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THE ULSTER MEDICAL JOURNAL

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The Ulster Medical Journal

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THE ULSTER MEDICAL JOURNAL

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THE ULSTER MEDICAL SOCIETY

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The Ulster Medical Journal, Volume 62, No. 1, pp. 1 – 3, April 1993.

Editorial

"Admit medical"

As the fog of uncertainty surrounding the purchaser/provider relationship in the restructured health service begins to clear, many doctors responsible for providing acute services find that darkness has already fallen. For those who are charged with managing acute medical admissions to hospital, difficult nights finding beds lie ahead. Hospital physicians and referring general practitioners will be forced to ration health care in a way for which they are unprepared and untrained. A service that has been taken for granted by many and whose worth has been assumed to be self-evident by most, is under strain. What is going wrong and what can be done?

Much of the difficulty that lies just around the financial corner relates to the fact that most emergency admissions, of which those to acute medical wards form a very large proportion, are paid for as part of relatively non-specific block contracts. Unlike much procedure-based medicine which is relatively easy to quantify and cost, the service of acute emergency admission is being purchased rather than a precisely defined number of medical interventions. Managers start from the assumption that acute medicine in Northern Ireland is characterised by over-referral, over-admission, over-staying and over-bedding, and so it is easy to see that steady downward pressure on the resources for provision of acute services is inevitable. These assumptions cannot in any absolute sense be proven to be true. Their only validity stems from comparisons, using simple measures of medical activity, with other areas of the country, whose level of need is probably different. Be that as it may, rationing of emergency health care has arrived.

Even before the financial pressures became acute, Internal Medicine faced several difficulties. Much of the acute service is provided by broadly trained and practising generalists, who combine to a greater or lesser extent a specific subspecialist interest based more in an outpatient or investigational setting. The image of the general component of the physicians' work has declined. The layman does not readily understand what general medicine is. Not every physician has cherished their general role as much as their subspecialist role, and some have been happy to allow accident and emergency departments to encroach upon their work. Amongst many patients and a few doctors a subspecialist ascendancy cult exists. Those in primary care, without much knowledge of the relative cost of services, see less need for referral to a general physician. In short, the image of the general component of Internal Medicine apparently stands shakily in today's health service.

What is the way forward? One approach is to abolish the generalist physician in hospital and develop an entirely subspecialist pattern of admission. After initial sorting in primary care or accident and emergency, firms or consultants would receive cases according to subspecialist designation. There is an appealing logic and neatness to this approach. But there are basic flaws which in the foreseeable future make this approach unworkable. First of all most hospitals do not have enough "ologies" to handle the wide variety of cases that we see. The financial and other implications of junior hospital doctors' hours of duty mean that even in large hospitals maintaining rotas for several medical subspecialities is difficult. Even if all cover at junior doctor level is through a common rota, how is true subspecialist advice (at Senior Registrar/Consultant level) to be provided? In all

but the largest hospitals there are just not enough consultants available. Finally if we go down the highly subspecialist path general skills will atrophy and the role of the generalist will be handed to specialists in accident and emergency medicine. Once lost the position will not easily be regained.

The alternative is to redevelop the physician generalist/specialist, as a practitioner possessing general skills for managing acutely ill patients, whilst conducting a special interest based mostly in an ambulatory care setting. Those physicians willing to take on this challenging task must continue to be identified as having trained in and as continuing to practise acute medicine. It has been encouraging to see some subspecialist groupings, notably those in geriatric medicine, rejoining this tradition. Acute medical workloads require to be better defined and valued. That this activity will take place in fewer beds will have one blessing — no longer will "admit medical" be acceptable for patients whose only fault is to be elderly or have relatively ill defined problems. Though one is best not to trust specialties which change their name, the term general medicine must go. It has a vague and woolly feel and is too easily confused with general practice. Internal Medicine is more distinctive and is internationally recognised. Physicians can usefully raise their profile by developing admission units and areas concentrating resources and technology.

The physician generalist/specialist of the future need not fear the growth of internists based in primary care though he will reasonably argue that entry to such practice will require properly supervised training and recognised professional qualification. He will also point out that a team of generalist/specialists will remain uniquely well placed to teach medical students for whom the prospect of the sum of hospital based subspecialist teaching or the mileage allowance book to reach widely spread general practice based teaching are the bleak alternatives. Finally and perhaps ironically the future physician generalist/specialist, far from being an anachronism, is likely, once accurate costing of alternatives becomes available, to continue to be a vital cog in the hospital service of the future which labours to combine accessibility, effectiveness, efficiency and flexibility with some degree of common sense. The casualty departments, the general practitioners unable to have their sick patients admitted and the medical disasters waiting to happen because of treatment delays, will eventually result in an outbreak of wisdom leading to the formulation of contracts which adequately take into account the level of need for emergency medicine.

P M BELL

Editorial

The Ulster Medical Journal meets the Vancouver Group

In January your editor was invited to meet the members of that rather elusive and élite band who edit the largest and most influential general medical journals. The Vancouver Group first met in 1978 and formulated the guidelines which most, though not all, of the European and North American medical journals now follow. Standardization of references and biochemical units is one important gain, but

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the group has also initiated useful interchange of information and standardization of ethical and legal practices for many publication procedures.

Under the cheerful and exuberant leadership of Dr Richard Smith, editor of the British Medical Journal, and the watchful eye of Dr Robin Fox, editor of the Lancet, we listened to editors from many places. The husband and wife team of Bob and Suzanne Fletcher who jointly edit Annals of Internal Medicine, George Lundberg, editor of JAMA, editors of large and small journals, general and specialist, English language or Croatian, even some published electronically — all participated in a series of workshops.

We learnt that there is already a society for medical journal editors, the European Association for Scientific Editors, and that the Vancouver Group (so called after their initial meeting in that city) actually represent a pressure group to maintain the special interest of medical journals. We heard of the problems of peer review, and how an editor not only has to choose his referees, but also educate them to be useful consultants to the journal. We listened to debate on the imminent arrival of electronic publishing and the CD disc, where £200,000 worth of paper journals can be purchased by a library for £15,000 worth of plastic disc (although there is an extra consultation charge).

Those of you who actually *read* this editorial will be glad to know that the printing and publishing trade has the opinion that medical journals will be the last to yield to these new-fangled devices, although scientific research will use the new technology in parallel. The day for the first electronic issue of the Ulster Medical Journal has not yet come.

Desktop sub-editing and preparation of papers on floppy discs is an attractive advance, and now that the journal has a computer-literate editorial assistant this process can begin. For it to be useful, our authors will also have to be computer-friendly, and to be able to use the appropriate layout and style packages. It will certainly facilitate the re-writing of papers after peer review which is often the lot of less experienced medical writers. It is alleged that the Vancouver Group first met because somebody's secretary was brave enough to complain publicly when asked to re-type a paper for the third or fourth time in yet another journal "style".

It is now possible to get an idea of the importance of a journal in the world scientific hierarchy. The Ulster Medical Journal is assessed by the Institute for Scientific Information in Philadelphia. The Journal Citation Reports for 1991 show that 36 citations of articles published in the Ulster Medical Journal were made in other journals in 1991: six of these citations were to articles published in 1989–90. Comparing these six citations to the 80 articles published in the Journal during the year 1989–90 gives an "Impact Factor" of 6/80 = 0·075. The Ulster Medical Journal ranked 94th by impact factor out of 123 journals listed in Journal Citation Reports under Medicine, General and Internal. That is at the 76th centile: send us your good papers and improve our rating!

After nearly ten years at the editor's desk, I am happy to continue with the advice of Francis Bacon —

"Reading maketh a learned man,
Conference a ready man,
but writing an exact man."

Typescripts in the exact Vancouver style will continue to be welcome.

D R HADDEN

The Ulster Medical Journal, Volume 62, No. 1, pp. 4 – 10, April 1993.

Differences between "geriatric" and "medical" patients aged 75 and over

Maree Todd, Vivienne Crawford, R W Stout

Accepted 20 December 1992.

SUMMARY

We analysed the characteristics of patients aged 75 and over admitted to the geriatric and general medical wards over a three month period in a teaching hospital. Patients admitted to the geriatric wards were slightly older, were more often female, more likely to be admitted during the day and during a week day, more likely to have been seen by their own general practitioner, had more chronic and multiple illness with non-specific presentations, and stayed longer in hospital. Referring doctors seem to discriminate between patients needing geriatric care and those more suitable for general medical care, but there is an overlap in the characteristics of the two groups.

INTRODUCTION

Departments of geriatric medicine specialise in the management of disease and consequent impairment, disability and handicap in older people in a more comprehensive way than the traditional medical model.[1] Specialists in geriatric medicine have particular skills in managing older people who have multiple medical problems and chronic disability and whose mental health and social circumstances influence their overall health. To manage these problems departments of geriatric medicine generally provide a range of services including acute medical care, rehabilitation, domiciliary assessment, respite care and long term care.

In the United Kingdom the style of provision of hospital services to older people depends on local traditions, resources and philosophy. Whatever the type of service available, it must respond to the needs of the elderly population appropriately, efficiently and without delay. The initial decision to refer the patient to a department of geriatric medicine is usually taken by a doctor who is outside the

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department — a general practitioner, accident and emergency doctor or other hospital doctor. It is, therefore, important to assess if appropriate referrals are made. If patients are selected appropriately, the patients admitted to the geriatric medical unit and to the general medical wards should differ in the ways described above. The aim of this study was to determine if patients referred to a geriatric medical service were different from those admitted to the medical wards of the same hospital.

METHODS

All patients aged 75 years and over with acute medical problems admitted to the general medical wards and geriatric wards of the Belfast City Hospital were studied between November 1990 and January 1991. Excluded were patients admitted for planned investigations, treatment or respite care, patients transferred to the geriatric medical unit from surgical and fracture wards, and patients admitted from the day hospital or outpatient clinic.

Information was collected retrospectively on a standard questionnaire from the medical notes, nursing notes, nursing and medical staff. Demographic data included age, sex, marital status and residence before admission. Admission data included the admitting practitioner (patient's own doctor, partner or deputising service), mode of admission, time and day of admission. Daytime was defined as 09.00 – 17.00 hours, and public holidays were classified as weekends. The main diagnoses on admission were classified into several groups: cardiovascular disorders including myocardial infarction, heart failure, cardiac arrhythmias, and vascular lesions; respiratory disorders including respiratory tract infection, chronic obstructive airways disease, asthma and pulmonary fibrosis; malignancy of any type; stroke; other central nervous system disorders — mainly epilepsy; musculoskeletal disorders — mainly osteoarthritis; urinary tract disorders; gastrointestinal tract disorders; illnesses primarily due to alcohol, drugs or polypharmacy; falls with no acute precipitating illness; haematological diseases; endocrine disorders; and dementia. A patient with multiple disorders was defined by the presenting problem when a single diagnosis could not be achieved.

We identified whether the breakdown in health was due to monosystem or multisystem disease; details of the onset of illness — sudden, acute or acute on chronic; the length of time the patient had been unwell; the necessity for immediate admission (immediate admissions included all those with acute medical illnesses, and generally all those patients admitted to medical wards from the accident and emergency department; patients admitted the day after a domiciliary visit were not classified as requiring immediate admission). The accuracy of general practitioners' diagnosis was assessed. Admissions due to incontinence, immobility, confusion, or falls were only classified as due to one of these problems if there was no other immediate cause for the admission, so that immobility due to an acute stroke or acute confusion due to pneumonia would be classified under the disease.

Functional status on discharge (Barthel score[2]): in the geriatric wards all patients had been assessed by the occupational therapist, whereas in the medical ward information was obtained from the nursing staff by interview using a questionnaire.

Mental state on admission and discharge: all patients in the geriatric wards had a 10 point mental state questionnaire[3] recorded; a patient scoring less than seven points was classified as confused. Not all medical patients had a mental state questionnaire recorded, and patients with no score were classified as normal or confused according to comments in the notes or from the staff. Outcome: discharge destination, mortality and length of stay were recorded.

The data were analysed using SPSSX2.1[4] on an ICL mainframe computer and STATVIEW on an Apple Macintosh computer. Chi-squared and independent Student's t-tests were used.

RESULTS

There were 198 eligible patients admitted during the study period, 133 to the 170 beds in the medical wards and 65 to the 10 beds in the acute geriatric wards. The records of 46 eligible medical patients and 8 geriatric patients were missing. The missing data were analysed for age, sex, length of stay and mortality using the ward registers. The medical patients whose notes were missing had a significantly shorter length of stay, younger age, and were more often male compared with those whose notes were available for study, whereas there were no differences in the characteristics of the geriatric patients whose notes were either missing or available. Inclusion of the medical patients whose notes were missing would thus have accentuated the differences between the medical and geriatric groups.

Demographic data

The mean age was 84·7 years (95% confidence interval (CI) 83·4 to 85·9 years) in the geriatric group compared with 83·2 (95% CI 82·2 to 84·1 years) in the medical group ($p = 0·07$). There were 10 males (15·4%) and 55 (84·6%) females in the geriatric group and 46 males (34·6%) and 87 (65·4%) females in the medical group ($\chi^2 = 7·02$, $p = 0·008$). The percentage of males aged 75 and over in Belfast in the 1981 Census was 34·2%.[5]

There was no difference in marital status between the two groups. Approximately 60% were widowed and 20% still married in each group. There were no significant differences in place of residence before admission (although a greater proportion of those admitted to the geriatric ward came from residential or nursing homes).

Admission data

Thirty-nine (60%) geriatric patients were admitted following a domiciliary visit, 11 (17%) following direct (telephone) discussion with the general practitioner, and 15 (23%) were admitted through the accident and emergency department. One hundred and eleven (83%) of the medical patients were referred by their general practitioner to the medical wards through the emergency medical "take-in" service which operates in Greater Belfast, and 22 (17%) were admitted directly from the accident and emergency department. It is not known how many patients had been in telephone contact with a general practitioner before presenting to the accident and emergency department. More patients in the geriatric group than the medical group had been referred either to the ward unit or the accident and emergency department by their own general practitioner (Table I).

TABLE I

Differences in referring practice between patients admitted to the geriatric and medical wards

Referring general practitioner	*Geriatric ward (n = 65)*	*Medical ward (n = 133)*
Patient's own doctor	45 (69·2%)	61 (45·9%)
Other doctor	5 (7·7%)	51 (38·3%)
None	15 (23·1%)	21 (15·8%)

$x^2 = 20{\cdot}234$, $p = 0{\cdot}0001$

There were significant differences between the groups for time and day of admission. 54 (83·1%) geriatric compared to 72 (54·1%) medical patients were admitted during the day, ($x^2 = 12{\cdot}85$, $p = 0{\cdot}0003$). 59 (91%) geriatric admissions were admitted on weekdays compared with 104 (78·2%) medical admissions ($x^2 = 4{\cdot}74$, $p = 0{\cdot}03$).

Of those patients who presented to the accident and emergency department with no referral by a general practitioner, most of the medical group had illnesses of sudden onset (seven had a stroke, five acute shortness of breath due to pulmonary oedema or airways disease, three had gastrointestinal haemorrhage and three were comatose). The geriatric group had more chronic problems, eight (53%) having had a fall as the major presenting feature.

Details of illness

Medical patients had significantly more monosystem illnesses, sudden onset illness, immediate admission was more often required and they were less likely to present with the classical 'geriatric' problems of incontinence, confusion, falls or immobility (Table II). General practitioners were more likely to have the correct diagnosis on the letter for medical patients — 83 (78%) with letters available, compared with 21 (48%) of geriatric patients ($x^2 = 12{\cdot}27$, $p = 0{\cdot}0005$). Geriatric patients had been unwell for longer before admission (mean length of illness 22·6 days; 95% CI 9·8 to 35·4 days) compared to the medical patients (mean length of illness 8·9 days; 95% CI 6·6 to 11·3 days) ($p = 0{\cdot}04$, t-test). Cardiovascular and respiratory disorders were the most common reasons for admission to the medical wards (53·4% of all admissions), with stroke being the only other diagnosis made in more than 10% of admissions. Cardiovascular disorders and falls were most common in the geriatric patients (33·8% of admissions) and only respiratory and musculoskeletal problems were found in more than 10% of further geriatric admissions.

The functional state on discharge (the Barthel score) was similar in both groups; the mean score for the geriatric group was 14·7 (95% CI 13·7 to 15·8) and for the medical group 15·4 (95% CI 14·5 to 16·4) ($p = 0{\cdot}37$, t-test). There may be a bias in the scoring as all patients in the geriatric wards are assessed by occupational therapists, whereas in the medical wards occupational therapists are used more selectively and medical staff often underestimate or fail to recognise

TABLE II

Differences in illness patterns between patients admitted to the geriatric and medical wards. 'Geriatric' reasons for admission were incontinence, confusion, falls or immobility

	Geriatric patients (n = 65)	*Medical patients (n = 133)*	*p*
Breakdown in health			
monosystem	14 (21·5%)	73 (54·9%)	0·0001
multisystem	51 (78·5%)	60 (45·1%)	
Illness onset			
sudden	13 (20·1%)	54 (40·6%)	
gradual	43 (66·2%)	46 (34·6%)	0·0001
acute on chronic	9 (13·8%)	33 (24·8%)	
Required immediate admission			
yes	29 (44·6%)	119 (89·5%)	0·0001
no	36 (55·4%)	14 (10·5%)	
'Geriatric' reason for admission			
yes	49 (75·4%)	49 (36·8%)	0·0001
no	16 (24·6%)	84 (63·2%)	

functional disabilities in their patients.[6] There were no significant differences in the proportions of medical and geriatric patients confused on admission or discharge. 43·4% of all patients were confused on admission and 26·3% were confused at discharge.

Outcome

The mean length of stay for geriatric patients was 24·1 days and for medical patients 18·5 days (p = 0·11). Median stays were 17 and 12 days respectively. A greater proportion of medical patients were discharged early and the missing data would have accentuated this difference (Table III). Eight geriatric patients died (12·3%) compared with 26 medical patients (19·5%). The discharge

TABLE III

Proportion discharged by 14 and 28 days

	Geriatric patients (n = 65)	*Medical patients (n = 133)*
Length stay < 14 days	24	79
Stay 14 to 28 days	14	33
Discharge after 28 days	20	16
Still in hospital	7	5

$x^2 = 16·409$, p = 0·0009

destinations of the two groups were not different, 45–50% of patients were discharged home; 40% of geriatric patients were discharged to either residential, nursing home or other supervised non-family care compared to 26·3% of medical admissions ($\chi^2 = 3 \cdot 67$, $p = 0 \cdot 16$).

DISCUSSION

This study has shown some differences between elderly patients admitted to general and geriatric medical units in a large general hospital. Geriatric patients stayed in hospital longer, had more chronic and fewer acute problems, and were more likely to have been referred by their own general practitioner than medical patients. The fact that differences were found between the groups implies that general practitioners and accident and emergency staff are in general differentiating between patients for referral to geriatric or to medical departments. However, there was overlap between the groups. Among the medical patients 49 (37%) presented with one (or more) of the geriatric problems of incontinence, immobility, confusion and falls, 46 (35%) had a gradual onset to their illness, 60 (45%) had a breakdown in their health due to multisystem disease, 34 (26%) were confused at discharge and 22 (17%) were living in residential or nursing home care. Some of these admissions to the medical wards will have occurred because there were no empty beds in the acute geriatric ward. The fact that a greater proportion of medical patients were not seen by their own general practitioners, or were admitted at night or at weekends means that emergency services are less good at discriminating between geriatric and medical patients.

The two major teaching hospitals in Belfast, the Royal Victoria and Belfast City Hospitals, admit medical emergencies from the Greater Belfast area on alternate days. On its 'take-in' day, a hospital will admit a large number of patients to the medical ward on duty, some of the patients having attended the other hospital for a previous illness. In general, patients are referred for acute admission to the medical ward through the ambulance service, without direct contact between the general practitioner and the hospital medical staff. In contrast, the geriatric services operate on a catchment area basis, close relationships with the general practitioners in the area are developed, and domiciliary visits are used much more often. However, this service is only available from 9.00 am to 5.00 pm on weekdays. While some of the differences which this study identified between elderly 'medical' and 'geriatric' patients may have resulted from structural differences in the two services, a general practitioner faced with a serious medical illness in an elderly patient has the choice of arranging for the patient to be admitted via the "take-in" service or making direct contact with the geriatric service. One of the aims of this study was to try to identify differences in the patients referred by the two routes.

In a previous study[7] of patients aged 70 and over admitted to acute medical wards, admission factors associated with prolonged length of stay were advanced age, stroke, confusion and falls, while incontinence and loss of independence for everyday activities were also important. Although the factors were interrelated, the most important influence on length of stay was the medical reason for admission. An age related admission policy in which all patients over 75 years old would be admitted to the geriatric wards would have ensured that all these patients would have received "geriatric" care from the time of their admission to

hospital.[8] However, studies in the United Kingdom[1] and in the United States of America[9] have also found that roughly half of patients admitted to hospital aged 75 and over have uncomplicated medical illnesses. Such a system would have high sensitivity but low specificity as it would have meant that the geriatric unit would have admitted a large number of patients who had uncomplicated medical illnesses and who could be effectively managed in medical wards.

Although this study suggests that referring doctors discriminate between patients requiring geriatric care and those requiring medical care, some geriatric patients were admitted to medical wards. Early involvement of the geriatric multidisciplinary team in the management of such patients results in decreased length of stay[10] and better discharge arrangements.[11, 12] Selective referral combined with close liaison between geriatric and general medical wards would provide an effective way of meeting the needs of elderly patients for hospital care. Rotation of junior medical staff between the medical and geriatric wards also aids the dissemination of expertise.

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Myeloma — Results of treatment 1986 – 1990

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SUMMARY

Sixty-nine patients with multiple myeloma diagnosed during a five year period at the Belfast City Hospital were followed until death or for a minimum of one year in a retrospective study of survival. Although the patients were unselected, survival data was found to be similar to results from trials in which patient selection had occurred. Overall median survival was thirty-two months. Median survival fell with advancing disease and was 47, 27 and 18 months for Durie-Salmon stages I, II and III respectively. Those patients presenting with a platelet count of $<100 \times 10^9/1$ had a median survival of eight months in contrast to those with a platelet count $>100 \times 10^9/1$ whose median survival was 36 months. Patients presenting in renal failure had a shorter median survival of 28 months compared to 46 months for those with normal renal function.

