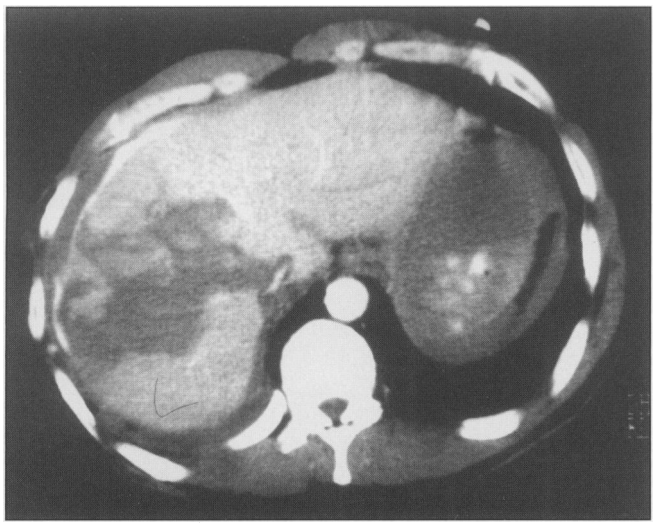

Fig 1. CT scan demonstrating a deep parenchymal laceration between segments V and VIII anteriorly (anterior sector) and segments VI and VII posteriorly (posterior sector).

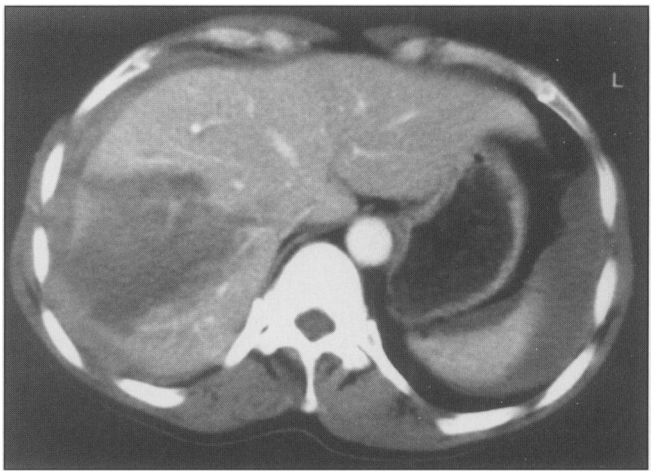

Fig 2. CT scan demonstrating a laceration and large intraparenchymal haematoma.

to the hilum (figure 1). He was transferred to our unit for further management. In view of his stable condition it was decided to manage him conservatively. However, during the following 24 hours, his haemoglobin decreased from 15 gm/dl to 9.7 gm/dl and a significant drop in blood pressure occurred on two occasions. An emergency laparotomy was performed. This revealed 3 litres of blood in the peritoneal cavity in addition to active bleeding from a deep laceration between the anterior and posterior sectors of the right lobe of the liver which was treated by closure of the laceration and compression with Vicryl® mesh. Postoperative recovery was complicated by a right subphrenic abscess. This was treated by percutaneous drainage. Follow up scans confirmed complete healing of the liver laceration.

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CASE 2 A 44-year old man was admitted with a history of a fall down stairs. He complained of pain in the right upper abdomen but was haemodynamically stable. Examination revealed tenderness in the right hypochondrium. A CT scan revealed a deep laceration in the right lobe of the liver (figure 2). He was transferred for further management but remained haemodynamically stable, with a normal haemoglobin. It was therefore decided to treat him conservatively. During the 24 hours following transfer his haemoglobin dropped to 9.8 gm/dl and 2 units of packed cells were transfused. Conservative management was continued. He remained stable but, despite aggressive physiotherapy, he developed right lower lobe consolidation and a right pleural effusion, which required intercostal tube drainage. A repeat CT scan revealed a large subphrenic collection (figure 3), from which 1.5 litres of bile was drained percutaneously. Following this, his condition gradually improved and he was discharged on the 23rd day.

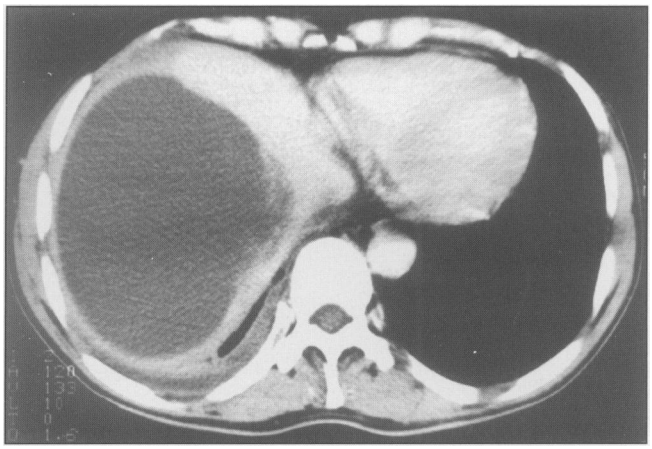

Fig 3. CT scan 10 days post-injury demonstrating a large subphrenic bile collection.

DISCUSSION

Conservative management of blunt liver trauma was first reported in 1972 and was recommended for the management of less serious injuries such as capsular tears and small intraparenchymal haematomas (type I - II).[5] Strict selection criteria were used, including haemodynamic stability, absence of other signs of intra-abdominal injury, good quality CT scanning, the ability to monitor the patient in an intensive care unit and the facility for immediate surgery by experienced hepatobiliary or trauma surgeons.[2-7] A further criterion of a CT estimation of less than 125 ml of intraperitoneal blood was initially used but later extended to 250 ml.[8,9] With increasing experience and reported success rates of up to 90%, the level for CT estimated blood loss was increased to 500 ml and the type of injuries managed was extended to include deeper parenchymal lacerations and larger intraparenchymal haematomas (type III - IV).[6-12] By the end of the 1990s most authors accepted that the deciding factor in favour of conservative management should be the haemodynamic stability of the patient, irrespective of the grade of liver injury or the amount of haemoperitoneum. It is also now generally accepted that there is no indication for frequent repeat CT scanning and the decision to abandon the conservative approach is largely a clinical one, based on haemodynamic instability, as illustrated by our first case.[8-14]

It is important to emphasise, however, that patients successfully managed conservatively may develop significant complications, including lung collapse and pleural effusion, secondary to subphrenic blood or bile collections, as our second patient demonstrated. Recurrent bleeding may occur, although it is not as likely to happen as with conservative management of splenic trauma. Sepsis is also a significant risk, particularly if subphrenic or pleural collections require drainage. However, complication rates in patients managed conservatively have been shown to be no higher than those in patients treated operatively.[2] It has also been demonstrated that patients treated conservatively require significantly fewer blood transfusions than surgically treated patients with comparable injuries.[13]

In conclusion, conservative management of liver injury should be considered in the majority of cases provided there are no signs of other intra-abdominal injury, the patient remains haemodynamically stable and strict criteria for ICU and experienced surgical back-up are fulfilled.