INTRODUCTION

Over the last 25 years a series of multicentre studies by the Medical Research Council has shown a progressive improvement in the survival of patients with multiple myeloma.[1-4] This has been achieved through an increase in the intensity of chemotherapeutic regimens and an improvement in supportive care. The outcome of any trial will be affected by the preselection of patients for the trial and may often lead to apparently significant improvement in progress.[5] The present study describes the outcome for an unselected group of patients diagnosed and treated at this hospital during a five year period with follow-up to death, or for one to five years survival.

In 1990, the most recent year for which accurate figures are available, 92 patients were diagnosed as having multiple myeloma in Northern Ireland. (Northern Ireland Leukaemia Research Fund data collection service).

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METHODS

Sixty-nine patients with multiple myeloma diagnosed in the Belfast City Hospital between 1 January 1986 and 31 December 1990 were identified using the records of bone marrow examination and protein biochemistry. Administration of chemotherapy was supervised by the staff of the haematology department. The clinical haematology charts of all the patients were analysed to determine outcome. Laboratory findings utilised for diagnosis of myeloma included plasma cell infiltration in the bone marrow greater than 5%, a paraprotein band in serum or urine, and lytic bone lesions on skeletal radiography.

Patients were staged according to the Durie-Salmon classification.[6] In stage I all of the following are present — haemoglobin >10 g/dl, normal serum calcium, normal bone structure on X-ray (or a solitary plasmacytoma only) with low paraprotein production rates [IgG <60 g/l, IgA <30 g/l, urine light chains <4 g/24 hours]. Stage III is defined by the presence of any one of the following — Hb $<8{\cdot}5$ g/dl, serum calcium $>2{\cdot}62$ mmol/l, advanced bone lytic lesions, high paraprotein production rates [IgG >70 g/l, IgA >50 g/l, urine light chains >12 g/24 hours]. Stage II are those patients between I and III. A further subclassification into subgroup a (serum creatinine <176 ug/dl) or subgroup b (serum creatinine ≥ 176 ug/dl) was also used (Table I).

TABLE I

Stage and age of patients

Stage	*No*	*Median age yr*	*Age range yr*
Ia	23 (34%)	68	39 – 83
Ib	3 (4%)	66	53 – 75
IIa	13 (19%)	67	47 – 78
IIb	3 (4%)	65	60 – 69
IIIa	16 (23%)	65·5	44 – 82
IIIb	11 (16%)	68	59 – 84

Statistics

Median duration of survival was estimated by the Kaplan-Meier life table method. Univariate analysis using the log rank test was performed to identify the relationship between variables recorded at diagnosis and duration of survival. These variables included age, sex, paraprotein class, paraprotein index,[7] serum albumin level, Bence Jones proteinuria, presence of lytic lesions, β_2 microglobulin level, platelet count, serum urea level, serum creatinine level, Durie-Salmon stage and initial treatment. Cox's proportional hazard regression analysis was then used to identify those factors that were independently associated with survival. Statistical significance was taken as $p<0{\cdot}05$. Creatinine and urea values were distributed in a skewed fashion and were therefore log transformed before analysis Calculations were performed on an IBM compatible computer using EGRET software.[8] The concept of relative risk was used to compare the increased risk of death in

one category compared to a reference category; for continuous variables the change in risk associated with a one unit change in the variable is expressed.

PATIENTS AND TREATMENT

Two of the 69 patients were excluded from follow-up analysis as they moved away from the Belfast area. Of the remaining 67, 31 were male (46%) and 36 female (54%). Median age at diagnosis was 66 years for males (range 39–84 years) and 67·5 years for females (range 44–83 years). Twenty-eight patients (42%) were alive at the end of the study. The types of paraprotein were as shown in Table II.

TABLE II

Paraprotein type and relative frequency

Type	*No*
IgAK	5 (7%)
IgA λ	10 (15%)
IgGK	27 (39%)
IgG λ	13 (19%)
K only	5 (7%)
λ only	8 (12%)
Non-secretor	1 (1%)

The distribution of significant prognostic variables is compared with another unselected group of patients from Nottingham,[9] the IVth and Vth Medical Research Council myeloma trials and the US South West Oncology Group Myeloma trial (SWOG 8229)[10] and is shown in Table III. The unselected Nottingham group shows a higher proportion of patients with poorer features and shorter survival than the Belfast City Hospital group. The Belfast City Hospital and Medical Research Council trial survivals are similar, and the distribution of variables with independent prognostic significance between them was also similar, although a higher proportion of MRC patients were Durie-Salmon stage III.

Initial treatment was with melphalan and prednisolone in 22 patients; vincristine, melphalan, cyclophosphamide and prednisolone in 21; vincristine, adriamycin and dexamethasone in eight requiring aggressive therapy; melphalan alone in five; and other combination chemotherapy régimes in 6. Therapy was started if symptoms were present or there was evidence of disease progression. In general, aggressive therapy such as VAD (vincristine/adriamycin/dexamethasone) was reserved for those with advanced disease and was restricted to younger patients. Thus only one patient aged over 65 years received VAD as initial treatment and it was used in only one patient with stage I disease (who had spinal cord compression). Five patients had no treatment, two died within a month of diagnosis before chemotherapy could be given and three others have survived for intervals of 21, 40 and 44 months without chemotherapy. The diagnosis has been reviewed and confirmed in these 5 patients. Chemotherapy was withheld because of age or the presence of other illnesses, or lack of evidence of progression of myeloma. Interferon has been used in some patients during a plateau phase but it is too early to analyse its effect.

TABLE III

Patient characteristics: Clinical trial and unselected group results

	Clinical trials			*Unselected groups*	
	SWOG 8229 (%)*	MRC IV (%)*	MRCV (%)*	Nottingham (%)*	Belfast City Hospital (%)*
Haemoglobin (g/dl)					
< 7·5	4	13	11	—	6
(< 8·5)	—	—	—	(26)	(13)
7·5 – 10	20	19	24	—	30
(8·5 – 10)	—	—	—	(27)	(20)
> 10	76	68	65	47	67
Creatinine (μmol/l)					
< 130	62	59	57	50	69
130 – 200	21	22	21	20	7
> 200	17	19	22	30	24
Age (years)					
< 50	14	11	10	6	5
< 60	29	31	26	55 (50–70)	16
< 75	50	58	64	—	60
> 75	7	—	—	39 (> 70)	19
Calcium (mmol/l)					
< 2·6	—	—	—	69	81
> 2·6	—	—	—	31	19
Durie-Salmon stage					
I	3	8	5	15	37
II	19	5	9	17	24
III	78	87	86	65	39
Median survival months	29 (VCP) 48 (VMCP-VBAP)	29	24 (M7) 32 (ABCM)	25	32

V = Vincristine C = Cyclophosphamide M = Melphalan
A = Adriamycin B = Bi CNU P = Prednisolone

*percentage of each group identified by the criteria listed below.

RESULTS

Presenting features

Bone pain was the commonest presenting feature in 34 (51%) of the patients. Renal function was impaired at diagnosis in 17 (25%), and 6 (19%) presented with hypercalcaemia. Twenty-four patients (36%) had a haemoglobin level less than 10 g/dl at diagnosis. Eight patients (12%), all stage Ia, presented with features unrelated to myeloma.

Survival data

Fig 1 shows the survival curve for the study population (median survival 32 months). For males the median survival was 36 months and for females 30 months. The Kaplan Meier survival estimate at 12 months was 78% (95% confidence limits 66–86%) and at 36 months 43% (95% confidence limits 30–56%).

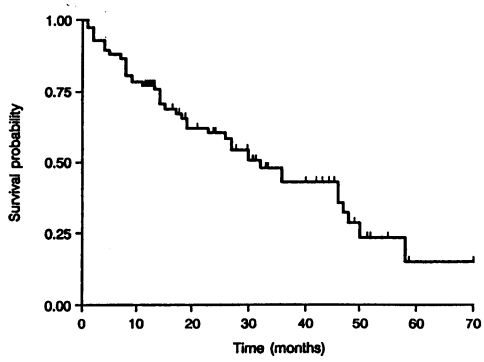

Fig 1. Survival curve for all 67 patients studied.

Fig 2 shows survival by stage. Stage III fared worse than stage I (median survivals 18 and 47 months respectively). Fig 3 shows the highly significant reduction in survival when the platelet count was $<100 \times 10^9/1$.

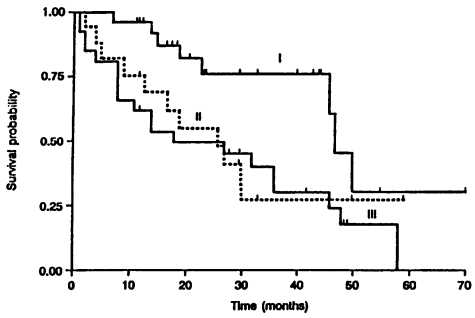

Fig 2. Survival curves for 67 patients, subdivided according to stage I, II, or III.

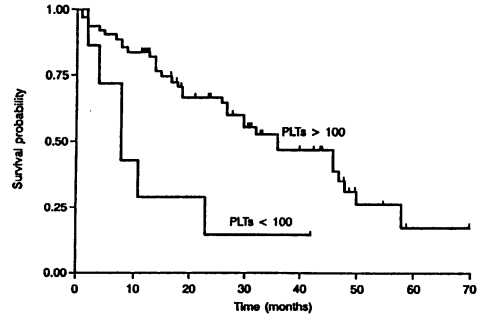

Fig 3. Survival curve for patients, subdivided according to platelet count (Plts) <100 and >100 ($\times 10^9/1$).

Table IV analyses the variables that were significant or approached significance as prognostic indicators. For categorical variables, the risk of each category relative to a reference category is shown — the relative risk of stage II compared to stage I was 2·6 and for stage III compared with stage I was 2·9. For a continuous variable the table shows the risk associated with a unit increase in that variable. For example, because serum creatinine was $\log_{10}$ transformed the relative risk of 2·4 is that associated with a tenfold increase in creatinine level. A 1·0 g increase in haemoglobin level is associated with a 21% reduction in the risk of death.

In the proportional hazard model, stage, age and platelet count were found to have independent prognostic significance. Although haemoglobin, creatinine and

TABLE IV

Relative risks of death from selected prognostic variables derived from univariate (log rank) and multivariate analyses of survival in 67 myeloma patients. 95% confidence limits in brackets

Variable	*Univariate results*		*Multivariate results*	
	Relative risk (95% CL)	*P*	*Relative risk (95% CL)*	*P*
Age				
> 70 yr vs < 70 yrs	1·8 (1·0–3·5)	0·062	2·7 (1·4–5·5)	0·005
Stage				
II vs I	2·6 (1·0–6·4)	0·024	3·6 (1·4–9·3)	0·003
III vs I	2·9 (1·3–6·7)		3·7 (1·6–8·9)	
Platelets ($\times 10^9$/l)				
< 100 vs > 100	0·3 (0·1–0·8)	0·006	0·4 (0·2–0·9)	0·037
Haemoglobin (g/dl)	0·8 (0·6–0·7)	0·004		
Creatinine (μmol/l) (log scale)	2·4 (1·0–5·8)	0·059		
Urea (mmol/l) (log scale)	3·7 (1·4–9·8)	0·015		

urea were individually significant they are already considered during staging. They do not therefore give additional prognostic significance when added to the model. In contrast to other studies[11] serum β_2 microglobulin levels (uncorrected for serum creatinine) were not found to be of prognostic significance but this measure was often not recorded in those patients who presented with advanced disease.

EARLY DEATHS

Eight patients died within six months of diagnosis. Of these, three were Stage IIa, two Stage IIIa and three Stage IIIb. One patient refused further admission to hospital and died at home two months after diagnosis. Three died of documented sepsis which was also strongly suspected as the cause of death of two others. One patient died of complications of renal failure and hypercalcaemia, and one from a probable pulmonary embolus. The number of hospital admissions for the 39 deceased patients ranged from 1 to 21 but with a median of 2 admissions during the course of their illness. The percentage of total time in hospital from diagnosis to death ranged from 0·5% to 100%, with a median 6·7%. Fifteen of the patients who died received at least one course of radiotherapy for palliation of bone pain during the course of their illness.

DISCUSSION

In general the diagnosis of myeloma is straightforward, but difficulties can arise during the early stages. Table V shows the minimal criteria for the diagnosis of myeloma from several centres.[5, 12, 13, 14] It is possible for example to meet the criteria for the diagnosis of myeloma and yet not be eligible for entry into the MRC V myeloma trial. Only about 15% of patients with myeloma are entered into trials co-ordinated by the MRC.[3]

TABLE V

Criteria for diagnosis of myeloma

Source	*A* *% Plasma cells in bone marrow*	*B* *Paraprotein level*	*C* *Osteolytic lesions*	*Minimal criteria for myeloma*
Chronic leukaemia myeloma task force[10]	>5% in marrow aspirate or other tissue	Monoclonal globulin	Osteolytic bone lesions	B+A or B+C
Hjorth[5]	>10%	IgG>30 g/l or IgG>20 g/l and/or BJ>1g/l	Osteolytic bone lesions	A+B or A+C
RA Kyle[11]	>10% abnormal immature plasma cells or histological proof of extramedullary plasmacytoma	M protein in serum (usually>30 g/l or in urine	Osteolytic lesions	A and usual clinical features of myeloma and either B or C
Maconduit[12]	>15% or infiltrates in biopsy	Associated M component	Not required	A+B
MRC V myeloma trial[4]	>20% or evidence of monoclonality if<20%	Band in blood or urine	Definite lytic lesions	Eligible for entry if any two of ABC
Belfast City Hospital	>5% in marrow aspirate	Monoclonal globulin	Lytic lesions	B+A or B+C

The present study, although encompassing a relatively small number of patients, was comprehensive in that it included all patients with myeloma (except two) diagnosed during a five year period. Comparison with the Nottingham unselected group[9] shows a slightly longer survival, which could be explained by the higher proportion of patients in the Nottingham study with poor prognostic features. Survival results from trials cannot be compared directly with those from unselected groups because of the exclusion of patients with unfavourable prognostic features. Such exclusions have been shown to have significant effects on survival results from trials.[5] Our results approximate to those of the MRC trials but it is not clear whether the patient populations are similar. Table III shows that the distribution of variables of individual prognostic significance is similar in trial patients and in our series, even though 19% of our patients are aged over 75. The Salmon-Durie

staging system suggests that a higher proportion of the MRC trial patients had advanced disease. Durie himself has questioned the wisdom of a staging system which gives undue importance to the presence of lytic lesions, which were demonstrated in 70% of trial patients and yet had limited prognostic significance on their own.[10] Differences in the interpretation of radiographic findings may be important as this is more subjective than the interpretation of the other paramaters used in staging, which could cause an apparent difference between our series and trial patients as judged by the staging system.

Eight of our patients had myeloma diagnosed at an early stage as an incidental finding. They were given various chemotherapeutic régimes; one died at 19 months from a ruptured abdominal aneurysm, the other seven remain alive and well at follow-up periods ranging from 12 to 70 months (median 40 months). While there have been no trials showing survival benefit from early treatment of myeloma, the experience with this small group of eight patients is encouraging. In the absence of a specific indication (such as bone plasmacytoma) such treatment remains a difficult decision.

In 1956 five year survival figures for myeloma averaged 5·6%.[15] There was an improvement following the introduction of melphalan and prednisolone about 1965. The recognition of the importance of infection and its improved treatment has also led to improved survival. There has been little further improvement despite the recent use of additional alkylating agents and anthracyclines. The VAD (vincristine, adriamycin, dexamethasone) regimen is very effective in relapsed and refractory myeloma but it has not been shown to improve survival when used in previously untreated patients.[16, 17] Indeed there is some evidence that the most important part of the VAD regimen is dexamethasone,[18] although the other agents contribute to its effectiveness.

Marrow ablative therapy with haemopoietic stem cell support has been shown recently to produce complete remission rates of 20–30%.[19, 20, 21, 22] Allogeneic bone marrow transplantation (from HLA matched donors) has been used in myeloma patients under 55 years of age. Of the typical population with myeloma, 75% would be excluded on the basis of age with a further reduction due to lack of HLA matched siblings. Gahrton[22] reported a mortality of 40% from treatment-related complications, which seems unacceptably high especially as most survivors ultimately relapse. Two-thirds of myeloma patients could be eligible for autologous bone marrow transplantation (using their own bone marrow) as mortality from this procedure has been shown not to increase up to age 70.[21] Recently it has been demonstrated that peripheral blood stem cells may be harvested following the use of chemotherapy and the cytokine granulocyte-colony stimulating factor (G-CSF).[23] The patient's bone marrow may be reconstituted using these peripheral blood stem cells avoiding the use of autologous marrow which may be contaminated with myeloma cells. The technique is limited as the yield of peripheral blood stem cells is much poorer in patients who have been heavily pretreated with chemotherapy or radiotherapy. The implication of these reports is that stem cell damage due to prolonged alkylating therapy should be avoided in potential candidates for autologous transplantation. Early assessment of suitability for such a procedure should be undertaken, ideally at the time of diagnosis, and peripheral blood stem cell harvest undertaken in the early stages of treatment, as is now the practice at this hospital.

Even though overall survival in myeloma may not have improved dramatically since the introduction of melphalan, much can now be done to palliate this devastating illness. The majority of patients have good quality survival and most are managed as outpatients. Recent developments such as the use of interferon to prolong plateau phase and the use of G-CSF to harvest peripheral blood stem cells and increase the safety of marrow transplantation suggest that further improvement in survival may now be obtainable.

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Identification of carriers of haemophilia by polymerase chain reaction

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SUMMARY

The gene for the coagulation protein factor VIII contains several common restriction fragment length polymorphisms which can be used to analyse the pattern of inheritance of factor VIII alleles within families. This can be exploited to identify carriers of haemophilia, an X-linked inherited disorder characterised by deficiency of factor VIII. In this study the polymerase chain reaction was used to analyse a polymorphism recognisd by the restriction enzyme BclI, located at intron 18 of the factor VIII gene. The restriction fragment patterns generated were used to track the inheritance of mutated factor VIII alleles within families allowing haemophilia carrier status to be determined in individuals at risk.

INTRODUCTION

Haemophilia is an X-linked inherited disorder which affects one male in 10,000. The condition is characterised by abnormal bleeding due to the deficiency of factor VIII, a protein necessary for normal coagulation. The deficiency is caused by heritable mutations within the factor VIII gene. Male off-spring of female carriers have a 50% chance of manifesting the condition. Female off-spring have a 50% chance of being carriers. Determination of haemophilia carrier status facilitates counselling of individuals at risk of having an affected child, allowing them to make informed choices regarding parenthood.

Initial attempts to identify carriers were based on measurements of the factor VIII coagulant activity in the plasma.[1] This approach proved unreliable due to the physiological variability in factor VIII levels and the random nature of X chromosome inactivaction in females.[2] The advent of recombinant DNA technology has permitted unequivocal identification of carriers in about two-thirds of cases using restriction fragment length polymorphisms (RFLPs).[3] These are naturally occurring variations in DNA sequence which alter the pattern of fragments produced when DNA corresponding to a particular gene is treated with a restriction endonuclease. The variations can be exploited to distinguish not only between genes carried by different individuals, but also between homologous pairs of genes (alleles) within individuals. Three common RFLPs occur in the factor VIII gene located at introns 18, 22, and 26. They are recognised by the

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restriction enzymes, *Bcl1*,[4] *Xbal*[5] and *Bgl1*.[6] By analysing the restriction fragment pattern of the factor VIII gene in DNA from a haemophilic patient using these enzymes, it is possible to identify the RFLP pattern associated with the X chromosome carrying the mutated gene. By comparing the pattern with that generated by the mother and sisters of the haemophilic, it is possible to trace the inheritance pattern of the mutated gene within the family and so to establish carrier members.

Restriction fragment length polymorphisms can be analysed using the polymerase chain reaction.[7] The technique allows an individual gene, contained within a complex mixture of genes such as chromosomal DNA, to be copied exclusively in a simple enzyme catalysed reaction until its DNA becomes the dominant species in the reaction mixture and enough is obtained to allow detailed analysis of that gene. Individual genes can be amplified about one million fold, and up to 1μg of specific DNA can be obtained.

This paper describes how the polymerase chain reaction was used to amplify the part of the factor VIII gene containing a RFLP recognised by the enzyme *Bcl1*, and how analysis of the restriction fragment pattern of the amplified DNA with *Bcl1* was used to identify carriers of haemophilia.

MATERIALS AND METHODS

Purification of chromosomal DNA: Human chromosomal DNA was prepared from 15ml of anti-coagulated blood.[8] A typical yield of 200μg of purified DNA was obtained.

Synthesis of oligonucleotide primers: Primers used to amplify the factor VIII intron 18 RFLP were synthesized by British Biotechnology Ltd. Their sequences have been described previously.[9]

Polymerase chain reaction (PCR): A DNA sequence corresponding to part of intron 18 of the factor VIII gene was amplified selectively from human chromosomal DNA. A reaction mixture (100μl) was prepared which contained: 1μg chromosomal DNA, 200μM each of dATP, dTTP, dGTP and dCTP (Pharmacia Ltd), 50 pmoles of each primer, 5 units of *Taq* DNA polymerase (Perkin Elmer Ltd) and PCR reaction buffer (10mM-Tris, pH 8·3, 50mM-KCl, 1·5mM-$Mgcl_2$ and 0·01% gelatin).

The chain reaction was carried out using an automated DNA thermal cycler (Perkin Elmer Ltd). Samples were initially denatured at 94°C for 4 min, followed by 25 cycles of 94°C for 1 min, 50°C for 2 min and 72°C for 2 min. After the reaction was completed, samples were stored at 4°C pending analysis.

Digestion of amplified DNA by Bcl1 restriction enzyme: Amplified DNA was precipitated from the PCR reaction mixture with ethanol and redissolved in sterile water. It was digested with *Bcl1* according to the manufacturer's instructions (Promega Ltd).

Analysis of polymerase chain reaction products: DNA, amplified by PCR and digested by *Bcl1*, was analysed by electrophoresis on 7·5% polyacrylamide gels.[8] The gels were then stained with ethidium bromide and visualised under UV light.

Patients: A total of 139 haemophilia A patients from 89 families in Northern Ireland are registered with the Regional Haemophilia Centre, based in the department of haematology, Royal Victoria Hospital, Belfast. Only families of severely affected patients (59/139) are investigated routinely. Of ten families studied, haemophilia carrier status was successfully assigned in nine using the intron 18 RFLP in combination with RFLPs in introns 22 and 26 of the factor VIII gene and the extragenic X chromosome probe DX13.[10] The details of two families are described showing the detection of one carrier and two non-carriers.

RESULTS

Analysis of the polymerase chain reaction products by polyacrylamide gel electrophoresis revealed a single species of amplified DNA represented by a band whose length was calculated to be 142 base pairs by comparison with DNA marker molecules of known length. This value is in agreement with that predicted from the relative positions of the primers on the factor VIII gene.[9]

Analysis of amplified DNA which had been treated with *Bcl1* revealed several different banding patterns depending on the DNA sample used in the PCR reaction (Fig 1). In some cases, the banding pattern was unchanged from that observed for undigested samples and a single band of 142 base pairs was seen. This corresponded to samples in which the factor VIII intron 18 DNA sequence was such that no recognition site for *Bcl1* was present. In other cases, the 142 base pair band was lost and was replaced by two smaller bands of 99 and 43 base pairs. This corresponded to samples in which the DNA sequence was such that a *Bcl1* site was present resulting in the fragmentation of the 142 base pair band into two smaller bands on treatment with *Bcl1.* In some cases, treatment of amplified DNA with *Bcl1* produced a 142 base pair band as well as bands of 99 and 43

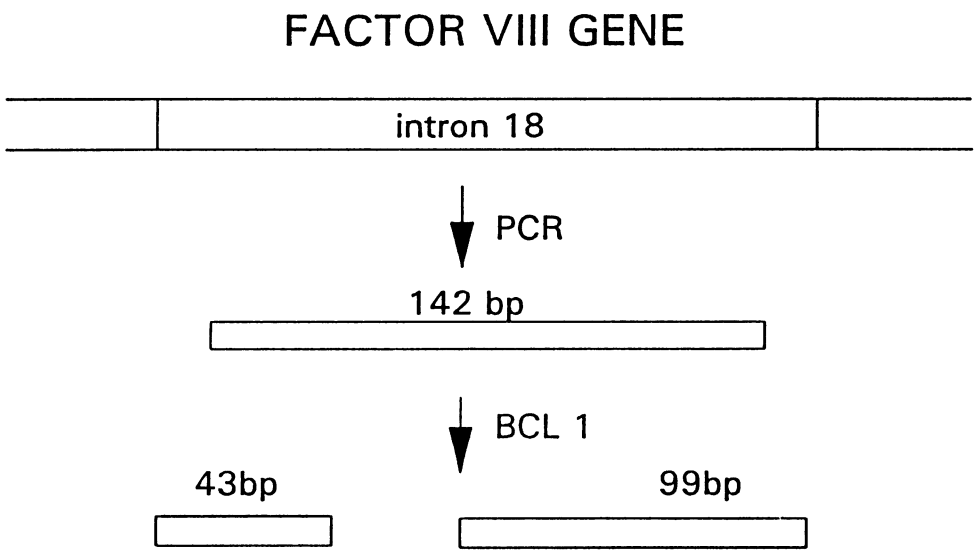

Fig 1. A 142 bp segment of intron 18 of the factor VIII gene containing a polymorphic *Bcl1* site was amplified by the polymerase chain reaction. Digestion of the reaction product with the enzyme *Bcl1* produced sub-fragments of 99 and 43 bp.

base pairs. This pattern represented heterozygous females with a *Bcl1* site present on one allele generating the 99/43 base pair bands and the other allele lacking a *Bcl1* site resulting in the 142 base pair band. It should be noted that the shortness of the 43 base pair band resulted in a reduced amount of ethidium bromide stain being bound causing it to be only faintly visible on gel photographs. The 99 base pair band is however clearly visible and indicates cleavage of the intron 18 *Bcl1* site.

TABLE

Intron 18 RFLP analysis in two families with haemophilia

Family	Individual	Genotype	Intron 18 *Bcl1* site	Phenotype
H1	I1	−/(99, 43)	+	unaffected
	I2	142 / (99, 43)	−/+	carrier
	II1	−/(99, 43)	+	haemophilic
	II2	142/−	−	unaffected
	II3	142 / (99, 43)	−/+	non-carrier
H2	I1	−/(99, 43)	+	unaffected
	I2	142 / (99, 43)	−/+	carrier
	II1	−/(99, 43)	+	haemophilic
	II2	142 / (99, 43)	−/+	non-carrier
	II3	(99, 43) / (99, 43)	+/+	carrier

Carriers of haemophilia were identified in several families by analysing the intron 18 RFLP in individuals. The strategy adopted was to identify the banding pattern associated with the X chromosome carried by a haemophilic and to use it to trace the pattern of inheritance of the affected X chromosome within the family. The results of typing for carrier status in families H1 and H2 are shown in the Table. The family tree and intron 18 PCR results for family H1 are shown in Fig 2. Interpretation of these PCR results is as follows: The father (I1) demonstrates two bands of 99 and 43 base pairs indicating that a *Bcl1* site is present on his single X chromosome at intron 18 of his factor VIII gene. The mother (I2) shows three bands of 142, 99 and 43 base pairs. This indicates that she is heterozygous with a *Bcl1* site present on one X chromosome (represented by the 99/43 base pair bands) but absent from the other (represented by the 142 base pair band). The son (II1) who suffers from haemophilia has the 99/43 base pair combination of bands indicating that of his mother's two X chromosomes, he has inherited the one which contains a *Bcl1* site and that this chromosome is associated with haemophilia in this family. In contrast, the unaffected brother (II2) has inherited the other maternal X chromosome indicated by the presence of a single band at 142 base pairs. The daughter's results (II3) indicate that she is heterozygous for the *Bcl1* site with all three bands present. The 99/43 base pair bands must be of paternal origin implying that, of the two maternal alleles, she has inherited the one represented by the 142 base pair band and, since it has been establised that this allele is not associated with haemophilia in this family, it can be said that she is not a carrier of haemophilia.

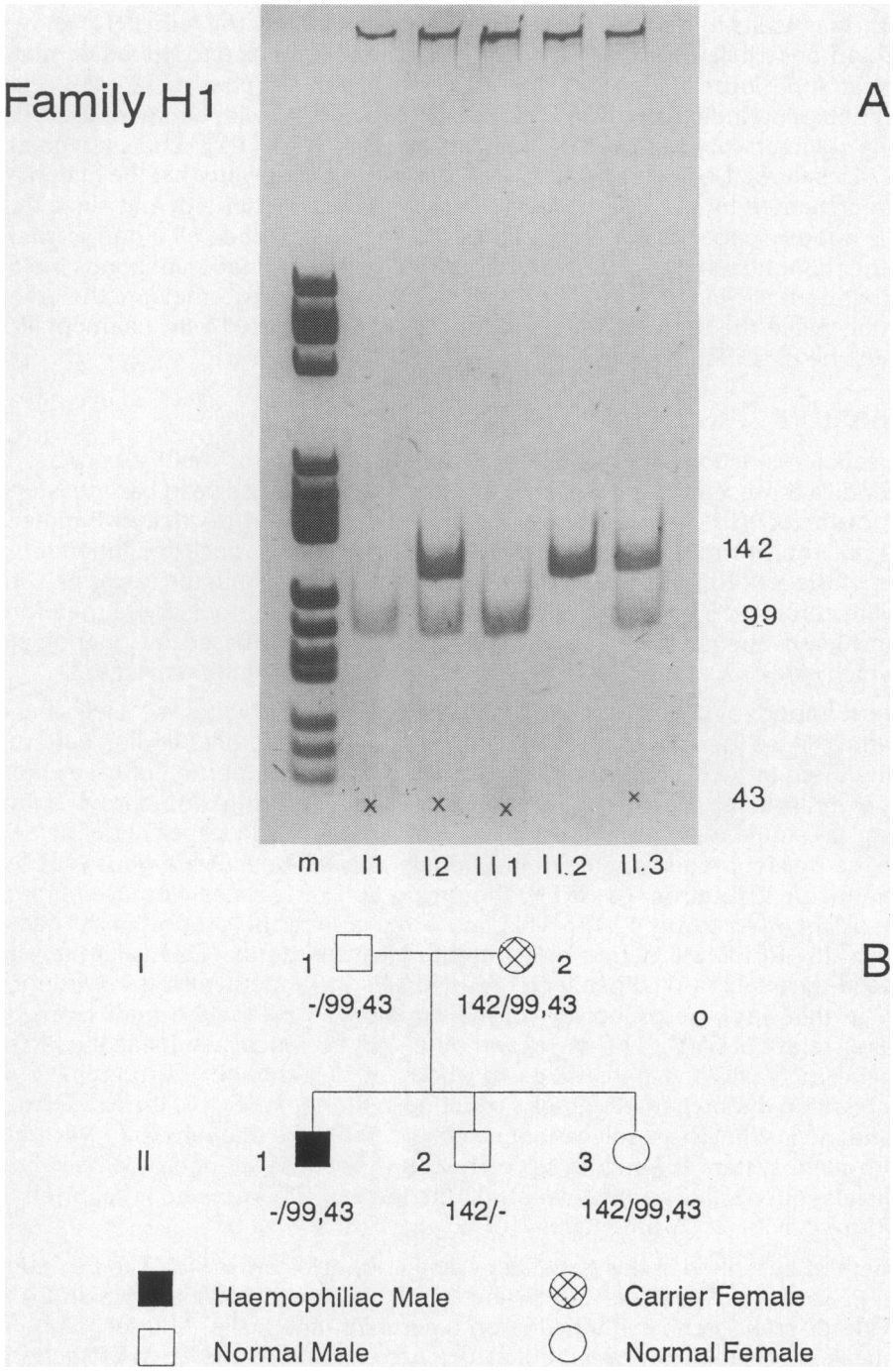

Fig 2. Family H1. (A) Polyacrylamide gel showing *Bcl1* digests of amplified DNA. (B) Family tree showing intron 18 genotypes and carrier status of individuals. The 43 base pair bands are only faintly visible and have been marked X.

Fig 3 shows results for family H2. As in the previous family, the father (I1) shows the 99/43 base pair combination and the mother (I2) is heterozygous demonstrating all three possible bands. The haemophilic son (II1) has the 99/43 base pair combination indicating the maternal allele associated with haemophilia. The patterns obtained for the two daughters are different. One (II2) is heterozygous; the 99/43 base pair combination are of paternal origin, implying that the maternal allele represented by the 142 base pair bands has been inherited, and since this allele is not associated with haemophilia, she can be classified as a non-carrier. The other daughter shows only the 99/43 base pair combination of bands indicating that both alleles possess a *Bcl1* site, one of which is paternal and the other maternal. Since the maternal allele in this case is associated with haemophilia, she must be classified as a carrier.

DISCUSSION

The use of restriction fragment length polymorphisms to identify carriers of haemophilia represents an improvement on previous methods based on measurements of factor VIII plasma clotting activity.[3] Because the restriction fragment length polymorphism used is intragenic, it was possible to track the inheritance pattern of the X chromosome carrying the mutated gene within the pedigree with complete certainty. The results of carrier testing by this method should therefore be considered unequivocal. This contrasts with methods based on phenotypic data which give only a probability of carriership and have a finite error rate.[1]

The most important limitation of this method is the necessity that the alleles have different DNA sequences at the RFLP, which generate different banding patterns allowing them to be distinguished from each other. In a proportion of cases both alleles of a carrier female will have the same sequence, making the X chromosome carrying the mutation indistinguishable from its homologous partner. For any RFLP, the maximum percentage of individuals who will be heterozygous is 50%. For the factor VIII intron 18 RFLP, the proportion of females who are heterozygous is reported to be 42%.[4] This figure represents the proportion of cases in which this RFLP will permit assignment of carrier status. This value can be increased by analysis of other factor VIII RFLPs in tandem with the intron 18 RFLP. In this way, the proportion of individuals who are heterozygous can be increased to about 65%. The use of two other RFLPs which lie outside the factor VIII gene increases the percentage to about 90% although the possibility of recombination during gametogenesis resulting in the separation of the RFLP from the gene means that the result cannot be considered to be unequivocal.[3] Recently a multi-allele system for identifying carriers has been developed. It is based on repetitive sequences of variable length in the factor VIII gene, and is reported to be informative for 95% of females.[11]

The method described in this paper allows haemophilia carrier status to be determined in about 40% of cases. It can be carried out rapidly (usually within 24h) and without great technical difficulty on a semi-routine basis. The technique is potentially applicable to any inherited disorder for which the aberrant gene is known and for which RFLPs have been characterised. The approach represents an important interface between clinical medicine and the rapidly expanding field of molecular biology.

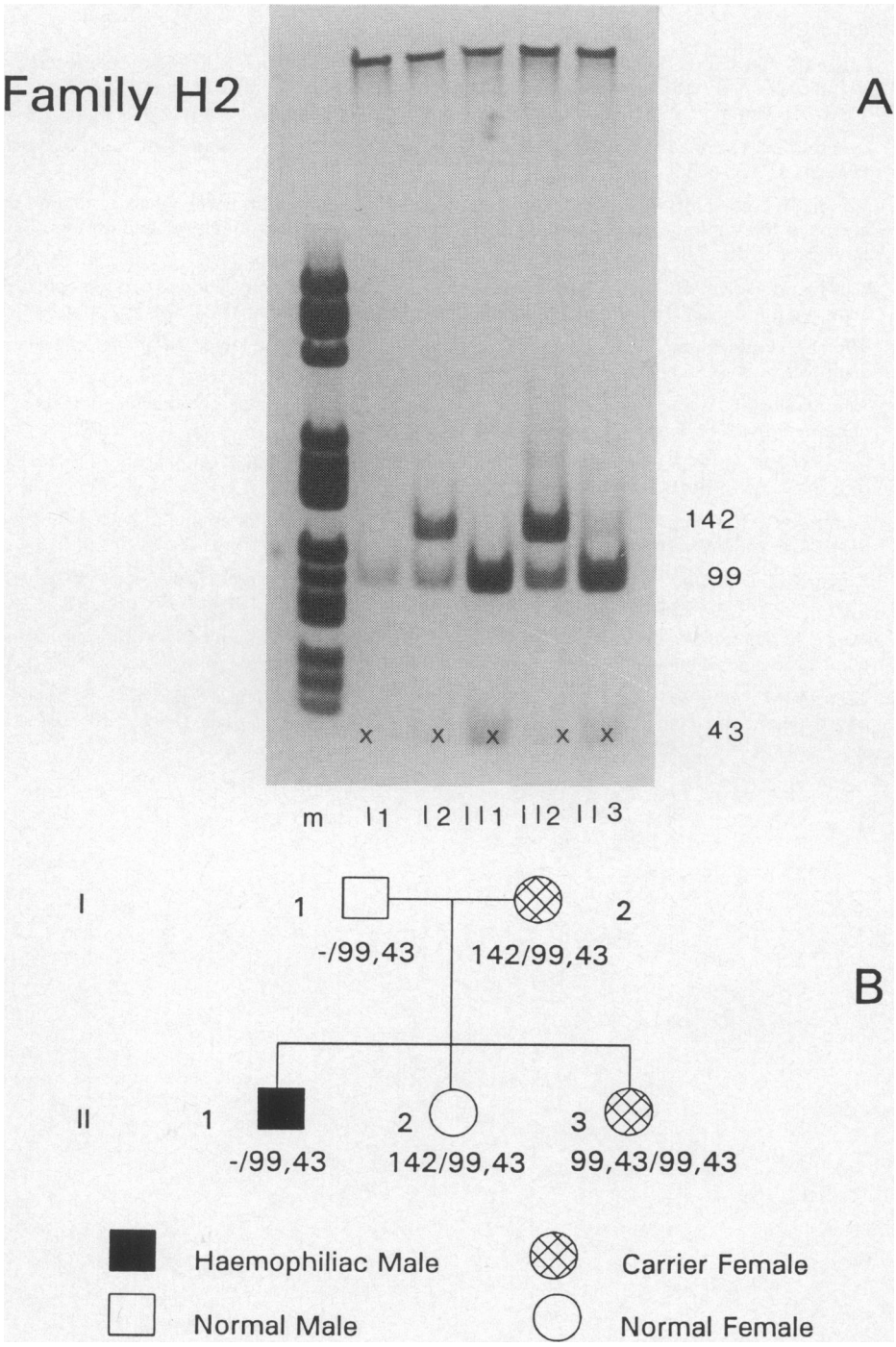

Fig 3. Family H2. (A) Polyacrylamide gel showing *Bcl1* digests of amplified DNA. (B) Family tree showing intron 18 genotypes and carrier status of individuals.

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Day-case arteriography

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SUMMARY

Outpatient femoral arteriography has been carried out in 100 consecutive patients presenting with evidence of peripheral vascular disease. Patients have been observed for seven hours in an observation ward bed. No bleeding or other complications have been encountered. The cost-saving to the hospital is approximately £60.00 per case. More importantly, the service to patients has been improved, with less chance of last minute cancellation due to unavailability of a surgical bed.

INTRODUCTION

Arteriography continues to be the standard method of investigation of patients presenting with intermittent claudication, providing an overall picture of the extent of arterial disease and directing the patients' further management. It has been usual practice for patients to be admitted to hospital, and confined to bed for a period of up to 24 hours following the arteriogram in an attempt to reduce the risk of post procedural bleeding.

During recent years technological developments have permitted the use of progressively smaller-gauge catheters capable of withstanding the high injection pressures and delivering the fast flow rates required for femoral arteriography. Consequently the risk of haematoma associated with femoral puncture has been reduced, and the likelihood of delayed bleeding lessened. The possibility of performing arteriography on a day-case basis was soon appreciated and there have been reports of this from the United States[1,2,3] and from the United Kingdom in 1990.[4] There is now a growing trend towards this approach.

We report on our experience of 100 day-case arteriograms performed over a 12 month period.

PATIENTS AND METHODS

All patients had a history and clinical findings which suggested vascular disease of the lower limbs. They had been referred for a vascular surgical opinion at the Belfast City Hospital. The only selection criteria for the day-case procedure were that the patient had a palpable femoral pulse and was not living alone. Elderly patients were not excluded, and ages ranged from 46 to 81 years.

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Patients were asked to report fasting to the radiology department at 8.30 am. It was emphasised that general medications such as antihypertensive and anti-anginal treatment should be taken normally. The injection area was infiltrated with local anaesthetic and the femoral artery punctured using a standard 18 gauge hollow needle and a single puncture technique. A guidewire and subsequently a 5 French straight catheter was introduced, its tip being positioned just proximal to the aortic bifurcation. Non ionic contrast (80 ml) was injected and a standard series of films obtained. The catheter was removed and local pressure applied for five to ten minutes to the puncture site until bleeding stopped. Two patients were studied in any one morning, each investigation taking an average 30 minutes, so that all day-case arteriograms would be completed before 10 am.

Following the application of a pressure dressing the patient was transferred from the X-ray table to a bed and then moved to the observation ward in the accident and emergency unit, which is adjacent to the radiology department. At approximately 5 pm that evening the groin area was inspected by the radiologist. The pressure dressing was replaced by a simple plaster and the patient was allowed to return home, having been advised that should there be any subsequent bleeding manual pressure should again be applied and the patient should report immediately to the casualty department. The patient was encouraged to spend the remainder of the evening resting.

RESULTS

All the patients were able to leave hospital on the evening of their arteriogram. A follow-up telephone questionnaire confirmed that none experienced any bleeding other than a few drops of blood, and none required emergency readmission. Any bruising associated with the procedure had resolved within the week, and all the patients said they would be quite prepared to have arteriography repeated on a day-case basis if required.

DISCUSSION

Day-case arteriography was introduced both because of the pressure on surgical beds and to increase the efficiency of the use of angiography equipment. Prior to its introduction patients had been admitted to a surgical bed on an appointed date, but due to last minute unavailability of beds, admission frequently had had to be postponed without prior notice. This produced both patient inconvenience and wastage of time in the vascular room in the radiology department. The pressure on surgical beds has been lessened by day-case arteriography. Observation ward beds are not normally occupied during the day, and the day cases use beds that are otherwise empty.

This study confirms that day-case arteriography offers a greater degree of flexibility. Arteriograms are obtained sooner following the patients' initial consultation and review appointments can be arranged within a few weeks of the procedure to discuss treatment options. This flexibility in turn has enabled significantly increased activity; the total number of arteriograms performed for intermittent claudication was 406 during the study year, compared to 292 for the previous year.

The actual radiological costs of performing an arteriogram are the same whether done as an inpatient or an outpatient. The overall cost-saving to the hospital for

the day patient service is the difference between an overnight stay in a surgical bed (£126) and an eight hour period in the observation ward (£64). In this hospital the saving has therefore been estimated at £62.00 per patient. In the context of the overall cost this saving is small but perhaps not insignificant. Our feeling is that day-case arteriography is a safe, inevitable step forward.

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Anaesthetic monitoring: clinical practice in anaesthetic rooms and theatres

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SUMMARY

Twenty anaesthetic rooms and operating theatres in Northern Ireland were visited in both 1990 and 1992. Data was collected on the availability and use of anaesthetic monitoring. In the anaesthetic rooms there were few pulse oximeters. In the theatres more monitors were available and in use. Some change in practice had occurred between 1990 and 1992, notably an increase in the monitoring of ventilation, and in the availability of printer facilities for documentation of anaesthetic records.