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Case Report

Cystic tumours of the pancreas – the importance of correct diagnosis and treatment

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Accepted 5 September 2000

Cystic tumours of the pancreas are relatively rare and are frequently misdiagnosed as pancreatic pseudocysts. The three cases described below demonstrate some of the typical presenting features of these lesions and emphasise the importance of correct diagnosis and treatment.

CASE REPORTS

Case 1

A 35 year old previously healthy woman presented with left subcostal pain. Ultrasound revealed a 10 cm cystic mass of the pancreas. This was confirmed by CT scan. CT-guided aspiration revealed a high amylase content. ERCP revealed normal pancreatic and bile ducts. The lesion was thought to be a pseudocyst and endoscopic drainage with stent insertion was performed. However, the lesion persisted. Surgical drainage (cystgastrostomy) was then performed. Biopsy of the cyst wall revealed gross dysplasia, highly suggestive of cystadenocarcinoma.

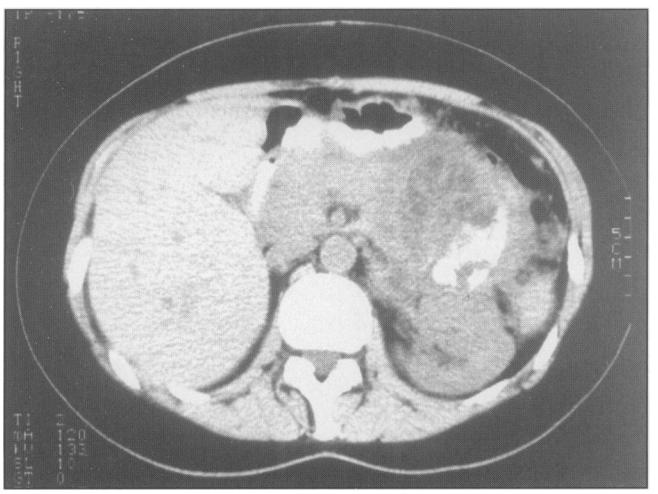

Fig 1. CT scan demonstrating a mucinous cystadenocarcinoma of the pancreas. Note the solid components. The contrast material within the cyst is due to the previous surgical drainage (cystgastrostomy), following misinterpretation as a pseudocyst.

She was transferred to our unit for further management. Repeat CT scan showed debris and fluid in the cyst cavity (Figure 1). In view of possible malignancy and the fact that the cyst was refractory to percutaneous, endoscopic and surgical drainage, resection (distal pancreatectomy and splenectomy) was undertaken. Histology confirmed a mucinous cystadenocarcinoma of the pancreas. She remains well 3 years post surgery.

Case 2

A 40 year old female presented with a history of epigastric pain radiating to the back. Of note, she had an attack of pancreatitis four years previously when seven months pregnant. On this admission investigation revealed a pancreatic cystic mass which was subsequently treated by cyst-gastrostomy for a presumed pseudocyst. The pseudocyst did not resolve and she was transferred to our unit.

Enhanced CT scan showed a cystic mass in the tail of the pancreas (Figure 2). ERCP revealed a normal pancreatic duct. Distal pancreatectomy and splenectomy was performed. Histology confirmed a benign mucinous cystadenoma of the pancreas. She remains well two years post surgery.

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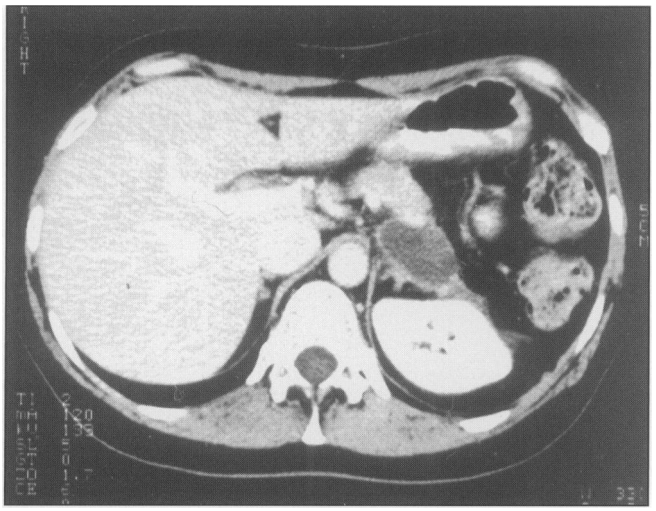

Fig 2. CT scan demonstrating a cystic mass (mucinous cystadenoma) in the tail of the pancreas.

Case 3

A 35 year old previously healthy housewife presented with a four month history of epigastric pain. Ultrasound revealed a 4.5 cm cystic mass in the distal body and tail of the pancreas. CT scan confirmed this. Surgical resection was planned but deferred as she became pregnant. Post-partum repeat CT scan showed the cyst had increased to 6 cm (Figure 3) and resection was performed (distal pancreatectomy and splenectomy). Histology confirmed a serous cystadenoma of the pancreas. She remains well one year post surgery.

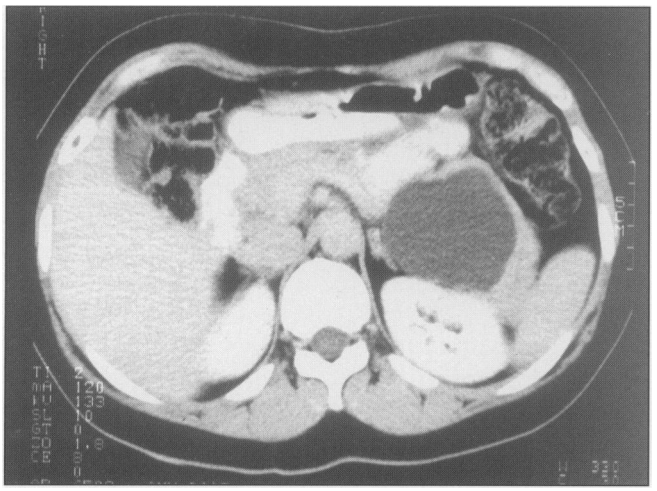

Fig 3. CT scan demonstrating a serous cystadenoma of the pancreas. Note the unilocular appearance with absence of any solid components.

DISCUSSION

When a cystic lesion of the pancreas is encountered the first priority is to determine whether it is a pseudocyst or a neoplasm.[1] The majority of these lesions are pseudocysts, which are of inflammatory or traumatic origin. Pseudocysts are collections of pancreatic secretions surrounded by a fibrous wall with no epithelial lining. Neoplasms account for 10-15% of pancreatic cystic lesions.[2,3] Ninety percent of neoplastic cysts are of epithelial origin. The commonest epithelial tumours are benign cystadenomas (serous or mucinous) and cystadenocarcinomas, which collectively account for 75% of all cystic tumours. Recently defined intraductal papillary and mucinous tumours represent 11% of cystic tumours whilst pseudopapillary tumours represent 4%.[4]

The definitive diagnosis of a pancreatic cystic lesion is often difficult. A history of antecedent factors or events that could generate a pseudocyst, such as pancreatitis or trauma, is extremely important. In the absence of such a history a pancreatic lesion should not be labelled as a pseudocyst and a neoplasm should be suspected. Cystic neoplasms are most commonly found in middle-aged women although the benign serous cystadenoma often occurs in elderly women. Abdominal pain is the most common symptom as our three cases demonstrate. Weight loss is also a significant feature.[3] Serum amylase level is usually normal in patients with a neoplasm but in 50-75% of patients with a pseudocyst it is increased.[3]

Some physical characteristics are helpful in diagnosis. Loculation and solid components on CT scan are indicative of a neoplasm. Calcification is common in cystic tumours. Hypervascularity on arteriography may indicate a neoplasm but not its type.[5,6] Size and location are not of much diagnostic value although most neoplasms occur in the body and tail of the pancreas.[6,12] ERCP usually demonstrates no communication between cystic tumours and the pancreatic duct, as in our cases, but communication with the ductal system is often found in pseudocysts.[3,7,8]

Percutaneous aspiration of cystic tumours for measurement of amylase, CEA, CA 19.9 and for cytology has not been evaluated sufficiently to allow determination of how sensitive or reliable these parameters might be for diagnosis of a neoplasm.[6] Cystic aspiration has been limited by the theoretical concern of spillage and seeding of tumour cells. Biopsy of the cyst wall, at the time of surgery, will usually make the differentiation between pseudocyst and neoplasm although the

absence of an epithelial lining in a limited biopsy does not preclude the diagnosis of a cystic tumour. In cases where surgical drainage of a pseudocyst is undertaken biopsy of the wall should always be performed if there is any clinical or radiological doubt about the diagnosis.

Although discrimination of cystic neoplasms from pseudocyts may be difficult it is imperative to make this distinction because the treatment for each is obviously different. Internal drainage is the treatment of choice for an uncomplicated mature pseudocyst.[9] Surgical options include drainage via the stomach, duodenum or jejunum. Pseudocysts can be drained endoscopically (with endosonography) via the transpapillary approach or transmurally (endoscopic cystgastrostomy or cystduodenostomy) . The former is preferred if cystenterostomy is not possible, as in the absence of cyst-gut wall apposition, and if pancreatic duct morphology identifies cyst-duct communication.[10, 11] However, as our first case demonstrated, percutaneous or internal drainage of a misdiagnosed 'pseudocyst' will fail to alleviate symptoms, may convert a sterile cystic tumour to an infected one or, more importantly, leave behind a curable cancer.[2, 5] This problem is likely to increase with the increasing use of endoscopic drainage techniques as the definitive management of pseudocysts.

The treatment of epithelial cystic tumours of the pancreas usually involves surgical resection. One exception is for unilocular benign serous cystadenomas in asymptomatic elderly patients, where conservative management is justified provided there is no pancreatic duct or vascular obstruction.[4, 12] Such patients should be followed by yearly ultrasonography. All other cystic tumours have the potential for malignant degeneration or may be malignant at the time of diagnosis and hence should be managed by resection.[1, 6, 13, 14] The majority of cystadenocarcinomas of the pancreas (up to 70%) are resectable [4, 6] as these tumours can be exceedingly slow growing, indolent and tend not to invade adjacent structures.[3] These factors and the relatively low incidence of metastasis permits curative surgery, even after previous drainage or bypass procedures.[3] Resection should be attempted even in advanced cases as the five year survival rate may exceed fifty percent.[3, 4] Hence, large locally invasive tumours should not be dismissed as inoperable without evaluation.[4] Neither tumour size nor previous intervention should preclude an attempt at curative resection.[3] Removal of an intact cyst should be the aim of operative resection because cystic rupture may disseminate malignant cells intraperitoneally.[1, 15]

In conclusion, cystic tumours of the pancreas are rare. Failure to recognize the true nature of such a tumour will lead to misdiagnosis as a pseudocyst and incorrect treatment. Given the difficulties of accurate pre-operative diagnosis, the high incidence of potential malignancy and the good outcome with resection, a review of the literature suggests that all suspected cystic tumours of the pancreas (apart from asymptomatic serous cystadenomas in elderly patients) should be managed primarily by resection.

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Case Report

Volvulus of the gallbladder

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A case of gallbladder volvulus is presented. This is a rare entity that most frequently affects elderly females. It is associated with anatomical variations relating to abnormal fixation of the gallbladder to the liver bed. Diagnosis is usually at laparotomy and early surgical treatment is essential. Cholecystectomy may be performed laparoscopically or as an open procedure. Gallbladder volvulus should be suspected in elderly patients with symptoms of acute cholecystitis

CASE REPORT An 86-year-old-female presented with a sudden onset of right upper quadrant pain and vomiting. Abdominal examination revealed right upper quadrant tenderness and a palpable mass in the right hypochondrium. Preliminary haematological and biochemical tests were within normal limits. Chest and abdominal radiographs were also unremarkable.

Initially she was treated expectantly. However within 24 hours of admission she developed signs of sepsis, with an associated leucocytosis and pyrexia. An ultrasound scan of abdomen (Fig.) demonstrated a grossly distended, oedematous gallbladder with evidence of cholelithiasis and surrounding free fluid. The patient was prepared for surgery. This revealed a grossly enlarged, necrotic gallbladder resulting from a 360 degree torsion of a pedicle containing the cystic artery and duct. Following detorsion, cholecystectomy was performed in combination with intra-operative cholangiography. The patient made an uneventful post-operative recovery.

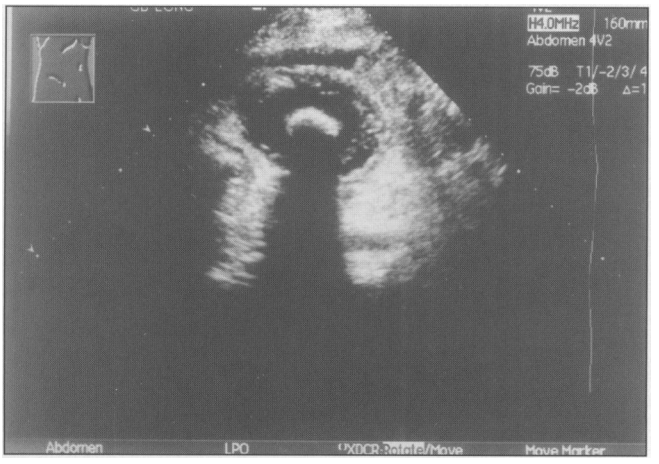

Fig. Ultrasound of liver bed demonstrating gross gallbladder distension with gallstones and surrounding free fluid.