INTRODUCTION

In 1985 the Harvard-affiliated hospitals in Boston USA adopted standards for the monitoring of patients during anaesthesia.[1] These included the continuous presence of anaesthesia personnel during the anaesthetic, measurement of blood pressure and heart rate at least every five minutes, continuous display of the electrocardiogram, continuous monitoring of ventilation and circulation, use of an inspired oxygen monitor, a breathing system disconnection monitor for use during mechanical ventilation, and the availability of patient temperature measurement. In the UK similar standards were advocated by the Association of Anaesthetists.[2] In 1989 Eichhorn presented a summary of the experience of the Harvard departments before and after adoption of these monitoring standards.[3] In a review of over a million anaesthetics he found that unrecognised hypoventilation was the most common cause of major intraoperative accident and injury, and suggested that the end-tidal carbon dioxide analyser was the best monitor of ventilation.

More specific guidance on monitoring has been given by McKay and Noble.[4] In an analysis of critical incidents in over 4,000 anaesthetics they reported that arterial oxygen desaturation was the commonest adverse physiologic change. A critical incident was recorded when an unexpected physiologic deterioration requiring intervention by the anaesthetist to prevent a likely bad outcome was signalled

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first by a pulse oximeter, and they recommended that a pulse oximeter be used for every anaesthetic. The UK confidential enquiry into perioperative deaths of 1987 also commented on the infrequent monitoring of end-tidal carbon dioxide concentration during anaesthesia, and also recommended that a peripheral nerve stimulator be readily available for the monitoring of neuromuscular blockade.[5] In the expectation of fewer claims and reduced payouts some malpractice liability insurers in the USA granted discounts on premiums,[6] but others expressed caution.[7-10] Orkin pointed out that minimal monitoring standards were likely to have minimal effect, because they merely required adherence to accepted practice[8]; with reference to pulse oximetry, Fairley stated that we do not know the threshold values of oxygen saturation at which physiology gives way to pathology.[9] In an editorial review of anaesthetic mortality in perspective, Keats found no evidence that improved patient monitoring had resulted in decreased mortality.[10] Very large numbers are required to demonstrate a difference in these already low mortality rates, and even Eichhorn's figures of over a million anaesthetics fail to show a statistically significant reduction in mortality.[3]

The purpose of this audit was to ascertain the degree of professional compliance with these standards of monitoring, in both the anaesthetic room and the theatre, rather than to demonstrate the value of these standards in the reduction of morbidity and mortality. Data was collected over a period of two months in 1990, and in 1992.

METHODS

Consultant anaesthetists in the Northern and Eastern Health and Social Services Boards in Northern Ireland gave consent to the random visitation of a junior anaesthetist to operating theatres during scheduled working hours. A form was designed to document the nature of monitoring available in the anaesthetic room and in the theatre, and the actual use of appropriate monitoring in theatre.

In 1990 nine separate hospital sites were visited. Data was recorded only in the operating theatres and anaesthetic rooms which were in use in a given afternoon session, but other theatres within the same theatre blocks were also visited to determine whether a similar standard of monitoring was available. In 1992 the same theatres were visited on the same afternoon sessions. Paired data from 20 operating theatres was recorded during established operations under general anaesthesia, when the anaesthetist concerned had no prior warning of the assessment. For the purpose of the audit end-tidal carbon dioxide analysers, disconnection alarms, and pulse oximeters were considered appropriate monitors to use, if available, and peripheral nerve stimulators in patients who had received muscle relaxants.

RESULTS

Facilities for the recording of an electrocardiogram and arterial blood pressure were available in all anaesthetic rooms, both in 1990 and 1992. Automatic arterial blood pressure recorders were present in only 75% in 1990, and in 80% in 1992. There was a lack of oxygen saturation monitors, which were available in 10% in 1990, and 20% in 1992, and no more than 10% had an end-tidal carbon dioxide analyser.

TABLE I

Monitoring in the theatre

Anaesthetic monitor	*Number available and in use*	
	1990	*1992*
Electrocardiograph	20 (100%)	20 (100%)
Automatic arterial blood pressure	20 (100%)	20 (100%)
Pulse oximeter	17 (85%)	20 (100%)
End-tidal carbon dioxide analyser	9 (45%)	13 (65%)
Inspired oxygen analyser	14 (70%)	16 (80%)
Peripheral nerve stimulator	1 (5%)	1 (5%)
Expired minute volume	11 (55%)	16 (80%)
Anaesthetic agent monitor	6 (30%)	12 (60%)
Disconnection alarm	16 (80%)	19 (95%)
Central venous pressure	3 (15%)	2 (10%)
Temperature	2 (10%)	2 (10%)
Urine output	3 (15%)	3 (15%)

Standards of monitoring were higher in the theatres. In 1992 all anaesthetists were monitoring arterial blood pressure, the electrocardiogram, and oxygen saturation. The number of end-tidal carbon dioxide analysers, inspired oxygen analysers, ventilation monitors, anaesthetic agent monitors and disconnection alarms had risen (Table I). Some monitors were not in favour; the simple praecordial stethoscope was not used at all in either year, and a peripheral nerve stimulator was used in not more than 20% of anaesthetics in which muscle relaxants had been given. Use of more invasive minitoring was similar in 1990 and 1992.

There was an increase in the availability of printer facilities for automated recording of monitor data. In 1992 60% of theatres had printer facilities for the recording of data from the electrocardiogram, automatic arterial blood pressure monitors, or pulse oximeters, compared to only 5% of theatres in 1990. Anaesthetic ventilators with built-in monitoring capabilities were more common in 1992.

Demographic data is presented in Table II. The operations and patient ages were similar in 1990 and 1992, and there was no difference in the grade or numbers of anaesthetic staff on duty.

DISCUSSION

This study suggests that monitoring facilities in the anaesthetic room are poor, with pulse oximetry available in only one out of five units. Some consider the pulse oximeter to be the single most important monitor in the anaesthetic room,[4] and as the majority of patients had anaesthesia induced in the anaesthetic room, it follows that an improvement in clinical practice is possible. The choices are to ignore the problem, to stop anaesthetising in the anaesthetic room, or to equip the anaesthetic room to a standard comparable to the theatre. The last involves considerable expense, so the second choice is the most favourable. The role of the anaesthetic room in modern anaesthesia seems to be diminishing.

TABLE II

Demographic data

Subspecialty	*Frequency*	
	1990	*1992*
General surgery	6	6
Orthopaedic surgery	3	3
Gynaecological surgery	4	3
Vascular surgery	2	2
Urological surgery	1	2
Cardiac surgery	1	1
Plastic surgery, dental surgery, ENT and eye surgery	3	3
Anaesthetist : patients ratio	1·3	1·25
Anaesthetist by grade		
Consultant	16	16
Senior registrar, registrar	6	4
Senior house officer	4	5
Patients by age		
0 – 15 years	1	1
16 – 30 years	4	5
31 – 60 years	6	5
61 – 80 years	9	9

In theatre, more of the basic and the complex monitors are available. More end-tidal carbon dioxide analysers are used, providing valuable information on ventilation, rebreathing, cardiac output, and in particular the position of the endotracheal tube. The resurgence in popularity of closed circuit anaesthesia has produced the need for increasingly sophisticated ventilation monitors, which are often built in to the newer generation of machines, providing data on expired minute volume, tidal volume, and anaesthetic agent concentration. The last is of considerable importance in a closed circuit at low gas flow. Although almost all theatres used these monitoring methods, there were exceptions, notably the lack of use of the peripheral nerve stimulator. Only a few anaesthetists monitor neuro-muscular blockade, perhaps due to the increasing use of the shorter acting muscle relaxants vecuronium and atracurium. The use of the praecordial stethoscope is also on the wane, despite some indication for its use, particularly in children.

There is an increasing diversity of monitoring devices available, and these are being accepted as useful weapons in the armoury of the modern anaesthetist. In anaesthetic audit we must set ourselves a standard of clinical practice to strive towards. With regard to standards of anaesthetic monitoring, we are performing reasonably well, but there is still room for improvement.

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Perinatal outcome and antenatal care in a black South African population

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SUMMARY

The relationship between perinatal outcome and antenatal care was investigated at King Edward VIII Hospital, Durban, by a case control retrospective study of pregnancy records in 165 perinatal deaths and 156 infants surviving the perinatal period. 82% of the mothers of live infants had booked for antenatal care compared with only 60% of those who experienced a perinatal death. Hospital booking was associated with a higher infant birthweight. For those who booked earlier there was no reduction in total perinatal mortality or the stillbirth: neonatal death ratio, and many of the mothers of highest risk failed to book. This suggests that the better perinatal outcome in booked mothers may have been secondary to the type of mother who chose to book, rather than the actual antenatal care. To help reduce perinatal mortality, methods must be employed which reach those mothers who are most likely to fail to book.

INTRODUCTION

In the 1987 Perinatal Lecture at the Royal Maternity Hospital, Belfast, entitled "Obstetrics and Poverty", Professor Hugh Philpott, University of Natal, presented startling data from two similar hospitals in Durban, South Africa. At that time, one was serving the white population, and the other the black population. Their respective mortality rates were 12 and 50/1,000: the higher figure in the black population apparently being the result of ignorance and poverty.

In 1991, during a Queen's University Final Year Medical elective, we decided to carry out further research into these perinatal mortality figures whilst based at

Research project undertaken during a final year elective period in Durban, South Africa.

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King Edward Hospital, Durban. There, 15,000 deliveries are carried out annually, and the perinatal mortality rate for 1990 was 81/1,000 births.[1] Antenatal care is probably the most important factor which determines perinatal outcome,[2-6] but is often underutilized by lower socioeconomic groups. As in many South African hospitals caring for the black population, mothers delivering at King Edward often fail to book for any antenatal care, and attend for the first time when in labour.[2, 4, 6-10] We investigate whether perinatal outcome is related to antenatal care in this population and if so, whether this relationship is to the actual antenatal care received, or if it is secondary to the type of mother who chooses to book for such antenatal care.

SUBJECTS AND METHODS

Data were obtained from the 1990 obstetric records at the King Edward VIII Hospital, University of Natal, Durban, South Africa. The study population consisted of 321 predominantly black South African mothers, drawn from all mothers whose babies were delivered at the hospital between January and March 1990.

A case control retrospective study was carried out. The cases comprised 165 consecutive records of mothers whose infants had died during the perinatal period, and the controls were 156 consecutive records of mothers whose infants survived the perinatal period. Case and control groups, although not individually matched, were comparable, with no significant difference in maternal age, parity, or in mode of delivery.

The perinatal period was defined as from 28 weeks' gestational age to seven days after delivery, or if this length of follow-up was impossible, to the time of discharge from hospital. A stillbirth was defined as an intrauterine death occurring after 28 weeks' gestation. Normal birthweight was defined by WHO criteria as $> 2 \cdot 5$ kg. A booked patient was defined as one who was recorded as attending an antenatal clinic one or more times, either at the King Edward VIII Hospital, another hospital or a peripheral clinic. Gestational age at booking was assessed clinically by doctors or midwives. Hypertension was defined as a blood pressure of 140/90 mmHg on one, or if possible two occasions.

The relationship between perinatal outcome and antenatal care was assessed by comparing antenatal booking status in the two groups. Antenatal abnormalities and birthweight were noted. To test whether a possible relationship between perinatal outcome and the antenatal care received was direct, or secondary to the type of mother who chose to book; we examined two criteria, to give an indication of the effectiveness of the antenatal care itself.

1. *Gestational age at first booking.* Antenatal care is more effective if the mother books early, and late booking may be associated with a higher perinatal mortality rate[11] due to inadequate care.[12] Thus, a reduction in perinatal mortality with earlier booking was used as an indicator of the effectiveness of antenatal care received.

2. *Birthweight.* Low birthweight is probably the most important factor in perinatal death,[13] due to either intrauterine growth retardation or to prematurity. Effective antenatal care should address factors causing growth retardation such

as hypertension, excess alcohol intake, and smoking, but will have little effect on the causes of prematurity such as premature rupture of membranes, antepartum haemorrhage or polyhydramnios.[14] Thus effective antenatal care should cause a greater reduction in intrauterine growth retardation than prematurity.

It was not possible in this study to ascertain directly whether a low birthweight was due to growth retardation or to prematurity, but an estimate may be made on the basis that intrauterine growth retardation tends to lead to stillbirth[14] whereas prematurity tends to lead to neonatal death.[15] Therefore effective antenatal care may be indicated by a reduction in the stillbirth:neonatal death ratio in booked compared to unbooked mothers. This reduction should be most marked with an earlier gestational age at booking.[16]

All statistical analysis was done by the chi square test with significance defined as $p < 0{\cdot}05$.

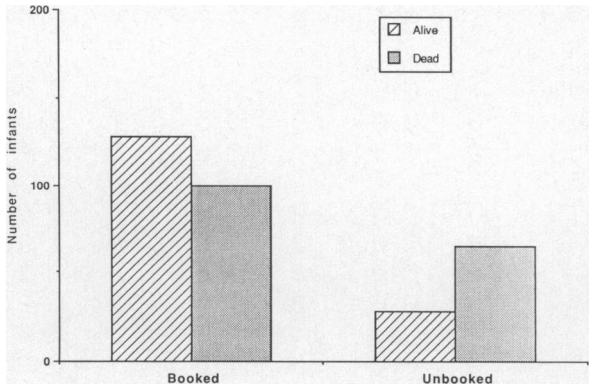

Fig 1. Perinatal outcome in selected booked and unbooked pregnancies at King Edward VIII Hospital, Durban.

RESULTS

Of the 321 mothers in the study, 228 were recorded as having booked for antenatal care, and 93 had not booked.

Fig 1 shows there was a significant association between perinatal outcome and booking for antenatal care in this population, with 82·1% of mothers in the live group having booked for antenatal care compared to only 60·6% in the perinatal death group ($p < 0{\cdot}001$).

The Table shows the distribution of the most commonly recorded antenatal abnormalities. The presence of an antenatal abnormality was more common ($p = 0{\cdot}002$) in the perinatal death group (63%) compared to the live group (45·2%). Hypertension was the most frequently recorded antenatal abnormality, affecting 22·4% of the study population. Proteinuric hypertension (including eclampsia) which represented 70% of all hypertension, was almost twice as common in the perinatal death group (19·4%) compared to the live group (11·4%), although the difference was not statistically significant.

The acceptance of antenatal care should allow detection and appropriate management of antenatal abnormalities and thus may partly explain the better perinatal outcome associated with mothers who had booked for antenatal care. However, our hypothesis is that this relationship may be secondary due to the type of mother who chooses to book, rather than to the actual antenatal care. For those mothers who booked, there was no significant difference in gestational age at first booking, between the perinatal death and live birth groups, and in particular no evidence of a lower perinatal mortality with earlier booking (Fig 2). Thus antenatal care itself did not appear fully responsible for the lower perinatal mortality seen in those mothers who had booked.

TABLE

Frequency and percentage of maternal antenatal abnormalities in pregnancies with live births and perinatal deaths

Antenatal abnormality	*Live*		*Dead*		*Total population*	
	n	%	n	%	n	%
Maternal						
Hypertension with proteinuria	18	11·6	27	16·4	45	14·1
Hypertension without proteinuria	15	9·7	7	4·2	22	6·9
Eclampsia	0	0·0	5	3·0	5	1·6
Cardiac disease	0	0·0	1	0·6	1	0·3
Anaemia	0	0·0	2	1·2	2	0·6
Rhesus negative	2	1·3	0	0·0	2	0·6
Positive	1	0·6	2	1·2	3	0·9
Obstetric						
Preterm labour treated successfully	1	0·6	1	0·6	2	0·6
Preterm labour failed treatment	0	0·0	9	5·5	9	2·8
Prelabour membrane rupture	2	1·3	1	0·6	3	0·9
Prelabour membrane rupture with infection	0	0·0	2	1·2	2	0·6
Post dates	4	2·6	2	1·2	6	1·9
Multiple pregnancy	6	3·9	1	0·6	7	2·2
Placenta praevia	1	0·6	2	1·2	3	0·9
Abruptio placenta	1	0·6	11	6·7	12	3·8
Polyhydramnios	0	0·0	3	1·8	3	0·9
Other	19	12·5	28	16·8	47	14·8

This study confirmed that low birthweight is an important factor in perinatal death, with a mean birthweight in the perinatal death group of only 1·8kg compared to 3·0kg in the live group. Fig 3 suggests that mothers who booked for antenatal care tended to have infants of higher birthweight, but perinatal death was still associated with low birthweight. Thus any beneficial effect of receiving antenatal care does not fully account for the better perinatal outcome in booked mothers.

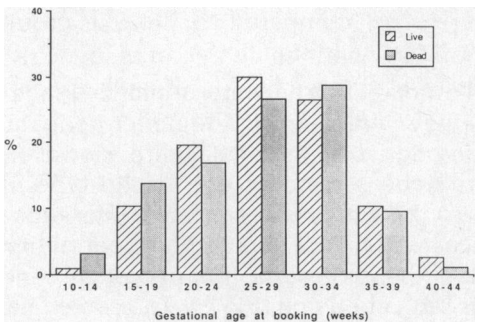

Fig 2. Perinatal outcome (alive or dead) related to gestational age at first booking.

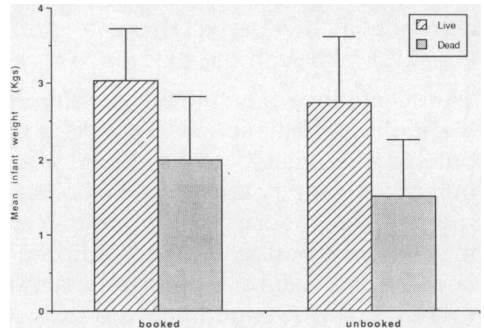

Fig 3. Mean birthweight (kg) in booked and unbooked mothers by perinatal outcome.

Most of the lower birthweights in the perinatal death group appear to have been due to intrauterine growth retardation rather than prematurity, as 81% of perinatal deaths were stillbirths and only 19% were neonatal deaths. There was no reduction in the stillbirth:neonatal death ratio in mothers who had booked, nor was any reduction seen with earlier booking, again suggesting that antenatal care was not fully responsible for the lower perinatal mortality in booked mothers.

DISCUSSION

The principal aim of antenatal care is the early recognition and management of the high risk patient.[14] In the United Kingdom, improved antenatal care has been an important factor in the large reduction in perinatal mortality seen over the past 30 years.[2, 16] Conversely, in populations such as we studied, even with improvements in antenatal care, perinatal mortality is still high, and this is often attributed to the underlying socioeconomic factors, and to a poorer level of nutrition and general health.[7, 9, 17] Whilst these factors undoubtedly play a major role in the high mortality rate, our study highlights two areas of particular interest.

Our results show that receiving antenatal care itself cannot fully explain the associated better perinatal outcome. Most mothers who book appear already to be of low risk in this population — the very action of booking probably a reflection of better overall health education and awareness. However, being a low risk mother does not necessarily correlate with having a low risk fetus. Recent work in the Royal Maternity Hospital, Belfast has shown that higher perinatal mortality rates may occur in so called low risk mothers and it is suggested that modern antenatal care should look at both maternal and fetal wellbeing, increasing emphasis being placed on finding the high risk fetus.[18] In our study population, being a low risk mother was associated with a better perinatal outcome, but further improvements may be possible if the high risk fetus is actively looked for in those mothers who book early. Simple methods include use of "kick counts" and cardiotocography. Full ultrasound biophysical profiles, even where available, are impractical and probably inappropriate, but simple assessment of liquor volume and growth alone may be very predictive.[18]

The major problem facing this population is that most high risk mothers fell into the perinatal death group, yet these were the very patients who were most likely not to book. For antenatal care to achieve its aim of early recognition and management of the high risk patient,[14] not only must uptake of antenatal care be encouraged in the general population, but specifically amongst those mothers who are failing to book. Illiteracy and poverty both contribute to poor antenatal care.[13, 19–21] Literacy is probably more important than the degree of affluence,[22] and a low maternal educational standard is associated with a lower application of maternity care routines and a lower perceived value of antenatal care.[23]

Widely dispersed populations in rural areas show an exponential decrease in outpatient attendance with distance.[13] Cultural and traditional practices often prefer a traditional birth attendant, and this influence may be so strong that even educated patients stay at home rather than attend the antenatal clinic.[22] Mothers are also more likely to underutilize care if embedded in strong tie-non disperse social networks, preferring the advice of friends and family to hospital staff.[8]

The long term solution to these problems is widespread education and provision of accessible antenatal care facilities. This may be difficult and expensive, and

even educated mothers may underutilize antenatal services. One simple improvement might be provision of flexible hours for antenatal care. A study from Kenya showed a 50% increase in utilization when antenatal care was integrated with other services provided daily.[24] A short term solution may be a variety of case finding methods. The use of outreach workers to locate unattended pregnant women is probably not cost effective,[25] but community health leaders (unpaid members of the community, trained for a week or less) have been used effectively in some projects.[24]

The principal aim of future health planning in this type of population must be to increase uptake of antenatal care in general, and in particular to employ methods of reaching those mothers in the community most at risk of a perinatal death. As well as quantity of antenatal care, improvement in the quality of care, with awareness of the high risk fetus, may help to reduce high perinatal mortality rates.

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Pancreatic polypeptide and exocrine pancreatic function in the elderly

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SUMMARY

The relationship between exocrine pancreatic function and plasma pancreatic polypeptide levels was studied in 14 normal elderly subjects and in ten elderly patients with exocrine pancreatic insufficiency determined by the para-amino-benzoic acid test. There was a decrease in the total pancreatic polypeptide response after a standard mixed meal in the group with pancreatic insufficiency ($t = 2 \cdot 753$, $p = 0 \cdot 01$). An increase above basal of less than 100% in plasma pancreatic polypeptide levels 30 min after a standard mixed meal is strongly associated with exocrine pancreatic insufficiency (Fisher's exact test, $p = 0 \cdot 005$).

INTRODUCTION

The para-aminobenzoic acid test is a standard non-invasive test for exocrine pancreatic insufficiency. Its high sensitivity and specificity in identifying cases of severe exocrine pancreatic insufficiency merit its use as a screening tool, although it is less accurate for moderate cases.[1] Elderly people have difficulty coping with this test, and a simpler, equally reliable, initial screening test for exocrine pancreatic insufficiency would be welcome.