DISCUSSION

The first description of gallbladder volvulus was by Wendel in 1898.[1] Since then over 300 cases have been reported in the literature.[1,2] The peak incidence of this condition is between 60 and 80 years[2,3] with a 3:1 female predominance.[3] Gallbladder volvulus has also been reported in children and young adults,[2] one patient being as young as two years of age.[4]

Normally the gallbladder is closely attached to the under-surface of the liver. For an organ to twist, it must have a mesentery with a relatively short base compared to its length.[5] Two anatomical variants exist which allow gallbladder torsion; visceroptosis with mesenteric elongation and the "free-floating" gallbladder [5] of which there are two types, one with a mesentery and one with a pedicle containing the cystic artery, vein and duct.[6] Between 4 and 5% of the population have

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free-lying gallbladders[2,6] and their existence is thought to be due to dyscoordination of embryological migration during development of the liver and biliary tract.[2]

Torsion may be incomplete (less than 180 degrees) or complete (270 to 360 degrees) and the volvulus can occur in either a clockwise or anti-clockwise direction.[2,3] Incomplete torsion only obstructs bile flow whereas complete torsion leads also to vascular compromise resulting in haemorrhagic infarction.[2,3,6] Perforation is however uncommon.[6,7]

The mechanisms for creating a torsion are not exactly known although several predisposing factors have been suggested. These include; vigorous peristalsis both within neighbouring organs and the gallbladder itself, brisk movements, blunt trauma and weight loss,[3-5,7] Kyphosis[2] has been observed in some cases but this is probably to be considered in the broader context of visceroptosis. Gallstones, though present in approximately 50% of patients, do not appear to play a role in the aetiology of volvulus.[2,3] Symptoms depend on the type of torsion.[2] Incomplete torsion resembles biliary colic whilst complete torsion mimics acute cholecystitis.[3,5] A mass may be palpable in the right hypochondrium[2,3,5-7] and a paralytic ileus may also co-exist.[2]

Pre-operative ultrasound findings are usually non-specific[6] and in the majority of cases the diagnosis is made at the time of surgery.[1,3] Surgical treatment consists of detorsion and cholecystectomy.[2,3,5] Detorsion is necessary to avoid bile duct injury.[3,5,8] Laparoscopic cholecystectomy for gallbladder volvulus has been reported.[4,8,9] Early treatment has a mortality of less than 5%.[2,3,6] Without surgery, septic shock usually ensues with catastrophic complications.[2]

Importantly, changes in population demographics associated with an increase in life expectancy may lead to an increase in this condition.[5] Therefore gallbladder volvulus should be considered in elderly patients, especially females, with symptoms of acute cholecystitis.

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Case Report

The delivery of the first babies conceived using testicular sperm in Northern Ireland

E K Steele, J A McNally, S E M Lewis, N McClure

Accepted 25 October 2000

This paper reports the delivery of infants conceived using testicular sperm aspirated from men with previously untreatable obstructive azoospermia.

CASE REPORT 1 Mr and Mrs C were aged 35. Mr C worked as a bus driver and his wife as a manageress. He was known to have obstructive azoospermia due to congenital absence of the vas deferens and was a carrier of the cystic fibrosis gene mutation R560T. His karyotype was 46XY and his hormone profile was normal. Mrs C was not a cystic fibrosis carrier, her menstrual cycle was regular and she was ovulating normally. She underwent ovulation induction for oocyte retrieval with subcutaneous injections of recombinant FSH (Puregon®, Organon) using a standard protocol. Transvaginal ultrasound guided oocyte retrieval was performed in August 1998 under intravenous sedation. Following retrieval, oocytes were incubated for 2 hours and then denuded of their cumulus matrix and coronal cells using hyaluronidase (80 IU/ml, IVF Science, Scandinavia) permitting assessment of oocyte maturity.

On the same day Mr C underwent testicular biopsy. Briefly, 10 ml of 0.5% bupivacine were injected around the spermatic cord. Two biopsies were taken using a 14 gauge Trucut needle (Baxter Healthcare Ltd, Norfolk, U.K.) inserted into the lower pole of the testis and advanced one centimetre. Sperm were retrieved from the biopsy sample by milking the seminiferous tubules with size 5 jeweller's forceps and enumerated after washing with in vitro fertilisation (IVF) media (Medicult, U.K.). Sperm were incubated for 3-4 hours at 37°C in 5% carbon dioxide prior to injection.

Only metaphase II oocytes with one polar body extruded were considered suitable for injection. Testicular spermatozoa were identified, retrieved from an IVF media drop and then placed in polyvinylpyrrolidine (PVP, Hunter Scientific, U.K.) using an Olympus JX50 micromanipulation microscope (Research Instruments, Cornwall, U.K.). After immobilisation of the twitching spermatozoa, metaphase II oocytes were injected and subsequently assessed for presence of pronuclei 16-18 hours later. Normally fertilised oocytes with two pronuclei were then incubated for 48-72 hours and the two embryos of highest quality transferred.

Mrs C had 21 oocytes retrieved and of these 19 were suitable for injection. Subsequently 10 of the injected oocytes fertilised normally and 2 embryos were replaced. Of the remaining embryos, 6 were suitable for storage. In September 1998 pregnancy test was positive and on transvaginal scan a viable twin pregnancy was confirmed.

In March 1999 healthy twin boys were delivered by emergency caesarean section at 31 weeks because of preterm labour. They weighed 1.7 and 1.5 kg and were phenotypically normal.

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CASE REPORT 2 Mr M was aged 29 and worked as a sales manager and his wife was aged 27 and was a nurse. Mr M had unexplained obstructive azoospermia with normal karyotype and hormone profile. Mrs M had a regular cycle and was ovulating normally.

In June 1998 Mr M had a testicular biopsy carried out under local anaesthetic as described in Case 1. Once the sperm had been milked from the seminiferous tubules they were stored in liquid nitrogen in multiple aliquots. Assessment of one stored aliquot to confirm sperm motility and hence viability post-thaw indicated suitability for future use. Freeze- thawed sperm were also incubated for 3-4 hours at 37°C in 5% carbon dioxide prior to injection.

Mrs M proceeded to ovulation induction and oocyte retrieval in July 1998. On the same day the sperm sample was thawed and the oocytes injected with freeze-thawed testicular sperm. Eight oocytes were collected, six injected with thawed testicular sperm and three fertilised nonnally. Two embryos were replaced and the remaining embryo was not suitable for storage. Transvaginal scan in September 1998 confirmed a singleton viable fetus. In April 1999 a healthy male infant weighing 3.7 kg was delivered at 38 weeks gestation by elective caesarean section.

DISCUSSION

In this paper we have reported the first ICSI babies to be conceived and delivered in Northern Ireland using fresh and freeze-thawed testicular sperm.

Azoospermia is the complete lack of sperm in the ejaculate and it occurs in about 2% of infertile men. Two thirds are due to genital tract obstruction and one third to germinal epithelium failure. In obstructive azoospermia spermatogenesis is known to be normal.[1] Men with obstructive azoospermia were considered to be untreatable until the advent of intracytoplasmic sperm injection (ICSI) in 1992.[2] With this technique one sperm is injected directly into the cytoplasm of the oocyte and excellent success rates have been reported for men with very poor semen quality.[3] In obstructive azoospermia, because spermatogenesis is normal, small numbers of sperm can be obtained from the testis or epididymis by open or needle biopsies.[4,5] However, as these sperm tend to be immotile they are unsuitable for standard in vitro fertilisation (IVF) but can be used for ICSI because motiliy is not required.[6] Since the first ICSI pregnancy using testicular sperm was reported in 1993 this procedure has become a standard treatment for men with obstructive azoospermia.[7]

Sperm have even been obtained from the testes of non-obstructive azoospermics and pregnancies have been reported using sperm from men with Klinefelter's syndrome (47XXY) for ICSI. However, the offspring of pregnancies conceived using sperm from men with non-obstructive azoospermia need to be carefully monitored in the future because spermatogenesis is grossly defective in these subjects, carrying a risk of genetic abnormality especially when the quality of the genome is unknown.[8]

All three of Northern Ireland's first testicular sperm ICSI children were phenotypically normal boys. Whether or not they are infertile like their fathers will not however, become obvious for many years to come.

ACKNOWLEDGMENT

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Case Report

Twin pregnancy with a living fetus and coexisting complete hydatidiform mole

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CASE REPORT A 26 year-old para 2 presented at 30 weeks' gestation with a small, painless antepartum haemorrhage. When booked at sixteen weeks' amenorrhoea ultrasound scanning confirmed her dates to be correct and no obvious fetal abnormality was seen. The pregnancy was uncomplicated and the patient was well and normotensive throughout. All of her pregnancies were conceived with the aid of clomiphene citrate and her other children were delivered vaginally at term.

On admission the patient's blood pressure was 115/58 mmHg. The fundal height was at the xiphisternum which was greater than expected and the uterus was soft and non-tender. There was a single fetus, the lie was longitudinal, the presentation was breech and the fetal heart was heard. On ultrasound scanning the liquor volume was normal and the placenta was posterior and slightly low-lying. A large mass of multiple sonolucent areas was visualised separate from the superior edge of the placenta. Intravenous access was established and blood was taken for haemoglobin, group and hold (B Rhesus positive) and human chorionic gonadotrophin (HCG) level. Intramuscular steroids were given to the patient to improve fetal lung maturity.

Four hours after admission the patient experienced a sudden, substantial, painless haemorrhage. A second intravenous line was inserted, blood was taken for coagulation profile and 500 mls colloid was infused over ten minutes while four units of packed cells were awaited. On examination she was pale but normotensive. The uterus was soft and non-tender, the fetal heart rate was 130 beats per minute and fresh blood was seen trickling from the vagina. Written consent for an emergency caesarean section was obtained from the patient.

An emergency lower segment caesarean section was performed under general anaesthetic and a male infant weighing 1410 g was delivered in good condition by breech extraction. A healthy placenta and membranes were delivered, and in addition 1200 ml of vesicular tissue were removed from the uterus. An infusion of oxytocin was commenced and carboprost 250 μg was injected into the myometrium to improve uterine tone and control blood loss.

The patient made an uneventful recovery and went home on the fifth postoperative day. The baby remained in the neonatal unit and made very good progress. The ßHCG result from admission was 251,478 IU/I and the pathology of the vesicular tissue was reported as a complete mole co-existing with a normal twin fetus and placenta. The patient's details were registered with Charing Cross Hospital in London for further follow-up and treatment. Her ßHCG was normal within 8 weeks of evacuation of her uterus (urine level 18IU/I, serum level 4IU/1 [normal values: urine 0-24IU/I; serum 0-4IU/I). Follow-up will be for 6 months with monthly urine samples being sent to Charing Cross. The patient has not met any of the criteria to commence chemotherapy to date.

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DISCUSSION

A twin pregnancy consisting of a complete mole and one normal fetus and placenta is extremely rare. An incidence of only 1/22,000 - 100,000 has been reported.[1,2] In the literature 43 cases have been reported since 1977 and from those only 13 infants have survived.[3] It has been suggested that the incidence of this condition may increase in the future due to the use of ovulation – inducing agents because of the increased multiple pregnancy rates associated with their use.[2]

Hydatidiform moles are abnormalities of placental tissue that involve trophoblastic proliferation and hydropic degeneration with absence of vasculature and are classified as being either complete or partial. The karyotype of a complete mole is usually 46XX with both chromosomes being paternal in origin. This occurs either by the fertilisation of an 'empty' egg by two sperm or by the doubling of the paternal 23X inside the egg.[4] A partial mole arises by the fertilisation of an egg by two sperm to give rise to a triploid conception and, therefore, even though a fetus is often present it is often abnormal.[5] It is important in cases of 'twin' molar pregnancies to make the distinction between a partial mole, which consists of a triploid fetus and placenta with hydatidiform changes and that of a normal fetus with a coexisting complete mole. This is because the evolution of a partial mole into choriocarcinoma has not yet been recorded in the literature.[6] In contrast, the risk for development of choriocarcinoma with a single complete mole has been reported as 14% and as significantly higher for twin pregnancies with complete moles (55%).[7]

Clinically, the patient may present with complications such as vaginal bleeding, severe pre-eclampsia prior to 20 weeks, hyperemesis gravidarum and hyperthyroidism. Vaginal bleeding is usually intermittent and variable in amount and vesicular material may even be passed vaginally. The uterine size may be large for dates as it was in this case. It is also of interest that the patient reported here conceived with the aid of clomiphene citrate predisposing her to a twin pregnancy.