Plasma levels of pancreatic polypeptide are related to exocrine pancreatic function in both normal and diseased states.[2-4] Pancreatic polypeptide, a 36 amino acid peptide, inhibits exocrine pancreatic secretion.[5] In healthy adults (aged 18 – 46 years) plasma pancreatic polypeptide levels following nutrient and hormonal stimulation are closely related to exocrine pancreatic function.[4] Stimulated levels of pancreatic polypeptide are reduced in exocrine pancreatic insufficiency.[3] This suggests that plasma pancreatic polypeptide measurement may be a useful screening test for exocrine pancreatic insufficiency.[6] It is not known whether such a relationship between pancreatic polypeptide secretion and exocrine pancreatic function also exists in the elderly. If it did, plasma pancreatic polypeptide levels

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after a standard mixed meal could be used as a screening test before proceeding to para-aminobenzoic acid or more invasive testing. The present study investigated the relationship between the plasma pancreatic polypeptide response to a standard mixed meal in elderly subjects with normal and abnormal para-aminobenzoic acid (PABA) tests.

SUBJECTS AND METHODS

Fourteen elderly subjects (group 1), mean (±SE) age 74·7 ± 1·4 years with normal para-aminobenzoic acid (PABA) tests, and five asymptomatic subjects (group 2), with a para-aminobenzoic acid excretion index of less than 55% were recruited from a previous study. In that study a sample of 21 healthy subjects, over the age of 65 years and living independently in the community, were screened for evidence of pancreatic insufficiency by para-aminobenzoic acid testing. Those with significant hepatic or renal disease or a history of gastrointestinal surgery, alcohol excess or diabetes mellitus were excluded from the study.[7] Five additional subjects, aged over 60 years, with moderate to severe exocrine pancreatic insufficiency (para-aminobenzoic acid excretion index less than 55% and symptoms/signs of malabsorption) diagnosed in the previous 12 months and studied pre-treatment were also included in group 2. The mean age of the ten patients in group 2 was 68·5 ± 1·5 years.

The modified para-aminobenzoic acid test[8] consists of two stages. On day 1, after overnight fasting, N-benzoyl-l-tryosyl-para-aminobenzoic acid is given along with a standard mixed meal of 50 g of carbohydrate, 18 g of protein and 20 g of fat and the urine is collected over the next 6 hours. N-benzoyl-l-tryosl-para-aminobenzoic acid requires pancreatic chymotrypsin to liberate para-aminobenzoic acid which is then absorbed and excreted in the urine. On day 2 the procedure is repeated with para-aminobenzoic acid to exclude causes of malabsorption other than pancreatic insufficiency. The para-aminobenzoic acid excretion index is then calculated as the percentage of day 1/day 2 urinary para-aminobenzoic acid excretion, a figure of less than 55% indicating exocrine pancreatic insufficiency. To ensure that all urine was collected, a named nurse accompanied each patient throughout each 6 hour period, a single toilet was set apart for each subject and urine was collected using a urinal. Blood samples for insulin and pancreatic polypeptide levels were taken at −15, 0, 15, 30, 60, 90 and 120 min following ingestion of a standard mixed meal. The samples were centrifuged and plasma was stored at −20°C until the study had been completed. The hormones were measured by radioimmunoassay.[9]

Statistical analysis: The unpaired t-test was used to compare the area under the curve and individual results for the log transformation of pancreatic polypeptide and insulin responses over the first hour (which covers the initial rise in plasma pancreatic polypeptide) after a standard mixed meal between groups 1 and 2. (The log transformation was applied to the data as the response for pancreatic polypeptide and insulin over time was skewed). Fisher's exact test was used to examine the association between para-aminobenzoic acid testing and the percentage rise in plasma pancreatic polypeptide levels at 30 minutes after a standard mixed meal compared with basal (−15 min) plasma pancreatic polypeptide levels (a rise of less than 100% was taken as indicating abnormal exocrine pancreatic function).

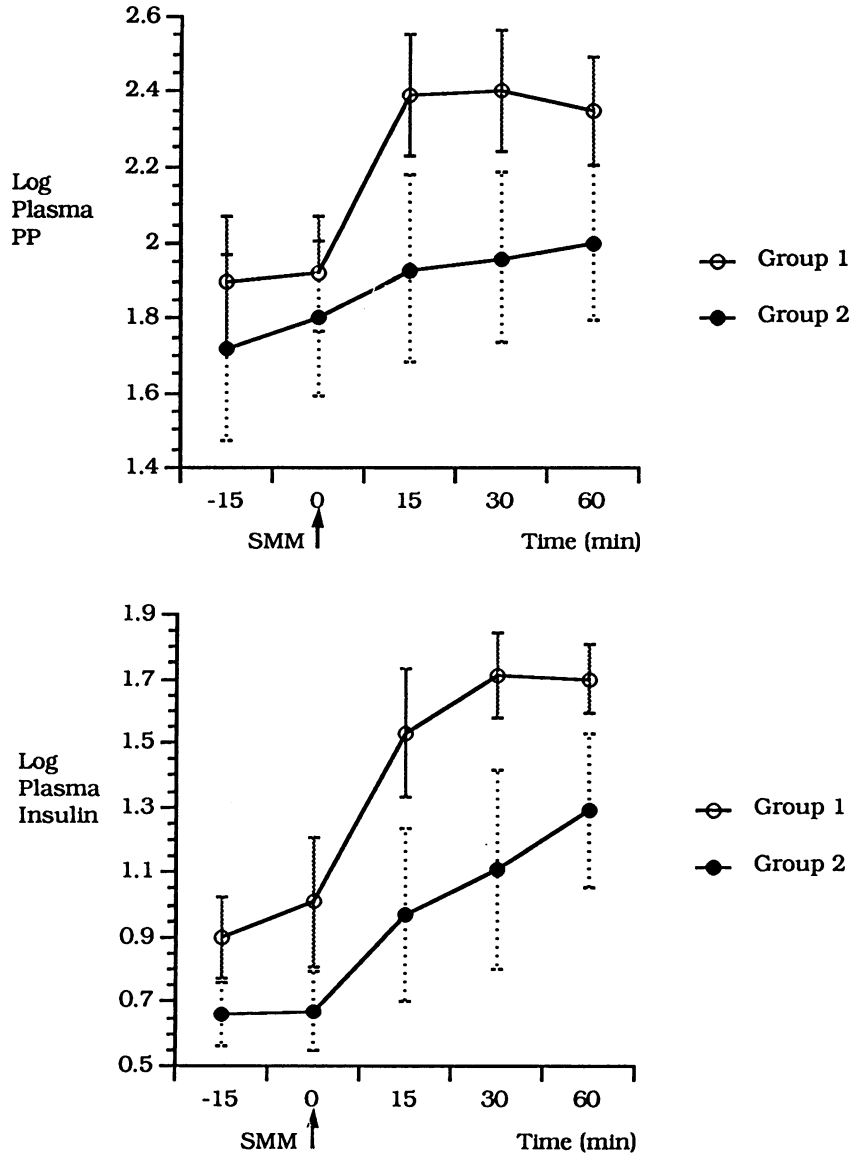

Fig 1. Log transformation, with 95% confidence limits, of plasma pancreatic polypeptide (PP) and insulin responses to a standard mixed meal (SMM) in elderly subjects with normal (group 1) and abnormal (group 2) responses to the para-aminobenzoic acid (PABA) test for exocrine pancreatic insufficiency.

RESULTS

All subjects had a serum creatinine of $\leq$131 umol/l. Urine volumes (mean ± SE) in group 1 on day 1 and day 2 of the para-aminobenzoic acid test were 794 ± 102 ml and 1233 ± 144 ml and in group 2, 708 ± 77 ml and 988 ± 106 ml, respectively. Basal (15 minutes prior to a standard mixed meal) and stimulated (15 to 60

minutes after a standard mixed meal) plasma pancreatic polypeptide and insulin levels were compared between groups 1 and 2 (Fig 1). The basal pancreatic polypeptide levels (mean SE) were 99·9 18·5 pg/ml and 69·5 17·1 pg/ml, respectively. The total area under the curve for log pancreatic polypeptide and log insulin responses over time was significantly less in group 2 (pancreatic polypeptide $p = 0{\cdot}01$, insulin $p = 0{\cdot}007$). The log pancreatic polypeptide and log insulin levels in group 2 at 15, 30, and 60 min after the standard mixed meal were also significantly less compared with group 1.

If the 30 minute plasma pancreatic polypeptide level was less than 100% greater than fasting, the patient very probably had an abnormal para-aminobenzoic acid test (Fisher's exact test $p = 0{\cdot}005$). (Fig 2).

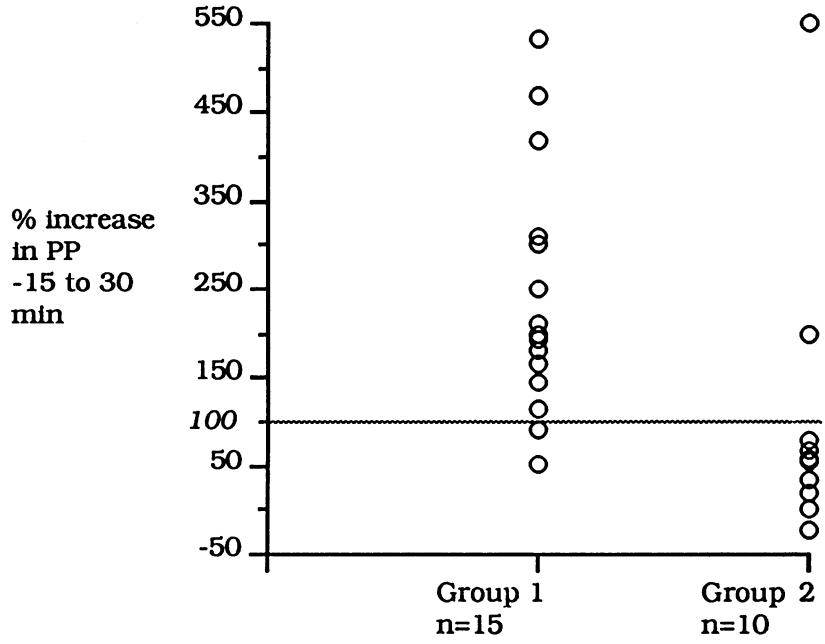

Fig 2. Rise in plasma pancreatic polypeptide (PP) from 15 minutes before to 30 minutes after a standard mixed meal in group1 (normal) and group 2 (abnormal PABA test). $p = 0{\cdot}005$, Fisher's exact test.

DISCUSSION

Within a few minutes of ingesting food there is a rapid initial rise in plasma pancreatic polypeptide, which tails off after 30–60 minutes. This is followed by a secondary rise lasting for several hours.[10] The initial rise, closely related to exocrine pancreatic secretion, is due to vagal stimulation,[11] the secondary rise may be neurohormonal.[12] In man, pancreatic polypeptide storage cells are located mainly in the head and uncinate process of the pancreas. They are widely distributed between the exocrine acinar and the endocrine islet cells.[13] Functionally, both pancreatic polypeptide and exocrine pancreatic enzyme secretion require an intact vagal pathway.[11, 14] They can be stimulated by ingestion of food or the intravenous injection of secretin/cholecystokinin.[6, 15, 16]

In animal models of exocrine pancreatic insufficiency the reduction in exocrine pancreatic secretion in response to food is associated with a decline in pancreatic polypeptide response in the first 60 minutes and a normal secondary rise due to an intact endocrine axis.[17] In patients with moderate to severe exocrine pancreatic insufficiency reduced pancreatic enzyme output is associated with low basal levels of plasma pancreatic polypeptide and a flat or attenuated rise following a standard mixed meal or cholecystokinin infusion[2,3] related to the degree of exocrine pancreatic insufficiency.[4] In normal elderly subjects basal levels of plasma pancreatic polypeptide are elevated.[18] The cause and the significance of this elevation are unclear.

In the present study the basal plasma pancreatic polypeptide levels in group 1 and group 2 subjects were within the normal range (0–200 pg/ml). There was no significant difference in basal plasma pancreatic polypeptide levels between the two groups. In both groups there was an initial rise in plasma pancreatic polypeptide levels in response to a standard mixed meal, but the magnitude of this response over time was significantly diminished in those with exocrine pancreatic insufficiency. This may in part be due to a decrease in pancreatic exocrine secretions in the duodenum or a decrease in the number or the function of pancreatic polypeptide producing cells.[4] Along with the flattened pancreatic polypeptide response in these patients there was a lower plasma insulin response, indicating concomitant beta cell damage or malfunction.

This reduced pancreatic polypeptide response in the elderly subjects with exocrine pancreatic insufficiency agrees with studies in younger subjects.[2-4] In this study, a strong association was found between a rise in plasma pancreatic polypeptide levels at 30 min of less than 100% and the presence of exocrine pancreatic insufficiency as determined by para-aminobenzoic acid testing, which may prove to be a simpler screening test for exocrine pancreatic insufficiency in the elderly. Para-aminobenzoic acid testing cannot be used to quantify the degree of exocrine pancreatic insufficiency, but it does help to differentiate patients with moderate to severe pancreatic insufficiency from those with normal exocrine pancreatic function or only mild impairment.[1,19] A similar limitation may also apply to pancreatic polypeptide measurement for assessing exocrine pancreatic function.[4]

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Antibiotic pharmacoeconomics: an attempt to find the real cost of hospital antibiotic prescribing

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SUMMARY

Antibiotics account for a large part of all hospital pharmacy budgets, but the actual cost of their prescription is unknown. These costs include intravenous administration, labour, serum antibiotic assay, monitoring of haematological and biochemical indices, disposal of sharps and adverse effects. An in-house method of costing antibiotic therapy is presented, to quantify these hidden expenses. Since not only an awareness, but an accurate quantification, of hidden costs is required, a study of various hospital procedures relating directly to antibiotic therapy was undertaken in an acute medical ward; this involved the identification of particular staff members performing various procedures, consumables used and time taken. The cost of five-day courses of gentamicin, penicillin G, ampicillin, flucloxacillin, cefuroxime, ceftotaxime and erythromycin has been calculated; drug and hidden costs for each are presented graphically for comparison. The breakdown cost for gentamicin is presented to illustrate the method. The costing of adverse effects has not been attempted. We suggest that costings of this sort are used in cost-benefit analysis of antibiotic use. These calculations have been incorporated into a computer spreadsheet and this costing service will be offered to clinical areas of our hospital.

INTRODUCTION

Financial restraints on the National Health Service have increased in recent years. One area in which there is scope for rationalisation and cost savings is drug prescribing. Antibiotics account for a large part of all hospital pharmacy budgets, but the actual cost of their prescription is unknown. It is a widely held belief among health care staff in general that the cost of antibiotic therapy is equal to the cost of the drug itself. Seldom considered are the 'hidden costs' such as maintenance of intravenous access, labour, serum antibiotic assay, monitoring

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of haematological and biochemical indices and waste disposal.[1, 2, 3] Almost never considered are those extra costs due to adverse effects of antibiotics in terms of finance,[4] human suffering[5] and environmental deterioration.[6]

In order to obtain a more accurate assessment of the cost of antibiotic therapy we have developed a costing structure within which subtotals will vary depending on the antibiotic and the hospital area in question. To assess the cost of antibiotics used in an acute medical ward, a study of procedures relating directly to antibiotic therapy was undertaken.

METHODS

After group discussion it was concluded that for any antibiotic the total cost could be divided into eight cost categories (Table I). The quantification of these cost categories requires, first, the basic costs of consumables, labour, transport and incineration of waste, and secondly, knowledge of consumables used and time spent by the various grades of staff on each of the procedures involved. The basic costs within these eight categories were obtained as follows: antibiotic costs were obtained from the Monthly Index of Medical Specialities (MIMS), contract costs of other consumables were obtained from the hospital purchasing department and the pharmacy, costs of standard haematological and biochemical tests (tests performed to assess the adverse effects of the antibiotic used, for example serum urea and electrolyte measurement for nephrotoxic antibiotics such as gentamicin and vancomycin) were obtained from their respective departments, costs of

TABLE I

Eight cost categories making up the cost of any antibiotic course

Cost category	*Summarised costs*
1. Antibiotic	The drug itself
2. Maintenance of IV access	Insertion of an IV cannula and maintenance of its patency
3. Drug delivery	Administration of the drug to the patient
4. Drug monitoring	Measurement of serum antibiotic to ensure therapeutic and to avoid toxic levels
5. Dose readjustment	Modification of the dose of antibiotic following serum antibiotic measurement
6. General monitoring	Haematological and biochemical indices relating to the use of the drug. For example, urea and electrolytes are measured during a course of a nephrotoxic antibiotic
7. Sharps disposal	Sharps are packed in plastic sharps boxes; these boxes are then packed in clinical waste bags, delivered to the place of incineration and incinerated
8. Adverse effects	A substantial cost: the costing of these has not been attempted in this study

labour were obtained from the various personnel departments, and information on employers' National Insurance and Superannuation contributions was obtained from the Department of Health and Social Services. For the labour categories staff nurse and porter, the most commonly occurring levels of each of these staff grades was taken as representative — grade D staff nurse and grade 3 porter. This simplification was not necessary in the case of the junior house officer labour category as all the participating members of staff in this category were employed at the basic point on the scale.

The times taken and consumables involved in the performance of various hospital procedures relating directly to antibiotic therapy were studied over a three month period in the acute medical ward. Intravenous cannula insertion, drug delivery and drawing of blood for laboratory tests were performed by the junior house officer. Packing of full sharps boxes into clinical waste bags and erecting new, empty ones was performed by the staff nurse. Portering staff are involved in the delivery of laboratory samples from the ward to the laboratory and in collection and transport of clinical waste bags. For delivery of laboratory samples from the ward to the laboratory, laboratory staff recorded the time taken to walk the same route. For collection of clinical waste bags, simulation was not possible and so the cost of this time has not been included. In the study the staff member performing a particular procedure recorded their own name, grade, the procedure, and the time taken and any consumables involved from setting out to perform the procedure to total completion of it, including disposal of waste and handwashing, if appropriate.

Also recorded was the number of gentamicin courses occurring in the ward, the length of each and how many times serum gentamicin and serum urea and electrolyte measurements were performed during each course for monitoring purposes. For each serum gentamicin assay performed it was noted whether or not the dose was readjusted, and how much time this process took. The number of courses of the other antibiotics were not noted as serum assay of these is not normally required. To assess the proportion of a sharps disposal box occupied by waste from the various antibiotic course regimens, the precise amount of waste for each regimen was calculated. In each case the waste was placed in the box and the proportion filled was noted; this varied from 33% for gentamicin to 50% for ampicillin.

It has been assumed that all blood specimens sent to the laboratory in a specimen bag for any routine test require the same time for the junior house officer and the porter. The cost of ward consumables for serum gentamicin and serum urea and electrolyte measurements were noted specifically. It has also been assumed that all antibiotics require the same time for administration by the junior house officer. The consumables for particular antibiotic courses were noted specifically where possible, and the times taken for the various procedures were arrived at by calculating average values (Table II). The consumables used in the various procedures were determined by noting the minimum number necessary to perform a particular procedure: it was found that serum gentamicin and serum urea and electrolyte measurements were each performed once for each course of gentamicin, and calculations were made on this basis. No dose readjustments were needed after any serum gentamicin assay, so this cost category was considered to be zero for this study. The cost of sharps disposal was based on the most common

TABLE II

Hospital procedures relating to antibiotic therapy: times taken, consumables used and staff members involved

Procedure (Cost category number)	*Staff member*	*Measurements (number)*	*Time (range) min*	*Time (mean) min*	*Consumables*
Insertion of IV cannula (2)	Junior house officer	69	4–9	6·7	IV cannula × 1 anticoagulant × 1 10 ml syringe × 1 cotton wool × 1 alcohol swab × 1 bandage × 1
Drug delivery (3)	Junior house officer	184	—	4·7	For 80 mg gentamicin: needle × 1 2 ml syringe × 1 For 1 g erythromycin: 20 ml sterile water × 1 20 ml syringe × 1 needle × 1 For 1·5 g cefuroxime, 2 g cefotaxime, 1 g flucloxacillin, 1 g ampicillin and 1·2 g penicillin G: 10 ml sterile water × 1 10 ml syringe × 1 needle × 1
Drawing of blood (4+6)	Junior house officer	90	—	5·3	For serum gentamicin assay; peak and trough: 10 ml syringe × 2 needle × 2 alcohol swab × 2 cotton wool × 2 blood bottle × 2 specimen bag × 1
Sharps box (7)	Staff nurse	41	2–6	4·0	—
Delivery of blood specimens to laboratory (4+6)	Porter (simulated by laboratory staff)	41	5–9	6·9	—

sharps box in use, how much waste filled this particular box to the recommended level, how many courses of a particular antibiotic regimen this represented, nursing time, and the cost of transport and incineration.

The resulting data were used to calculate the cost of the following five-day courses of IV antibiotics: gentamicin 80mg three times daily, penicillin G 1·2g four times daily, ampicillin 1g four times daily, flucloxacillin 1g four times daily, cefuroxime 1·5g three times daily, cefotaxime 2g three times daily, and erythromycin 1g four times daily. The five-day regimen chosen was used to facilitate comparison of cost between different antibiotics. The itemisation and costing of the gentamicin regimen is shown in detail. All costs were calculated as contract costs except the antibiotic cost which is taken from MIMS; the hospital contract cost of antibiotics and other specific items is not given and these costs therefore appear as subtotals. Value added tax has not been included on any item as it is paid by the hospital.

RESULTS

The study of procedures relating directly to antibiotic therapy in an acute medical ward showed the mean time for insertion of an intravenous cannula to be 6·7 minutes, for drug delivery, 4·7 minutes, for drawing of blood, 5·3 minutes, for sharps box management, 4 minutes, and for delivery of a blood sample to laboratory, 6·9 minutes (Table II).