The diagnosis of coexisting complete mole and normal 'twin' fetus can be made by assessing the clinical picture, measuring human chorionic gonadotrophin levels and abdominal ultrasound.[4] The diagnosis of complete mole can be difficult in these circumstances because it is often not suspected when a normal fetus is seen on ultrasound. Human chorionic gonadotrophin levels are usually much higher than in a normal pregnancy but a molar pregnancy can produce normal levels and HCG may be elevated in a normal pregnancy.[4] Ultrasound can be useful in the diagnosis of abnormal placental tissue, with the classic appearance of a complete mole being described as resembling a 'snowstorm'. With a coexisting twin it can be more difficult to make the diagnosis on ultrasound especially in the first trimester but Steller [7] found that 68% of twin moles were diagnosed correctly by scanning.

The optimal management of this condition is not known because of its rarity and because most of the evidence in the literature is from single case reports.[1] The management depends to a great extent on the gestation at which the diagnosis is made. Before intact fetal survival following delivery has become a realistic probability (<28 weeks) the patient's health is the priority and the pregnancy is usually terminated.[4,8,9] Once the diagnosis is suspected the mother should be cautioned with regards to the potential risks associated with the continuation of the pregnancy namely pre- eclampsia, antepartum haemorrhage and hyperthyoidism. In addition she should be advised that the risk of persistent trophoblastic disease is significantly higher in twin pregnancies with a hydatidiform mole than for single molar gestations and that subsequent chemotherapy is also required for 57% of 'twin' moles compared to 19% of single moles.[1,4] Should a patient opt to continue the pregnancy she should be made aware that there is no accurate way of predicting invasive growth and she would require very close monitoring throughout the pregnancy.

Controversy remains regarding the management of cases where a normal fetus coexists with a molar pregnancy and many still advocate termination of pregnancy if an early diagnosis is made. In the present case this difficult decision did not have to be taken because the diagnosis was made at 31 weeks when the chances of fetal viability were realistic. Continuation of the pregnancy beyond this stage was not possible because the quantity of vaginal bleeding necessitated urgent delivery. The lack of ultrasound diagnosis in this case until 31 weeks illustrates that the presence of a normal looking fetus does not rule out the possibility of trophoblastic abnormalities.

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Case Report

Acute bilateral anterior dislocations of the shoulders

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Bilateral dislocation of the shoulder is rare, and almost always occurs posteriorly. Such dislocations have been associated with epileptic seizures,[1,3] electrocution, sporting injuries,[4] trauma and connective tissues diseases. However, there are even fewer documented bilateral anterior dislocations of the shoulders in the literature. We report an unusual case of bilateral anterior dislocation of the shoulders sustained following a trivial fall.

CASE REPORT A 70-year old left-handed woman with no previous dislocation or other past medical history of upper limb injury was admitted to our Accident & Emergency department. She was making her bed and tripped over the wire connected to her electric blanket, fell forward and landed on her right shoulder. She did not recall any injuries to her left upper limb. Subsequently, she was helped to get up by her spouse but noticed she was unable to abduct either arm and that both shoulders were painful to move.

On examination, the patient's right shoulder was very bruised. Both shoulders appeared symmetrical but there was loss of lateral contour.

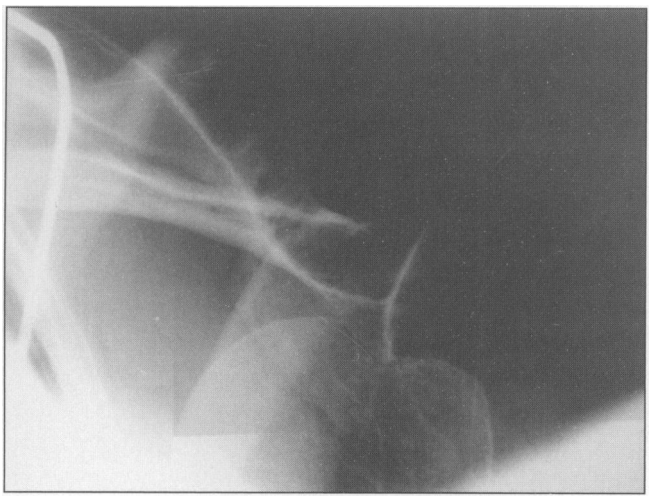

Fig 1a. Anterior dislocation of the left shoulder.

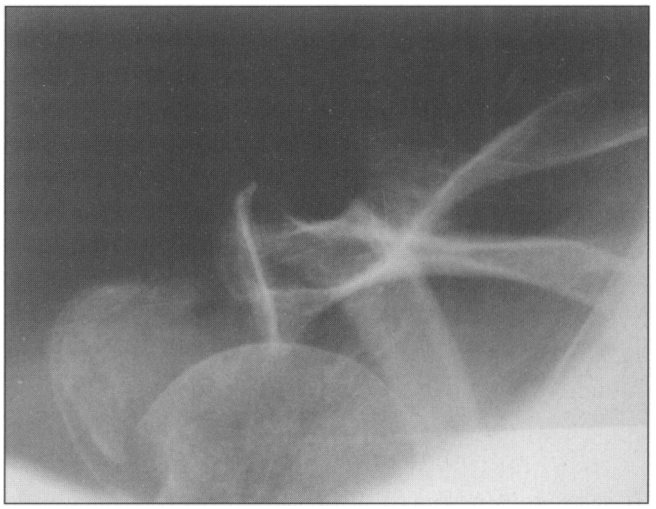

Fig 1b. Anterior fracture-dislocation of the right shoulder with displaced greater tuberosity.

There was no distal neurovacsular deficit and both axillary nerves were intact. No glenohumeral movement was possible in either shoulder and she found it painful to attempt this movement.

Radiography showed anterior dislocation of the left shoulder and anterior fracture-dislocation of the right shoulder with displaced greater tuberosity (Figures la and lb). Both shoulders were reduced using a closed method under Entonox. Bilateral broad arm slings were then applied

The patient was admitted to the ward for rehabilitation. She was discharged home one week later and went on to recover satisfactorily.

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DISCUSSION

Unilateral anterior dislocation of the shoulder is not uncommon and is one of the oldest reported injuries to man. Bilateral dislocations are very rare, however; to date only a few well-documented reports exist in the literature. Brown [2] analysed the aetiology of bilateral shoulder dislocation and found that trauma, seizure, electrocution and neuromuscular disorders, e.g. myasthenia gravis, cerebral palsy and scapular myopathy are the causes of bilateral anterior shoulder dislocation.

Classical dislocation of the shoulder can be treated satisfactorily with closed manipulation, sling immobilisation and gentle mobilization. However, treatment of shoulder fracture-dislocation can be difficult even in the acute stage. Inexperienced staff should not reduce them routinely as they are sometimes impossible to reduce by closed manipulation and further damage can be caused by over-enthusiastic attempts.[5] However, in our case, bilateral shoulder dislocations were treated successfully with closed manipulation.

We present this case firstly as a reminder to readers of the rare possibility of bilateral shoulder dislocations occurring after a relatively trivial fall, and secondly to illustrate some important diagnostic principles in trauma.

Looking for bilateral dislocations is the best way to find them. Taking a good history of the mechanism of injury is the first step in this search. A fall with both arms outstretched may be one such mechanism. Asking for any past medical history of connective tissue disease is also useful, as is obtaining a history of previous injury to the upper limb. Certain injuries will predispose to this dislocation e.g. Bankart lesion, Hill-Sachs lesion.

This case has reminded us of some general principles in diagnosing bilateral injuries. In this case making a diagnosis of a fracture and dislocation of the right shoulder did not prevent the contralateral dislocation being picked up as well, but we are aware of how easily a bilateral injury can be missed in the presence of asymmetrical signs and especially when, on one side, a diagnosis has already been made. Likewise, with the radiographs, a symmetrical appearance may represent normality, but may also represent bilateral dislocation. One should also not hesitate to obtain axial views of the shoulders when clinical suspicion is apparently denied by a normal-looking AP-radiograph.

Good results with bilateral anterior dislocation depend largely on early, accurate diagnosis. This in turn depends on the level of suspicion a doctor has for the diagnosis. Late presentation [2,5] and diagnostic difficulties were documented in the literature and this delay necessitates a large number of open reductions, with correspondingly poorer result. 50% of patients who presented late required open reductions.[2] Only early, prompt treatment will ensure a good functional outcome.

ACKNOWLEDGEMENT

We wish to thank Mr S R Bollen, Consultant Orthopaedic Surgeon, Bradford Royal Infirmary for allowing us to report this case.

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Case Report

An unusual case of patellar dislocation

A Case Report and literature review

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CASE REPORT We present a case of a 57 year old female whose patella became locked above a femoral osteophyte. She attended A & E at the Royal Victoria Hospital, Belfast. She had been pushing a chair forward under a table with her left knee when she felt a 'pop' inside it followed by severe pain. She was unable to bend or weightbear on the knee. Her left knee was previously asymptomatic with no recent trauma. She had a right knee arthroscopy and trimming of medial meniscus three years ago.

On examination the left knee was locked in full extension. There was a moderate sized effusion and the left patella was positioned higher than its counterpart. There was a prominent vertical sulcus immediately below the inferior pole of the left patella extending towards the tibial tuberosity. On palpation there was pain around the inferior pole of patella and overlying the patellar tendon. She could not actively straight leg raise. Active and passive knee flexion caused severe pain. Examination of collateral and cruciate ligaments was not possible due to inability to flex the knee. The knee lacked the typical boggy swelling of a true patellar tendon rupture but this was the clinical diagnosis.

Radiographic investigation demonstrated a high-riding patella on A-P view. The lateral view showed an osteophyte on the inferior margin of the patellar articular surface locked over an osteophyte on the superior aspect of the femoral articular surface (Fig. 1). The patella could no longer track freely downwards, explaining the patient's symptoms.

Reduction was easily achieved under intravenous analgesia. The limb was flexed at the hip by supporting the heel causing a relative hyperextension at the knee. The interlocking osteophytes of patellar and femoral articular

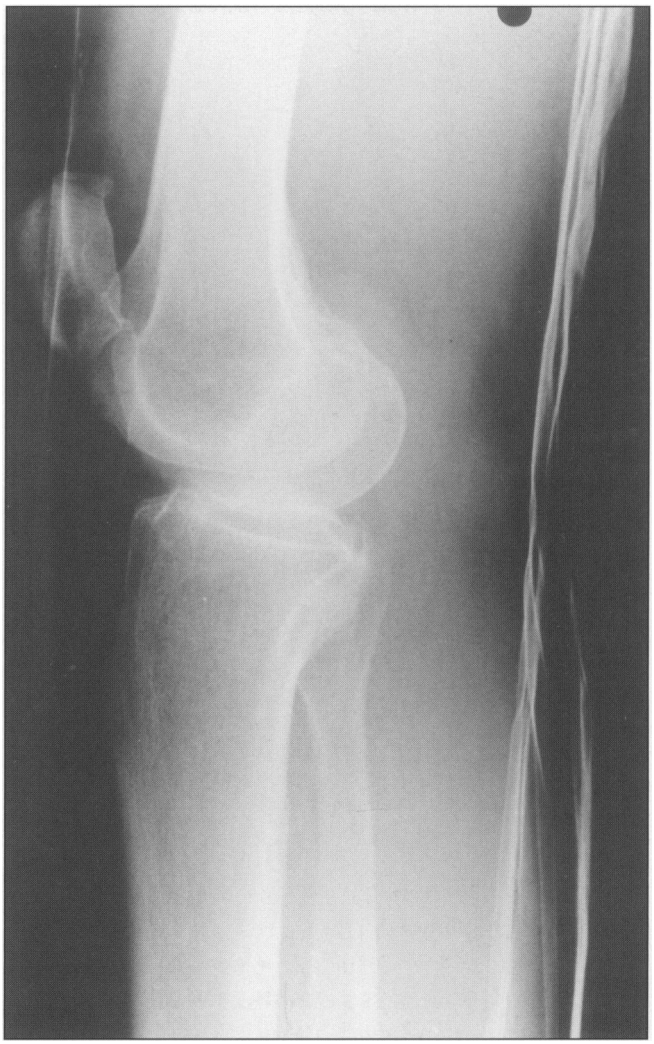

Fig 1. Lateral radiograph of knee demonstrating interlocking osteophytes of patellar and femoral articular surfaces.

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surfaces spontaneously disengaged and the patella reduced to its anatomical position. Pain was relieved, active flexion of the knee to 100 degrees was possible, the patella tracked normally, and straight leg raising returned. A radiograph confirmed the reduction (Fig. 2). The patient was then treated with a soft knee support and physiotherapy. Normal function returned in three months.