There were 4 only courses of gentamicin prescribed in the ward during the three month study period; ranging in length from five to nine days, and in each case one set of peak and trough serum gentamicin assays and one serum urea and electrolyte measurement was performed. The dose of gentamicin was not adjusted in any case. Table III shows the itemised cost categories and resultant subtotals for a five-day course of intravenous gentamicin. Fig 1 shows these subtotals graphically; drug costs and hidden costs account for 35% and 65% respectively of the total cost.

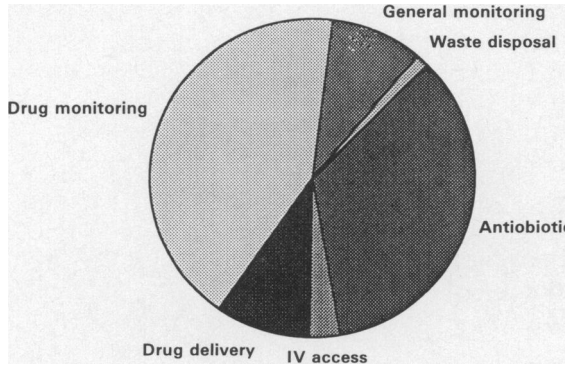

Fig 1. Graphical representation of the cost of gentamicin therapy shown in Table III.

The drug costs and hidden costs for 7 different antibiotic regimens, including gentamicin, calculated according to these methods are shown in Fig 2.

DISCUSSION

For gentamicin, the drug costs and hidden costs account for 35% and 65% respectively of the total cost. The true ratio of hidden cost to antibiotic cost is actually greater in this hospital as pharmacy contracting arrangements significantly reduce the drug cost below that shown in the Monthly Index of Medical Specialities. If the cost of adverse effects were quantified the drug cost contribution would decrease still further.

TABLE III

The itemised cost categories and corresponding costs for a five-day course of intravenous gentamicin 80mg three times daily

Cost category	*Items involved*	*Cost*
1. Antibiotic	80mg gentamicin × 15	£23.70
2. Maintenance of IV access	IV cannula anticoagulant 10ml syringe cotton wool bandage alcohol swab 6·7 minutes 9–5 pm JHO	£2.03
3. Drug delivery	needle × 15 2ml syringe × 15 47 minutes 9–5 pm JHO 23·5 minutes OnCall JHO	£6.41
4. Drug monitoring (peak and trough serum levels, measured × 1)	10ml syringe × 2 needle × 2 alcohol swab × 2 cotton wool × 2 blood bottle × 2 specimen bag gentamicin assay × 2 10·6 minutes 9–5 pm JHO 6·9 minutes 9–5 pm porter	£28.77
5. Dose readjustment	—	£0.00
6. General monitoring (urea and electrolytes measurement)	10ml syringe needle alcohol swab cotton wool blood bottle specimen bag U and E 5·3 minutes 9–5 pm JHO 6·9 minutes 9–5 pm porter	£6.29
7. Waste disposal	⅓ cost of 10l plastic sharps box 4/3 minutes 9–5 pm staff nurse Contract cost of waste, transport and incineration	£0.78
8. Adverse effects	Nephrotoxicity Ototoxicity Bacterial resistance Superinfection IV cannula site infection	not costed
	Total	**£67.98**

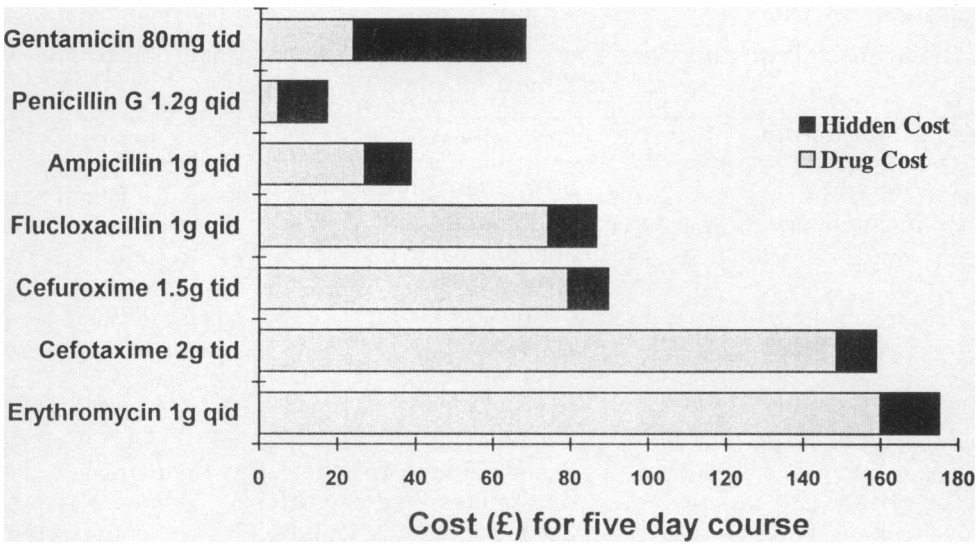

Fig 2. Published drug cost versus hidden cost for seven antibiotics

Labour and consumable costs vary from regimen to regimen, accounting for some of the variations in hidden costs. Antibiotics which require serum level monitoring, for example gentamicin, have larger hidden costs than those which do not, for example cefuroxime, other factors being equal. Antibiotics administered four times per day, for example penicillin G, will have a higher hidden cost than those administered three times per day, for example cefuroxime. Erythromycin is the most expensive of the regimens costed (Fig 2) because each dose costs over eight pounds, because it is administered four times daily, and because it is quite insoluble; a dose of 1g requires twenty millilitres of sterile water to dissolve it. In this hospital, on-call drug delivery by nursing staff has been about three times more expensive than that by junior doctors, and it has therefore been cheaper for the hospital to employ doctors rather than staff nurses to administer drugs at night. The recent changes in legislation relating to the workload of junior doctors will change this.

Although the numbers of measurements for all procedures are reasonably high, a weakness in the study is that the calculations on serum monitoring of gentamicin are based on data from only four courses. Although it is recommended procedure, it is our impression that only a fraction of courses of aminoglycosides are monitored with serum antibiotic and serum urea and electrolyte measurement. It has been assumed that all antibiotics require the same time for drug delivery; this is obviously not the case. For example, a water-soluble antibiotic will take a shorter time to prepare and administer than a relatively insoluble one; this is because a larger volume of water and more time are required to prepare an insoluble antibiotic for therapeutic administration. This is a very difficult area to quantify accurately as it is routine practice for junior doctors to batch the preparation and administration of intravenous antibiotics.

As these calculations are complex and ever-changing with cost variation, this system is at present being installed into the form of computer spreadsheets. The

spreadsheet chosen was Microsoft Excel, version 4.0 (Microsoft, UK), running under Windows 3.1 (Microsoft, UK), on a Compaq Deskpro 386s personal computer (Compaq Computer Corporation, USA). The system consists of one 'master' spreadsheet, containing all basic costs, linked to many individual antibiotic spreadsheets. The antibiotic spreadsheets each begin with a questionnaire which exactly specifies the course regimen. This information and the appropriate costs from the master spreadsheet are then used to calculate the cost for each cost category; these are then added to obtain the total. Both the published and the pharmacy contract costs are calculated and each is displayed both numerically and graphically. Computerisation simplifies (a) cost updating, as the costs are updated only in the master spreadsheet, (b) calculation, as the calculation mechanism is permanent in the individual antibiotic spreadsheet, and (c) data extraction, as only the last section of any antibiotic spreadsheet need be printed. The system is very flexible as an antibiotic spreadsheet can accommodate any drug regimen; the answers to the questionnaire are incorporated directly in the calculations. This costing service will be offered to clinical areas of our hospital; if costs are required, a questionnaire on the particular regimen would be completed by the ward and returned to the department of bacteriology for calculation of the cost of the regimen. A printout from the spreadsheet on cost analysis will be returned to the ward.

Efficacy of antibiotics is clearly of prime importance. As antibiotic cost awareness is still in its early stages, the primary issue of efficacy of antibiotics has not been addressed in this study. Cost is only one of a number of factors to be taken into account in antibiotic prescribing.

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Alcohol-related attendances at an accident and emergency department

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SUMMARY

Using a self-administered alcohol-related questionnaire and the clinical records a survey was made of the prevalence and severity of alcohol-related problems in the accident and emergency department at the Belfast City Hospital. Of 10,410 consecutive attendances during three months, 6,625 completed a questionnaire: 4,349 admitted they took alcohol at some time, 906 men exceeded 21 units weekly, and 490 women exceeded 14 units weekly. The majority of those who drank were under the age of 35 years. Only 182 considered that they might have an alcohol-related problem.

Possible health promotion initiatives for these at-risk patients are considered which might be used specifically in an accident and emergency department.

INTRODUCTION

Excessive alcohol consumption is associated with a wide range of medical, surgical and psychiatric disorders and has been implicated in trauma of every kind. Several studies have shown that a high proportion of emergency department patients have recently consumed alcohol.[1, 2, 3] Alcohol misuse is also at the root of many social problems and can be incriminatory in marital breakdown and child abuse. It is a causal factor in lowered work performance and absenteeism from work, and it undoubtedly contributes to the widespread violence in our community.

Many people in Northern Ireland, particularly young men, drink heavily, and frequently at levels well above the recommended safe limits. The Northern Ireland Strategic Plan 1992-97[4] states that by 1997 the proportion of adults drinking more than the "sensible limits" (up to 21 units per week for males and up to 14 units per week for females) should be reduced to 25% (from 33%) for men and to 7% (from 11%) for women. This may not be an easy goal to achieve in our community but, as health care professionals, we have a duty to address the problem with due concern.

METHOD

During a three month period all patients attending the accident and emergency department, for whatever cause, were asked to fill in a questionnaire about their drinking patterns, their knowledge of the unit system for measuring alcohol consumption, and whether they considered their present level of alcohol consumption harmful to health.

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A total of 10,410 patients attended during the period of the study, and 6,625 completed the cards. Of the 3,785 who did not, 522 were too seriously ill or injured, 642 were elderly and had difficulty with comprehension, 1,253 were children, 282 were too intoxicated to co-operate, and 1,086 refused.

The following data were then obtained from the clinical record card — age/sex, nature of the presenting complaint, time of attendance, whether the patient was noted either by the triage nurse or the casualty officer to have recently consumed alcohol, and whether they had previous attendances with a similar complaint which was possibly alcohol-related.

RESULTS

This analysis is confined to those patients who completed the questionnaires.

How much do people drink?

Out of a total of 4,349 people who said they took alcohol, 2,435 were men and 1,914 women. 1,320 women and 956 men had never drunk alcohol, and 1,330 women and 1,265 men only drank on special occasions.

906 men stated that they exceeded 21 units, and 490 women exceeded 14 units of alcohol weekly; 264 men exceeded 37 units, and 94 women 25 units weekly.

How often do people drink?

Most people who admitted to drinking alcohol did so only on one or two days per week, usually at weekends, (2,899 men and 1,450 women). A relatively small number, 742 men and 360 women, drank more often than three or four days per week, and very few people drank every day.

Age distribution

Of those who drank alcohol, 19 were under the age of 15 years, 942 aged 15 – 20 years, 1,604 aged 20 – 35 years, 1,342 aged 35 – 50 years, and 542 were over 50 years of age.

Attitudes to drinking

A total of 359 drinkers, (men and women) felt that their drinking was perhaps excessive but only 182 considered that they might have an alcohol problem.

Other factors

During the period of the study 132 patients attended as a result of assaults. Of these 88 were alcohol-related and 72 had injuries involving the head and face, 61 with multiple lacerations requiring sutures and 13 with fractures of the facial bones. Seventy-seven of these attendances were between 9.00 pm and 9.00 am, and 16 people had previously attended with similar alcohol-related injuries. Six males and one female were violent while in the accident and emergency department, requiring intervention of security staff.

Thirty-six people who had been involved in road traffic accidents had recently consumed alcohol but only four of these were the drivers of their vehicles, the remainder being either passengers or pedestrians knocked down.

The association between alcohol consumption and industrial accidents was not

strong. Only one patient seen as a result of a fall at work was noted to have alcohol on the breath. There were 92 alcohol-related falls, either in the street or at home, and of these 29 had been brought in by the ambulance as 'collapse' cases, found lying on the street.

Of patients who had consumed alcohol recently, 108 attended with medical complaints: these included drug overdose (38), abdominal pain (24), chest pain (12), haematemesis (8), fits (5), delirium tremens (4), cirrhosis, liver failure, bleeding varices or alcoholic cardiomyopathy (5), and others (10). Of these, 26 required admission to a general ward, which represents 2·4% of all admissions over the period of the study. In contrast there were 72 alcohol-related admissions to the observation ward, or 14% of all admissions.

In the Belfast City Hospital the approximate cost of occupying an acute medical/surgical bed is £229 per day, for the observation ward £190 per day, and for intensive care £989 per day. Thirty-two of the admissions to the acute units were for 24/48 hours only but the remainder stayed more than four days, which would have cost in excess of £87,500. The cost of the 72 observation ward patients would have totalled £13,680.

In addition to these basic accommodation costs are the numerous X-ray and laboratory investigations which these patients require. As an example, one small group of patients was considered, the assaults involving the head and face. Sixty-three of these had X-rays of the skull and facial bones, at an approximate cost of £1,890. For a significant proportion of patients admitted to the acute units there is also the expense of drugs, and three had added and very significant costs of theatre and intensive care. Patients with alcohol-related illnesses incur a very substantial financial burden on the health service. These hospital attendances are in most cases avoidable.

DISCUSSION

The results of this survey are similar to those of several other national studies. I found that 9% of men and 4% of women were at significant risk. These figures are similar to those of Wilson,[5] who found 14% of males and 3% of females were at significant risk, and to Yates,[6] who found in his accident and emergency department population 7% of men and 2% of women at high risk.

The occurrence frequently of alcohol abuse in the accident and emergency department raises points related to staffing, design and treatment resources. A high proportion of these patients present 'out of hours', when staffing levels are low. In the Belfast City Hospital, 88% of the assaults attended between 9.00 pm and 9.00 am, and 67% were alcohol-related. This compares with Hocking,[7] who found in his survey of patients attending Lewisham Hospital as a result of deliberate physical violence that 82% attended at night and in at least 50% alcohol was a contributing factor.

Of the overall attendances at night at the Belfast City Hospital accident and emergency department, 20% were associated with alcohol. Another Irish study found that 26% of patients attending an accident and emergency department at night had taken alcohol and that they were often not adequately managed.[8] It has also been shown that medical staff under-diagnose problem drinking. Patients in the accident and emergency department often have their drinking problem

overlooked and only their presenting disorder attended to.[9, 10] I would agree with this, and there is a need for integrating alcoholism treatment resources in the accident and emergency service. This is not an easy task. Patients under the influence of alcohol are often noisy, aggressive and abusive. Many are violent to staff and intimidate other patients in the waiting area. They can be uncooperative and pose difficulties with obtaining adequate X-rays, suturing of wounds and applying of plaster casts and splints. Once admitted to a ward they may develop delirium tremens or seizures. Proposed treatment may have to be delayed until they are sober and some may even take their own discharge from hospital before treatment can be given. Following discharge they may damage casts, disturb splintage and often fail to attend for follow-up.

In the accident and emergency environment, where time is often at a premium, preventative medicine tends to be given little attention. Nevertheless this setting could offer the opportunity to both medical and nursing staff to use brief intervention strategies to help people early, before alcohol dependence has become apparent. It has been suggested that treatment of patients with alcohol-related problems is more likely to be successful if it is begun before physical, psychiatric and social problems have developed.[11] The percentage of patients who perceive that they have a problem is low and it is unlikely that these people will seek advice spontaneously; with a careful approach such people could be suitably guided. The Salisbury Alcohol and Drug Advisory Service in conjunction with the accident and emergency department at Salisbury General Infirmary has developed a system of brief counselling by accident and emergency nurses. In the USA, the Maryland Institute for Emergency Medical Services Systems has set up a rather unusual adolescent trauma prevention programme. They have shown that teenagers who are known to have been drinking alcohol would become more cautious about drink driving if they were shown what happens to persons of their own age who are injured in alcohol-related accidents.

In a busy department, time is of the essence and lengthy counselling is not practical. However, the triage nurse, who is the first member of the health care team to come in contact with the patient could, in many instances, provide this initial brief intervention and advice. The first task is to identify the patient whose accident or injury may have been related to alcohol, and then to help this patient make a link or connection between his drinking behaviour and what has happened to him. The second part of the intervention would be the giving of factual information. This could be either verbal facts and figures; for example relating alcohol to the incidence of fatal road accidents or alternatively relating excess alcohol consumption with liver disease, brain damage and various forms of cancer. In addition leaflets such as "Drinking and Accidents" or "That's the Limit" could be given to the patient, or to the relatives.

Apart from the potential benefit from early intervention, knowledge of an underlying alcohol problem would aid more accurate diagnosis and avoid inappropriate investigation. Enormous financial savings could be made within a Health Service which is currently grappling with very serious financial strictures. The results of this survey support the view of Zimberg[12] and Murray,[13] that the accident and emergency department offers a high yield of alcohol-related problems and could be the appropriate setting for the introduction of early intervention techniques. The challenge is now to provide such services.

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Hysteroscopic metroplasty

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SUMMARY

Four patients with reproductive failure associated with uterine septa had transvaginal hysteroscopic metroplasty performed. Two successful pregnancies have occurred and a third patient is now in the second trimester of pregnancy. This method of treatment should replace the traditional open method of surgical repair of these malformations.

INTRODUCTION

The development of excellent fibre-optics, camera systems and small hysteroscopes has made the procedure of hysteroscopy increasingly important to the gynaecologist. The further development of operative systems and instruments has facilitated intrauterine surgery, with transcervical resection of the endometrium as an alternative to hysterectomy and resection of submucous fibroids as an alternative to myomectomy. Removal of uterine septa by endoscopic techniques is now advocated.

Uterine malformations arise from deficient development, non-fusion or defective canalisation of the Mullerian system. Patients with these defects are prone to recurrent pregnancy losses.[1] The incidence of these abnormalities is unknown as most defects are minor and not detected, but most authorities agree that the incidence of symmetric uterine abnormalities is between 0·1% and 1·5%.[2,3]

Traditionally, metroplasty to correct the malformed uterus has been performed by the transabdominal route, usually by a Strassman, Jones or Tompkins procedure or modified versions of these procedures. These techniques give excellent results in terms of successful viable pregnancies[4,5,6] as well as in producing pregnancies that go to full term. The problems with these procedures are associated with the operative and post-operative morbidity of laparotomy.

In recent years several large series of hysteroscopic metroplasty have been reported[7,8,9] which have now exceeded in numbers those cases reported in transabdominal series. The evidence from these reports has prompted Daly[7] to refute an editorial comment that it is too soon to say that this is the preferred method of therapy for septate uterus, and to state that hysteroscopic metroplasty appears to be the treatment of choice in patients with uterine septa associated with pregnancy loss.

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Four cases of hysteroscopic septum resection are described, including the first performed in Northern Ireland; traditionally metroplasty had been performed by the transabdominal route mostly by one surgeon using his own modification of the Tompkins procedure, (JMG Harley — personal communication, 22 cases, successful outcome 95%).

CASE 1

A 33 year old woman, para 2 + 2. In 1981 she had an unexplained intrauterine death at 28 weeks' gestation. In 1982 she gave birth to a pre-term live infant at 35 weeks' gestation. In 1985 and 1990 she had spontaneous abortions at seven and nine weeks. At the time of evacuation of retained products a uterine septum was suspected, and hysterosalpingogram confirmed a septate uterus.

Septum resection was performed in February 1991 and she subsequently became pregnant within three menstrual cycles. In January 1992 at 40 weeks' gestation a male infant weighing 3,500 g was delivered successfully by forceps.

CASE 2

A 28 year old woman, para 0 + 1. In 1990 spontaneous abortion occurred at 8 weeks' gestation. During evacuation of the uterus the obstetrician suspected a uterine septum, and hysterosalpingogram confirmed the diagnosis. Septum resection was performed in February 1991, and she became pregnant within three menstrual cycles. A female infant weighing 2,890 g was delivered normally at 39 weeks' gestation.

CASE 3

A 28 year old woman, para 0 + 3 had spontaneous abortions at eight, 10 and 11 weeks' gestation. Hysterosalpingogram was performed as part of the investigation of recurrent pregnancy loss and demonstrated a deep septum in the uterus with an acute angle at its apex. Uterine septum resection was performed in March 1992. Follow-up hysterosalpingogram showed an improvement in the uterine shape but a further resection was performed in July 1992 and the subsequent hysterosalpingogram then showed a nearly normal cavity (Figure). She is now in the second trimester of pregnancy.

CASE 4

A 22 year old woman, para 0 + 3 with spontaneous abortions at seven, nine and ten weeks had similar hysterosalpingogram and operative findings to Case 3. Septum resection was performed in July 1992. She lives in Germany and follow-up is awaited.

All patients were discharged from hospital the day after the procedure was performed and no morbidity has been reported.

METHOD

The patient is anaesthetised and placed in the lithotomy position. The hysterosalpingogram is displayed in theatre for reference. Concurrent diagnostic laparoscopy and hysteroscopy are performed. Laparoscopy is mandatory in order to ensure that the uterine fundus has a broad base in keeping with a septate uterus and that it is not a bicornuate uterus which cannot be corrected by this method.