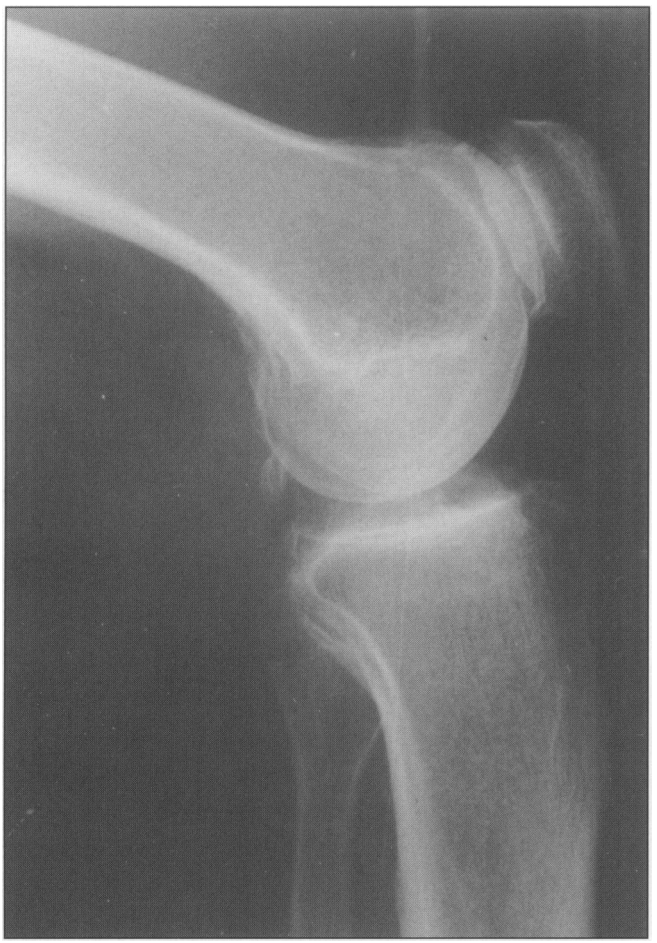

Fig 2. Lateral radiograph of knee showing reduced dislocation of patella.

DISCUSSION

A dislocated patella is a common clinical problem in A & E departments. Lateral dislocation is most frequent although medial, inferior and intra-articular dislocations have also been described. Superior dislocation of the patella is a rare and potentially confusing condition. The clinical differentiation between superior dislocation and the more common patellar tendon rupture can be difficult. Both conditions present with an acutely painful swollen knee. Clinical findings are similar; high-riding patella, inability to straight leg raise, pain localised to the infrapatellar area and reluctance to flex the knee. The differential diagnostic sign is the typical boggy infrapatellar swelling of patellar tendon rupture compared with the vertical infrapatellar sulcus of superior patellar dislocation. Radiographs of the knee are mandatory to make the diagnosis and eliminate the possibility of unnecessary surgical intervention in patients with superior dislocation of the patella.

Superior dislocation has been reported four times in the past;[1-4] three out of four cases have been elderly females with early degenerative changes present in the knee joint. The mechanism of injury is a direct upward force to the anterior aspect of patella associated with quadriceps contraction with the knee in a semi-flexed position. The patella tracks to the top of the patello-femoral joint. The presence of an osteophyte on the inferior pole of the patellar articular surface and on the superior articular margin of femoral condyle permits the interlocking of the two surfaces. Reduction may require intravenous analgesia, sedation or general anaesthetic and is achieved with the minimum of manipulation. Return of function is rapid, reported as being between four and seven weeks following injury.[3,4] There has been one case of recurrent dislocation.[2] Recurrence may require surgical intervention by cheilectomy.

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Case Report

Aspirin-related small bowel diaphragm disease identified during emergency laparotomy

S M Crowther, J G W Matthews

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Small bowel diaphragm disease is a rare complication of NSAID and aspirin ingestion. We report a case diagnosed following emergency laparotomy for an associated jejunal perforation.

CASE REPORT A 67-year-old man presented as an emergency admission with a 4 hour history of severe central abdominal pain. This was initially colicky and subsequently sharp and constant in nature with no other associated features.

He had no history of peptic ulcer disease, nor of any similar pain previously. Of note, his medication included aspirin NS 75 mgs mane.

On examination the patient was distressed but haemodynamically stable and apyrexic. His abdomen was rigid with maximal guarding and rebound tenderness in the epigastrium and central abdomen. Bowel sounds were present and hernial orifices intact.

The patient's white cell count was mildly elevated at 11.6 x 10^9 per L^3 but all other blood investigations including serum amylase were within normal limits. A presumptive diagnosis of a perforated peptic ulcer was made and following fluid resuscitation a laparotomy was performed.

Approximately 200 mls of turbid free fluid was found, principally in the upper abdomen. Both stomach and duodenum were intact; however, an isolated segment of inflamed jejunum approximately 10 to 12 centimetres in length was identified. Midway along this section of bowel a perforation was noted. The remainder of the small bowel appeared normal and no other intra-abdominal pathology was identified.

A small bowel resection was performed and closed with an end to end anastomosis prior to copious saline lavage and a post operative course of antibiotics. Recovery was uneventful and the patient was discharged eight days later.

Histopathology of the resected segments confirmed perforation with surrounding transmural inflammation with necrosis of the mucosa and muscle wall with fibrin deposition on the serosal aspect. There was no evidence of vasculitis away from the perforation and no evidence of malignancy.

Of interest, however, was the presence of several diaphragmatic strictures in which there was a proliferation of the mucosa with a central fibrovascular sub-mucosal core and some inflammation at the tip. These diaphragms within the lumen of the bowel wall were acting to cause a decrease in its diameter.

At subsequent outpatient review eight weeks following admission the patient had made a full recovery, having had his aspirin therapy stopped whilst an inpatient.

DISCUSSION

The damaging effects of NSAIDs and aspirin on upper GI mucosa have long been recognised, contributing to ulceration and perforation.[1] Less well recognised is the occurrence of damage to small bowel mucosa distal to the duodenum and with the common usage of enterically coated and slow release preparations, even the large bowel may be involved representing a distal shift in NSAID toxicity.[2]

A much less common complication of NSAID and aspirin ingestion is diaphragm disease. This

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is the formation of thin circumferential mucosal diaphragms within the lumen of the bowel. This usually affects the small bowel but large bowel diaphragms have been reported rarely.[3] The exact patho-physiological basis for the formation of these diaphragms is unclear but due to the stricturing of the bowel lumen which they produce it would seem from reported cases that they would most commonly present clinically with an obstructive picture.[4] Inflammation and ulceration however can also be present.

In this case the patient proceeded to laparotomy with a presumptive diagnosis of perforated duodenal ulceration. The interesting features of the case were, firstly the finding of an isolated jejunal perforation in an otherwise healthy-looking small bowel, and, secondly, the discovery of the associated diaphragm disease. As there were no clinical features or findings at laparotomy to suggest significant small bowel obstruction, it may be that the dual pathologies are merely synchronous and that the perforation and associated inflammation were not directly caused by the mucosal diaphragms. However, we were unable to find any report of diaphragm disease of the small bowel having been previously diagnosed following emergency laparotomy for an acute abdomen caused by perforation.

NSAID and salicylate ingestion can therefore, in addition to being responsible for recognised gastric and duodenal inflammation and perforation, cause more distal gastro-intestinal pathology. In addition, it can also be the cause of intestinal lumenal stricturing secondary to mucosal diaphragms. This also implicates this family of drugs as a rare cause of intestinal obstruction.

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