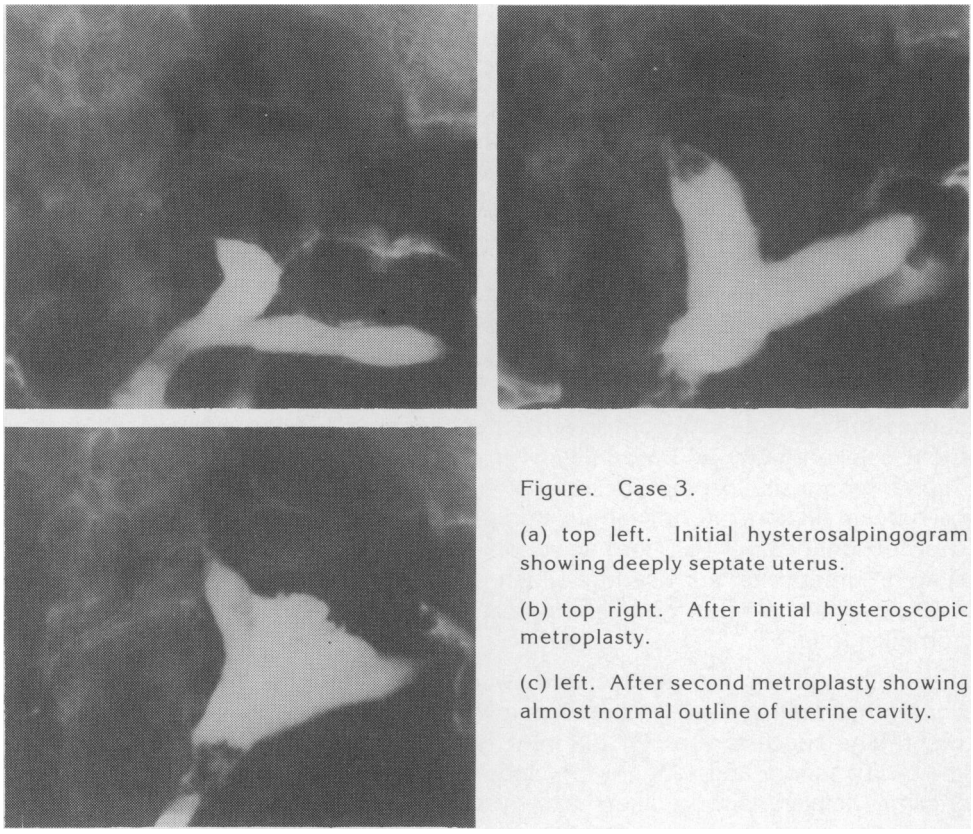

Figure. Case 3.

(a) top left. Initial hysterosalpingogram showing deeply septate uterus.

(b) top right. After initial hysteroscopic metroplasty.

(c) left. After second metroplasty showing almost normal outline of uterine cavity.

It is necessary to inspect the pelvis in general and the laparoscopist can also inspect the uterus during the metroplasty looking for evidence of the hysteroscopic light penetrating near the serosal surface indicating close proximity of the instruments. Evidence of thermal damage could also be detected.

Hysteroscopy is performed following dilatation and sounding of the uterine cavity. An operating hysteroscope with a continuous flow irrigation/distension system is used. The distension medium is 1·5% glycine, and a diathermy knife is used to perform the resection. Cutting and coagulation current is adjusted as necessary to ensure the lowest power necessary for efficient cutting. A pressure bag is used to deliver the glycine through the system. The pressure used should be the lowest to give adequate and continuous uterine distension as the higher the pressure the greater the possibility of forcing glycine into the circulation.

The uterus is inspected to identify both horns and the septum. The depth of the septum can be gauged by the use of the "gun" of the resectoscope and the width by moving the 7 mm cutting knife across the surface of the septum. Once orientation is achieved the septum is excised using the diathermy knife. The edges retract and the septum opens as if something was pulling the septum in opposite directions. A larger and more normal shaped cavity results. Great care is taken not to cut into the normal cornual tissue which is the thinnest part of the

uterus. The first part of the septum is reasonably avascular but as myometrium is approached more bleeding occurs which is a warning that the resection is nearing completion.

Regardless of the type of instrumentation used, the surgeon must be able to see the right and left cornual regions completely and be able to keep the septum in view at all times.[10] Care must be taken to account for the glycine used in the procedure as intravasation of the distending medium does occur. Circulatory overloading could lead to pulmonary oedema, convulsions, coma or death. The recommendation is that if a deficit of two litres is reached, surgery must be stopped. The greatest deficit of glycine during these four procedures was 400 ml.

DISCUSSION

Patients with uterine septa can have successful pregnancies, up to 50% having a successful outcome with conservative management.[11] Rock and Jones[4] reported increased morbidity and mortality over a period of seven years in patients with "good prognosis" septa. The rate of pregnancy loss was 44%, with a 35% caesarean section rate for labour complications including malpresentation (8), dysfunctional labour (6), cord accident (2) and placenta praevia (1 case). There is an argument that a procedure which carries minimal morbidity could be used even in patients with "good prognosis" septa in order to prevent pregnancy complications.[7]

It is unlikely that a prospective study will ever be undertaken to compare transabdominal metroplasty, hysteroscopic metroplasty and conservative management. The success rates for different types of metroplasty appear similar and morbidity (short and long term), subsequent management of the pregnancy (normal delivery is more likely with hysteroscopic metroplasty because there is no uterine scar), and cost-effectiveness make the hysteroscopic procedure the treatment of choice.

Hysteroscopic metroplasty should only be undertaken by an experienced hysteroscopist familiar with the instruments and the techniques of intrauterine endoscopic surgery. Laparoscopy and the use of camera systems enhance the safety factors. Some questions have not been addressed and may never be answered. Which method of hysteroscopic surgery is best — incisional, diathermy or laser? Should all septa be removed to reduce morbidity from labour complications? What is the place of ultrasound guided incisional metroplasty which may be a safer technique than hysteroscopic metroplasty?[12, 13]

The increasing interest in this technological advance will probably ensure that hysteroscopic metroplasty will stand the test of time as transabdominal metroplasty has done for previous generations.

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The health of the public — from Cos to Maastricht

J F McKenna

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The medical profession above all others has reason to be grateful that health has been and remains of vital importance to the individual and the public. Throughout history, health and hygiene have been recurrent topics in literature and philosophy, even featuring in early mythology: the Greek god Asclepios had a large family, most of whom had health and medical functions. One daughter, Hygeia, was the deity of health. Another daughter was Panacea who represented treatment. It is a tribute to their sagacity that the ancient Greeks separated the concepts of health and sickness, of prevention and cure.

My title gives notice of an historical perspective on public health, but not a systematic review of public health history. Rather, I shall look at three phases of history, the ancient world, the 19th century and the renaissance of the past 20 years. I have dubbed the first the Age of Ignorance, the second the Age of Enlightenment, and the third the New Public Health.

THE AGE OF IGNORANCE

The island of Cos is famous in some quarters for having given its name to a variety of lettuce but for the medical profession down the ages and throughout the world it has been famous as the birthplace of Hippocrates, and the home of an early school of medicine which represents above all an ethical ideal embracing commitment to the profession and to patients and encompassing compassion and discretion. Even today, the majority of practitioners recognise the Hippocratic Oath as the basis for their professional conduct.

The thinking of the school of Cos is transmitted down the years through the so-called Hippocratic Corpus or Hippocratic Collection.[1] There are 60 treatises which vary widely in subject matter and in style and date. Not all of the writings could possibly have been by Hippocrates. They were probably written between 430 and 330 BC when Hippocrates would have been aged between 30 and 130 years old! Some may even be later. The major preoccupation of those Greek doctors, not unlike that of their successors of today, was the curing of the sick. In 'The Science of Medicine' the author writes: "I would define medicine as the complete removal of the distress of the sick, the alleviation of the more violent diseases and the refusal to undertake to cure cases in which the disease has already won mastery, knowing that everything is not possible to medicine."

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Although concentrating on sickness, there was a definite orientation towards what we would now describe as the prevention of disease and the promotion of health: "We must consider the patient's customs, mode of life, pursuits and age . . . Are they heavy drinkers and eaters, and consequently unable to stand fatigue or, being fond of work and exercise, eat wisely but drink sparely."

The 'Regimen for Health' provides some lasting advice on diet, exercise and hygiene. "In winter a man should walk quickly, in summer in a more leisurely fashion. Fat people who want to reduce . . . should take only one meal a day . . . Those who enjoy gymnastics should run and wrestle during the winter. Those who find that exercise causes diarrhoea and who pass undigested stools resembling food should have their exercise cut by at least a third while their food should be halved." [Is this the earliest recorded reference to joggers' trots?]

The early Greek doctors had an awareness of the influence of the environment, including weather and water supply, on the prevalence of disease. The author of 'Airs, Waters and Places' says: "The best water comes from high ground and hills covered with earth. This is sweet and clean and when taken with wine, little wine is needed to make a palatable drink. Moreover it is cool in summer and warm in winter because it comes from very deep springs."

Galen, born 129 AD, brought together the medical knowledge up to his time including that derived from Hippocrates. His writings dominated medical thinking for many centuries and held sway until science struggled through from the 17th century onwards. For Galen, bathing and food are important. So is exercise — walking, riding, gymnastics. The elderly require less exercise than the young. Sleep and sexual activity are to be controlled. Excrements are to be evacuated with great care and attention; exercises help in this.

Thus there was in very early days an awareness of the importance of hygiene and of what we now call lifestyle. Doctors were hampered by lack of knowledge: the arguments of the Hippocratic writings and of Galen are wearisome to read today, but their instincts served them well. Many even earlier civilisations had practical public health measures which seem correct even today. Among the most primitive peoples it is known that excrement was buried, a practice observed in the breach on the pavements of Belfast today. Tribes of Africa practised a type of protection against smallpox by variolation. The Chinese blew powdered smallpox scabs into the nostrils.

Water has been especially important since ancient times. Public health measures involving water are known to have been of concern to early Egyptians. The cleanliness of the Nile was in early times assured by religious requirements, but alas later deteriorated in Greek, Roman and Moslem times. Public baths and water systems were developed in ancient India. The culmination of the cult of water in the ancient world occurred at Rome. During the reigns of the Tarquins (from the 7th to the 5th century BC), the Romans constructed underground drains including the Cloaca Maxima which is still in use today. They brought water by aqueduct from the Sabine hills. Their wonderfully elaborate baths were centres of leisure and culture — and if you go to Rome today the remains of the baths of Caracalla are still there to amaze you.

Public health measures in the ancient world displayed characteristics which remain relevant today: first, an innate acceptance of the importance of health,

and an intuition that there are things which can and should be done to secure and improve health. Second, the recognition of the need for collective action by the body politic — what Acheson[2] later describes as "the organised efforts of society". It need hardly be said that the extent of public involvement has not been the subject of universal agreement throughout history. Nor is it today: witness the difficulty European Governments have in agreeing whether or not to ban tobacco advertising.

THE AGE OF ENLIGHTENMENT

For me, two men stand out as heralds of the age of enlightenment, one an Austrian, the other an Englishman. Johann Peter Frank was born in Austria in 1745. His first public health post was as District Medical Officer of Baden and he was appointed Director General of Public Health of Austrian Lombardy in 1786.

Frank perceived very clearly that poverty was the main cause of disease. He regarded health problems as one aspect of broader social and economic problems and he associated medical reforms with social and economic reforms. "Starvation and sickness are pictured on the face of the entire labouring class. You recognise it at first sight. And whoever has seen it will certainly not call any one of these people a free man." His basic concept was that government can accomplish a great deal that would be beyond the power of the individual physician. He wrote of "medical policing" which he described as a defensive art. Its object was the promotion of the physical welfare of the people in such a way that they may put off death as long as possible. He complained that only recently had people considered the welfare of a population. He had very positive views of the responsibility of the state and of its capacity to improve the lot of the citizen so that "without suffering from an excess of physical evils, they may defer to the latest possible term the fate to which, in the end, they must all succumb." Today the World Health Organisation talks of adding life to years and years to life.

Despite Frank's enlightenment he did not exert a great deal of influence beyond his death. This was largely because the paternalistic political framework which he took for granted did not persist long into the 19th century, which makes the timeless point that conditions must be right for change to occur. I find it saddening that such perspicacity somehow got lost because the ideas were sown on unreceptive soil.

An interesting comparator in England at that time was the great utilitarian Jeremy Bentham,[3] born three years after Johann Frank. He was an enthusiastic proponent of the principle "the greatest happiness of the greatest number". The study of legislation was the central preoccupation of his life and he wrote extensively on how he thought the law ought to be. He also wrote widely on the welfare of individuals. He presumed the existence of a state authority which was committed to the promotion of the greatest happiness. He discussed the difference between state intervention and individual autonomy. Bentham believed there was some degree of evil in all forms of government intervention but if the benefits outweighed the costs the measure would be good rather than bad. He recognised that the population would benefit from more state intervention than occurred in the latter part of the 18th century. Bentham was a major influence in creating an ethos in which it was possible on the heels of the Industrial Revolution for another

revolution to occur in England — the great sanitary movement of the 19th century. He certainly influenced John Stewart Mill and Edwin Chadwick.

I need not recount in detail the well-known and fascinating story of public health in the 19th century in England nor dwell on the famous names which resonate in public health history — Chadwick, Thomas Southwood-Smith, John Snow and Sir John Simon, who became the first Chief Medical Officer of England in 1859.[4] The sanitary revolution culminated in the great Public Health Act of 1875. This revolution was very largely about sanitation, about the provision of clean water, the disposal of sewage, the condition of dwellings, the adoption of measures to prevent epidemics, the burial of the dead, the registration of deaths and of infectious disease — all things now taken for granted in the west, but not yet achieved in the third world.

The pattern in Ireland in the 19th century followed a similar if not exactly identical course to that in England. The Act of Union came into effect in 1801 and in 1805 the Government provided grants for the medical attention of the poor. Boards of Health were established in 1918. Workhouses were established in 130 unions throughout the country. Official dispensary districts in the charge of Boards of Guardians were created under the Medical Charities Act 1851. In 1864 the city of Dublin appointed a Medical Officer of Health. The first occupant was Edward Dillon Mapother who was Professor of Hygiene in the Royal College of Surgeons of Ireland. In 1870 Dublin University introduced a Diploma in State Medicine, the first of its kind in these islands. The Public Health Act of 1875 was followed by a Public Health (Ireland) Act of 1878 and in 1880 the first Medical Superintendent Officer of Health was appointed in Belfast, Dr Samuel Browne.[5]

The history of public health in Ireland must be dominated by the famine, and by epidemic disease. There was of course widespread poverty. Sir William Wilde who conducted the Irish census of 1851 wrote of "the poverty, dirt, misery and destitution of our people". I wonder had he read Frank? Many people lived just above subsistence level depending very heavily on the potato. As early as 1829 Dominic Corrigan in a paper published in the Lancet[6] had warned the authorities that unless Irish peasants were made less dependent on the potato for survival there would eventually be a blight followed by famine and pestilence. Sadly his predictions were all too true. Blight destroyed potato crops in 1845, 1846 and 1847. The total mortality in the Irish population was estimated to be about one-eighth of the population, or one million people, most of whom were probably killed by infectious disease. Typhus was endemic; typhoid, dysentery, smallpox and measles were rampant. Cholera caused thousands of deaths between 1847 and 1849. In Belfast, Malcolm recorded 13,600 hospital admissions in 1847, estimating that one in five of the population were attacked. In 1849 there were 2,000 cases of whom 600 died. Dr David Hadden wrote in Skibbereen in 1847[7]: "This place is one mass of famine, disease and death; the poor creatures hitherto trying to exist on one meal per day are now sinking under fever and bowel complaints — unable to come for their soup, and this not fit for them: rice is what their whole cry is for; but we cannot manage this well, nor can we get food carried to the houses from dread of infection. I have got a coffin with moveable sides constructed to convey the bodies to the church yard in calico bags in which the remains are wrapped up. I have just sent this to bring the remains of a poor creature to the grave, who having been turned out of the only shelter she had —

a miserable hut — perished the night before last in a quarry, she was found with some flax around her, lying dead"

It would of course be wrong to get the impression that Ireland was the only country beset by epidemics at this time. The United States was attacked by cholera three times in the 19th century. Yellow Fever swept up through the States from the Gulf of Mexico with cases reaching a peak in the 1850s. A vast epidemic of cholera swept across India and came first to Europe in the south east of Russia in 1829, and soon reached Moscow. The first English case was recorded in Sunderland in 1831. In the succeeding years cholera caused major epidemics in most European countries. Belfast had epidemics in 1832/1834; 1836/7 and 1847/9. In 1854 in London there were reckoned to be 14,000 cases of cholera with over 600 deaths. Quarantine was the only precaution applied, which resulted in long delays and great expenditure because ships were immobilised. Their crews and their passengers were held up, and their cargoes were ruined. France tried to generate interest in holding international meetings in order to resolve the differences and stop the disruption of trade, but it was not until 1851 that the first International Sanitary Conference was held in Europe.

In the United States the National Quarantine and Sanitary Conventions of 1857 to 1860 had a very similar background. The first convention came about in 1857 out of the Philadelphia Board of Health and was the brain-child of Dr Wilson Jewell.[8] The existing quarantine laws displeased merchants because of the restriction on trade. Health officers knew that the measures did not protect the public and there was no uniformity — for example, Baltimore and New Orleans operated entirely different systems. This led to the Americans moving in a very similar direction and not long after the movement in Europe.

There were 10 international sanitary conferences in the 19th century beginning in 1851 and continuing to 1897.[9] The six held between 1851 and 1885 came to no useful conclusion, largely bacause of lack of scientific knowledge. However, the 7th international sanitary conference was held in 1892 and there was by then general agreement on the etiology of cholera, so the first international sanitary convention was adopted. Further conventions in respect of cholera were adopted in 1893 and 1894. The 10th conference held in 1897 adopted a convention referring to plague.

Lest anyone should think these changes took overlong, it might be a useful corrective to recall that in 1896 Belfast Corporation set up a special committee to consider "the present high death-rate of Belfast and the general unsatisfactory condition of the public health in the city".[5] There was no proper sewage system. People still threw their excrement into the streets and animals were kept in residential districts.

The pace of international change quickened after the turn of the century. The Americans got in first with the Pan American Sanitary Bureau established in 1902. In 1907 the Rome Arrangement led to the foundation of l'Office International d'Hygiène Publique (OIHP), which consisted of a permanent committee with delegates from all member states, a small permanent staff and provisional head-quarters which it occupied for 40 years. After the first world war the Health Organisation of the League of Nations held an annual general conference. It had a secretariat in Geneva. It was assumed that the OIHP would be subsumed into

the League's Health Organisation. However, the United States repudiated the League of Nations and for the 20 years between the wars two independent international health organisations operated, one from Paris and the other from Geneva. It was not until 1952 that the World Health Organisation finally put to rest the Rome Arrangement of 1907. This was the untidy background to the formation of the World Health Organisation as we now know it, an organisation which is doing enormously important public health work across the world and which remains a force in public health matters in Europe today.

Perhaps I should explain why I associate the horrors of the 19th century with enlightenment. Firstly, I think the term is well used to describe the people involved, whether forward thinkers like Frank and Bentham, or doers such as Chadwick, Sir John Simon, Dominic Corrigan, or the local Dr Samuel Browne, or his successors. They introduced new insights and energies and commitment.

Secondly, I applaud society for allowing itself to be propelled along an enlightened road — and Governments which responded on behalf of society, though perhaps too often as shepherds who led their flocks from behind. It was, after all, the initiative and foresight of our 19th century predecessors that got the international health movement going against all sorts of odds, including their own ignorance and the trials of international travelling 150 years ago.

Thirdly, I celebrate the explosion of scientific knowledge in the second half of the 19th century and especially the birth of microbiology. This provided a theoretical basis for the public health movement and created the atmosphere which allowed it to develop headlong into the 20th century. Who rank higher in the history of medicine than the early microbiologists: the brilliant Koch who discovered anthrax in 1876, tuberculosis in 1882 and the cholera vibrio in 1883; Eberth who discovered the causative organism of typhoid in 1880 and Widal of the agglutination reaction; the great Louis Pasteur and many others? If you mention together the two phrases '19th century' and 'public health' the Pavlovian response is 'infection'. It would I think be a great mistake ever to forget that the main subject of public health for two centuries has been communicable disease. It is still the case that the major gains in child survival are, if I may put it this way, the deaths from infection which we prevent.

If we look at the wider world, the persistent need is obvious. The public health fight is against poverty, hunger, over-population and communicable disease. Recent World Health Organisation figures are horrifying.[10] There are annually 1·7 million deaths from measles, neo-natal tetanus and pertussis. There are 100,000 cases of poliomyelitis. Parasitic diseases are rampant. It is believed that there are 5·2 million cases of malaria. 200 million people have schistosomiasis. American trypanosomiasis (Chagas' disease) afflicts between 16 and 18 million people. Three million suffer from guinea worm infestation and 12 million have leishmaniasis. If there is any doubt about the public health problems of the world today we need only think of the famines of Ethiopia and Somalia. Is it not shaming that at the end of the sophisticated 20th century those countries are suffering the privations which people endured in Ireland in 1847? It is poor consolation that we have the knowledge to solve the problems if we lack the will to tackle them, or the generosity to commit a greater share of our western luxury to meeting the basic necessities of our neighbours worldwide.

If we foolishly believe that communicable disease is a third world problem, we need think only of AIDS which has provided a timely reminder of our continuing susceptibility. Meningococcal meningitis, hospital infection and resistant organisms still frighten us all. Easy air travel and a venturesome population introduce new hazards. If a medical student of my time had listed malaria in a differential diagnosis he would have risked being marked down for being esoteric and perhaps even impertinent: not so today. Infections old and new make complacency the major public health risk, a risk which the enlightened public health workers of the 19th century would have found unthinkable.

THE NEW PUBLIC HEALTH

One of the most important developments in the history of public health, nothing less than another revolution in which we are all privileged to play a part, is what has been called the New Public Health. I referred to figures such as Frank and Bentham as heralds of the Age of Enlightenment. The outstanding herald of the New Public Health must be Marc Lalonde, a Canadian lawyer who was Minister of National Health and Welfare. On May 1, 1974, he tabled in the Canadian House of Commons a Working Document which proceeded from a series of Canadian health reports emphasising social values in health, and the importance of environment and lifestyle.[11]

The working document 'A New Perspective on the Health of Canadians' was a set of proposals based on these concepts. "The approach we have outlined", said Lalonde "I believe, offers great potential for the prevention of disease and the promotion of health on a much broader scale than has been previously considered. For many health problems the possibilities for prevention extend beyond the boundaries of the traditional health field." He pointed out that the five most important causes of death before the age of 70 were road accidents, cardiovascular disease, other accidents, respiratory disease (including lung cancer) and suicide. Changes in lifestyle and environment could obviously make major contributions to reducing these diseases. He strongly emphasised the need for a variety of agencies to contribute to health.

Other nations moved quickly. The ideas were soon taken up by the United States. A document 'Healthy People: The Surgeon General's Report on Health Promotion and Disease Prevention' was published in 1978. In a conference in Alma Ata in 1978 the nations of the world met to discuss health matters and emerged with the Declaration of Alma Ata[12] to which the UK Government was a signatory. In 1984 the member states of the European Region of WHO adopted a common health policy and a common set of targets.

In Britain a Working Group on Inequalities in Health was set up and reported to the Department of Health in 1980. The Group had been chaired by Sir Douglas Black, then Chief Scientist to the Department and later President of the Royal College of Physicians, and the Report became known as the Black Report.[13] I have avoided technicalities in this discourse, but allow me to mention one point of record from the report: the age-standardised death rates per 100,000 people living at the ages 15 – 64 showed a gradient between those of social class I and II and those of social class V in 1971. The ratio is a staggering 1½ : 1 in favour of the better-off. Poorer people had a 50% worse experience of premature death than

the well-off. Sadly, the gap between the underprivileged poor and the well-off has widened since then. The working party emphasised that economic factors such as income, employment, environment, education, housing and lifestyles all affect health and all favour the better-off. Their recommendations strongly echoed Lalonde and Alma Ata.

The United Kingdom did not rush to implement the principles of the Declaration of Alma Ata, or the recommendations of the Black Report. Other pressures were required and two were of great significance. The first was the publication in 1988 of the Acheson Report[2]: 'Public Health in England' commissioned by the Secretary of State for Health "to consider the future development of the public health function". The Committee which produced the report was chaired by Sir Donald Acheson. The remit to which the Committee worked was a wide one: "The science and art of preventing disease, prolonging life and promoting health through organised efforts of society."

The report was wide-ranging. The core recommendations concerned the public health responsibilities of District Health Authorities: –

1. To review the health of the population. To define objectives and set targets to deal with the problems.
2. To relate investment in health services to health problems.
3. To evaluate progress.
4. To deal with communicable diseases.
5. To advise and co-operate with other agencies in their locality to promote health.

The importance of the Report is nowhere more clear than in the NHS review 'Working for Patients'.[14] In the foreword Margaret Thatcher wrote "Taken together the proposals represent the most far-reaching reform of the National Health Service in its 40 year history." This document created very significant pressures for change. Its echo of the Acheson Report is very clear in the section at which it sets out the functions of District Health Authorities: "District Health Authorities can concentrate on ensuring that the health needs of the population for which they are responsible are met; that there are effective services for the prevention and control of diseases and the promotion of health; that their population has access to a comprehensive range of high quality value for money services; and on setting targets for and monitoring the performance of those management units for which they continue to have responsibility. The Government will expect Authorities to provide themselves with the medical and nursing advice they will need if they are to undertake these tasks effectively."

We in Northern Ireland can claim to be the first of the four territories of the United Kingdom to have formally adopted the principles of what has come to be called the Health for All movement. We enshrined those principles in our Strategy 1987/92. Wales came later to the ideas and adopted them in an enviably systematic way through the Welsh Planning Forum, now recognised as a WHO collaborating centre. England has finally joined the movement with the recent publication of 'The Health of the Nation' and Scotland has also come aboard.

At national level, Government intervention is now readily accepted as essential on public health issues. The way, however, is rarely simple. Governments do not like

to be thought patronising and show a proper reluctance to engage in anything that looks like over-legislation. Governments, like people, have identity problems and may be reluctant to take action because they are fearful of foreigners trenching on national sovereignty. Governments tend to have to reconcile differing interests within a country: the interests of farmers and the food industry may not, for example, coincide entirely with those of the public health. One good result of AIDS is that within the United Kingdom a cabinet committee was formed. This not only provided a central forum for AIDS problems to the great benefit of the public health; it paved the way for a cabinet committee to drive forward the Health of the Nation. This is real progress in promoting public health and moves public health higher on the agenda than it has been for over a century.

In Northern Ireland several activities are contributing to a renewed drive to promote public health. Among them are the Regional Strategy of the Department of Health and Social Services which adopts health promotion as a major theme; the adoption by Government of the policy of Targeting Social Need to tackle areas of social and economic difference; the creation of an Interdepartmental Committee on Public Health, chaired by the Permanent Secretary of the DHSS; the establishment of the Health Promotion Agency for Northern Ireland; the reaffirmation of the central role of Directors of Public Health and the requirement that they produce an annual report; the important programmes in health promotion adopted by general practitioners; the growing realisation that health is an inter-sectoral matter, requiring the involvement of a wide array of contributors.

For doctors in public health medicine, the problems to be addressed become more and more complex and the decisions are less and less based on certainty and more and more on balancing probabilities — witness the difficulty in explaining that the young, the immunocompromised and pregnant women should beware of listeriosis while those in rude health should enjoy soft cheese; the difficulty in reassuring the Northern Ireland public that they may eat local eggs while advice in England was to be cautious; the difficulty in giving clear advice on folic acid supplements in pregnancy. Issues presenting nowadays are rarely clear and never simple.

I have sometimes been asked about the future of public health medicine. I am convinced that, because of the growing complexity of the evidence and the growing difficulty of its assessment, doctors have an increasing role in public health and an assured place for the future. I think we in Northern Ireland are especially fortunate in our public health practitioners. Training programmes began in the early seventies; we set high standards and we attracted good people. It is a young, vibrant specialty, substantially better in both quantity and quality than can be found anywhere else in these islands.

What of the profession outside public health medicine? Every doctor has a role in preventing disease and promoting health. Clinicians stand in a unique relationship to patients. The credibility of the profession with individuals is high and the influence of personal doctors is great. I believe clinicians should stand back and take a broad view: the value of immunisation relates to herd immunity as well as to personal protection. The greatest good of the greatest number is relevant to all our activities. This does not in any way oppose the role of the clinician in the important work of delivering care to individual patients. Lalonde emphasised

" . . . the importance of basic, good health services. Preventive health measures and promotion of healthy lifestyles are not an alternative to the health care services needed by a person who is actually ill."[11]

While emphasising that public health is not exclusively a medical function, it must be said that the medical profession does have a special role in informing, in inspiring, in driving, in energising, and in helping all the others from Government to the individual. It is not too much to say that the display of a positive attitude to public health is the most important collective function of the profession today. When data about the number of beds or of operations or of prescriptions written in the last decade of the 20th century are confined to dusty, unopened files or some forgotten floppy disc in the deepest Government depositories, history will ask rather what successes were recorded in this decade in eliminating the inequalities, in reducing the morbidity and in improving the health of the population of Northern Ireland.

Maastricht

The Treaty of Rome did not feature health, though there have been European Community initiatives: manpower directions have cleared the way for exchange of health workers and the effects of this for doctors will be very profound; biomedical research including work in medical informatics is increasingly important; the single market affects topics as diverse as medicines and smoking; environmental directives are vital to health — the levels of water purity are much in the news.

The draft Treaty of Maastricht signed on 7 February 1992 introduced for the first time a direct competence in health and, significantly, in the field of public health:

> "The Community shall contribute towards ensuring a high level of human health protection . . .
>
> " . . . action shall be directed towards the prevention of disease, in particular the major health scourges. . . .
>
> "Health protection demands shall form a constituent part of the Community's *other* policies.
>
> "The Community and Member States shall foster co-operation with third countries and the competent international organisations in the sphere of public health."

This last is vital. The entry of the European Community to health matters must mesh with the World Health Organisation and especially its European Region. We cannot have the repetition of the silly international overlap between the League of Nations Health Organisation and the International Office of Public Hygiene which existed in the inter-war years.

Postscript

The fascination of history is more to do with insights into human behaviour than with any recitation of facts. The story of public health does not fail this test. A current perspective on public health in the light of history must proclaim that public health has a distinguished past and a certain future. Thirty years ago it would have been pronounced dead or at least dying, its practitioners

unfashionable and near to extinction. Today, whether coping with the affluence of the west or the desolation of the third world, the importance of public health is growing. As an aspect of collective human endeavour it is a wakening giant clamouring for the attention of Government and citizen alike. As a medical specialty, it is enlivening, demanding and rewarding and nowhere in the world is it more determined to pull its weight or, in the persons of its young practitioners, better stocked with talent than here in Northern Ireland.

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"An image for tomorrow"

An image for change — Annual Oration at the opening of the 1992 – 93 teaching session at the Royal Victoria Hospital.

E M McIlrath

A common thread that binds me with previous orators is the degree of respect with which we all view the tradition of this Oration, and its place in the history of this institution, which in our many and varied ways we seek to serve. The opportunity to address an audience which includes one's teachers, colleagues, future generations of doctors, and many friends leaves me both humble and nervous, but if I may quote Oscar Wilde — "On an occasion of this kind it becomes more than a moral duty to speak one's mind. It becomes a pleasure."

Today the increasing emphasis on the necessary scientific aspects of medicine leaves little time for either student or clinician to spend on the study of a more broad based philosophical and generally more objective view of our vocation. There is a relentless and increasing pressure for change, frequently under the misnomer of progress. Little attention is paid to previous history and experience, and the reinvention of the wheel, no matter how square, is frequently greeted with plaudits.

There are two forthcoming anniversaries which form the backcloth of my image for tomorrow. The 8th November 1995 is the centenary of Röntgen's discovery of X-rays. It was this discovery which led to the specialty of radiology and the later development of diagnostic medical imaging. In 1997 we will celebrate the bicentenary of this our beloved hospital, and consideration of this second anniversary allows observation of a broader spectrum of medicine. It is my hope that by outlining some of the history of radiology and some similarities with the recent history of the Royal Victoria Hospital, that our futures may be more clearly defined.

It is frequently stated that the pace of life increases but I wonder if this is really true. Rontgen's discovery in 1895 was given consideration by the Medical Committee of the Frederick Street Hospital, Belfast, in July 1896, and in November of that year the necessary apparatus was purchased. This at a time when there were few medical journals, and electronic media and air travel did not exist. I suspect that a similar fundamental discovery in 1995 would still be undergoing the necessary amendments required by the Editorial Board of some medical journal prior to publication in 1997 or even later. Consideration of purchase would indubitably have required the formation of several committees, sub committees, working parties and numerous option appraisals, before the establishment of a commissioning team, all in the nature of consensus — personal responsibility having been devalued, if not excluded.

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Initially radiographs were taken by the firm of John Clarke and later by Messrs Lizars of Wellington Place. The latter organisation employed a Mr J C Carson, who it is said carried out domiciliary radiography by jaunting car at a cost of 50 pence — an early example of both ecology and economy. In September 1903 the patients were transferred from the Frederick Street Hospital to the new Royal Victoria Hospital where the electrical department was established under the supervision of Dr J C Rankin. Johnny Rankin was an enthusiastic advocate of the value of radiographs in the teaching of anatomy; he worked closely with Professor John Symington and his assistant Dr P T Crymble, and gained his MD in 1906.

In 1912 new X-ray apparatus and a darkroom were installed at a price of £400. As a comparison, the cost of the present magnetic resonance imaging installation is in the region of £1.7 million. In 1913 some 1,347 X-ray plates were recorded, a far cry from the 3·5 million images obtained in 1990. In 1919 Mr Ralph Leman was appointed radiographer to the hospital. He held this post for some forty years, and his appointment was a landmark in that he was the first paramedical employed to carry out duties previously within the domain of the doctor. A year later Dr Maitland Beath joined the staff. He and Dr Rankin were to exert their influence both at the local and the national level to further the progress of radiology.

In 1924 Dr Frank Montgomery was appointed assistant to Dr Beath, and in 1929 was elected an honorary consultant radiologist. His career is worthy of some enlargement as it represents those less regimented and perhaps happier days. He came from a family with strong religious convictions, and initially entered the Queen's University of Belfast and the Presbyterian College with a view to gaining the degree of Bachelor of Divinity. Having gained selection to the University rugby 1st XV as a freshman, he found that the longest available undergraduate course was in medicine and proceeded to persuade his mother that while he felt inadequate to ascend the steps of the pulpit, the life of medical missionary might beckon. The necessary transfer having been effected, he gained several Irish Caps at full back. After qualification in 1915 he served with distinction in the Western front where he was awarded both the Military Cross and the Croix de Guerre. On demobilisation he joined the Egyptian Medical Service, being made redundant in 1923 with the then not inconsiderable payment of £2,000. He returned to London where he worked as an assistant in Harley Street, obtaining later that year the Diploma of Medical Radiology and Electrotherapy at Cambridge.

I suspect that today such training would scarcely garner the approval of the Royal College. It might perhaps lead to European specialist registration, and would certainly gain plaudits from the Adam Smith Institute. Like all the radiologists of that era, Frank Montgomery practised both diagnostic and therapeutic radiology and his name is still associated with the Northern Ireland Radiotherapy Centre. From 1948 – 56 he was Chairman of the Northern Ireland Hospitals Authority — the last practising clinician to chair such a body; a knighthood for services to medicine was bestowed upon him in 1953.

My career in radiology overlapped his by two months in 1957, and much of the foregoing information is the result of his hospitality in later years. The last appointment to the Hospital prior to inception of the National Health Service was that of Dr David Porter — even by today's standards a superb gastroenterological

radiologist. He was always the perfect gentleman, and he guided the transition of the department through an evolutionary period with calmness and security. The respect in which he is held is evidenced by the award of the Annual Junior Staff Prize in his name.

The period from 1903 until 1950 was characterised by the appointment of general radiologists. This was not surprising, as both medicine and surgery remained generalist in outlook, and the range of imaging investigations remained predominantly plain radiographs, barium studies, cholecystography and urography. In 1950 the appointment of Dr Harry Shepherd was notable in that he had a subspecialty interest in neuroradiology. The beginning of sub specialisation was to produce a period of remarkable advance. The equipment manufacturers were beginning to make use of the improvements in electronics that had occurred during and after the second world war. The list of technical advances is large — image intensification, leading to cine fluorography and coronary angiography, and real time ultrasound leading to duplex and colour doppler vascular imaging.

The introduction of computer processing, allowing the development of computed tomography, magnetic resonance imaging and digital image recording and transmission, represent just a few such advances. The quality and reliability of all equipment is now superb and we owe a debt not only to the innovative designers and manufacturers, but also to local engineers — an unsung group who work day, night and at weekends, like any other health care professional. The more enlightened firms also fashioned an improving liaison with the profession, and it is sad to recount that there no longer exists an independent British X-ray manufacturer. The pioneering research of Godfrey Housfield, in the development of computed tomography, the two Nottingham groups involved with the development of magnetic resonance imaging, and early British work in ultrasound and nuclear medicine is now the province only of American, European and Japanese companies.

The range of investigations was to increase at an outstanding pace as the imaging capabilities of other forms of radiation were discovered, and it was clear that the training of both medical and paramedical staff would have to evolve to meet the new demands. Belfast was deeply involved from the beginning. Dr Maitland Beath became President of the British Association of Radiology in 1938, probably as a compromise candidate between another diagnostician and a radiotherapist whose mutual antipathy was legendary. Beath with wisdom, and his willingness to travel to London, when it was not just a day return on an aeroplane, nurtured the formation in 1939 of the Faculty of Radiologists. This body was in 1975 to become the Royal College of Radiologists, which remains to this day a conjoint body of diagnosticians and oncologists. It is greatly to his credit that after the second world war there was an institution prepared to take responsibility for the direction and standards of training.

In 1948 the diploma in radiodiagnosis and radiotherapy of the Conjoint Board remained the minimum consultant requirement within the United Kingdom. In Northern Ireland however, this diploma was viewed as insufficient and all appointees held additional qualifications, usually an MD by thesis. Dr Harry Shepherd served on numerous committees of the Faculty of Radiologists, and later became Vice President. He was ideally placed to develop postgraduate

training in Northern Ireland, and the first locally trained candidate gained Fellowship of the Faculty of Radiologists in 1962. This qualification soon became a mandatory requirement for the post of Senior Registrar in Northern Ireland, a position achieved elsewhere within the United Kingdom at a very much later date.

Since 1950 more than a hundred and twenty doctors have received part or all of their radiological training in this centre. Postgraduate medical training in Great Britain and Ireland has always demanded sound general experience before the doctor proceeded to specialise. Radiology is no exception — the fellowship requires a broad based knowledge of the subject to honours standard. Higher professional training then allows each doctor to make a choice — whether to increase those general skills, which will more readily be required in the smaller more peripheral departments, or to concentrate upon a particular are of medical imaging.

Neuro-Science was the first example in the radiological field, followed by increasingly specialised radiological experience in paediatrics, vascular and interventional techniques, gastro-enterology and orthopaedics. These were to be joined by specialists using the newer technically based advances in ultrasound, computed tomography and magnetic resonance imaging. Both in patient care and clinical teaching the improvements are manifest — a fact regretfully proven by the recent absence, through illness, of our beloved and respected colleague, Manton Mills.

The "jack of all trades and master of none" philosophy is obsolete, as shown by the recommendations of the Royal College of Radiologists regarding the National Breast Screening Service. In this document are set out a minimum number of examinations per radiologist per annum, quality assurance and audit requirements at regional and supra regional levels. A sensitive balance however must be retained between the lure of the exotic high technology areas, and the more basic examinations — a balance the examiners have recently noted as being somewhat disturbed when they commented on the expertise of candidates for the fellowship — the excellent interpretation of computed tomography and ultrasound being at variance with poor interpretation of chest, abdominal and skeletal radiographs.

The value and quality of our paramedical staff have always been appreciated by their colleagues but their treatment by the National Health Service has been at best tawdry and at worst mean and occasionally almost malicious. In 1926 Ralph Leman, a founder member of the Society of Radiographers, instituted radiographic training in the Royal, and the School flourished, moving from place to place on site and finally finding a permanent home when the late Mr R J Spence established a purpose built school close to Musson House. The year 1990 was another milestone when the first group of radiography students entered the University of Ulster. The Bachelor of Science honours course in Radiography was developed and approved in less than twelve months, together with postgraduate diplomas, and considerable progress towards the degree of Master of Science. I can only comment that the meetings of the course committee, when all the parties involved were in general agreement on fundamental objectives, were a total joy to attend and an almost total antithesis to so many meetings within the National Health Service. It is ironic that when funding was required for clinical tutors the National Health Service introduced major difficulties.

I cannot leave the profession of Radiography without mention of Leslie Irwin, whose premature death robbed us of a lady who showed exceptional intellectual capacity, integrity and practical ability, unmatched, in my experience, anywhere within the world.

The availability of the necessary facilities, or even the time required to train to an adequate level, becomes steadily more difficult. In the clinical field beds are closed or mattresses removed, and operating sessions cancelled on the basis of dubious histograms or fiscal exigency. To paraphrase Oscar Wilde, "There are those who know the price of everything and the value of nothing." The purchase of imaging equipment poses similar problems. Initially we not only kept pace with the rest of Europe, on occasions we were in the forefront. Today the picture is much more sombre. A five year delay in the purchase of computerised tomography in the 1970's was but a foretaste of a ten year delay in the provision of magnetic resonance imaging in Northern Ireland.

Magnetic resonance imaging was in 1982 our image for tomorrow, but is now a tool of today. These instruments are not toys for doctors, they are significant advances in patient care, representing both a non-hazardous and non-invasive method of diagnosis. Their potential can only be realised by patient application and by the increased awareness of doctors, in every branch of medicine, of their vastly improved diagnostic capabilities. Are we going to suffer similar problems with the rash of new technological advances such as microwave tomography, infra-red imaging, electron spin resonance imaging, magneto encephalography or electrical impedance tomography? I trust that better counsel prevails, with subsequent improvement both in patient care and in the training of all our professional staff.

A review of the proceedings of the medical committee of the Frederick Street Hospital in 1896 offers a more appropriate precedent to the new Royal Trust Board than the expensive advice of management consultants. Equally, the anatomical perfection of magnetic resonance images would support John Rankin's thoughts on the teaching of anatomy — a potential that I can only hope the Faculty of Medicine will exploit.

The relationships between the history of radiology, the development of sub specialisation and overall hospital practice are quite clear. Firstly, in acute hospital practice both the technical requirements and the investment in technology will continue to increase. Secondly, experience and review of the medical literature confirm that sub specialisation improves both clinical outcome and postgraduate training.

The whole question of generalist versus specialist has exercised the columns of the *British Medical Journal* and the *Lancet* for over one hundred and fifty years. Sub specialisation was initially promoted in London by those doctors unable to obtain appointments within the major teaching hospital. These appointments were in the 19th century frequently gained by patronage or the ability to pay a large fee. In 1824 an attractive surgical post could cost in excess of 600 guineas.

The British Medical Association opened a petition against the establishment of St Peter's Hospital for the Stone — now part of the Institute of Urology. The journal commented that "special hospitals will never furnish great surgeons or advance

the art beyond mere manipulative smartness." Why then did they succeed? Patient demand certainly increased, and as in today's world, consumer satisfaction is a powerful argument. Perhaps more cogently in 1850 only 20% of Fellows of the Royal College of Surgeons practised in specialist hospitals — by 1950 over 60% of Fellows were so associated.

In a statement referring to the Röntgen centenary, the Royal College of Radiology stated that in the next century the College will ensure that future patients will be served by members working to the highest attainable standards. As our bicentenary approaches, this sentiment holds equally good for the Royal Victoria Hospital. The bicentenary provides an opportunity to look forward to the necessary rebuilding of the ward units. Leeds General Infirmary, which has many features in common with our own hospital, (including limitation of resources, while the necessary improvements to the neighbouring St James Hospital were undertaken) has recently been allocated seventy-four million pounds to rebuild on site. I can see no reason why this institution should be less generously treated.

The rebuilding scheme must encompass a breadth of vision which will ensure that patients will not only be certain of the best possible care but also of enhanced environmental facilities within a new patient and visitor concourse. Similarly, with the greater awareness of our dependence on team work, the training and continuing educational requirements of all our staff should be recognised by the development of an education centre. This centre would provide the group of hospitals, and both Universities, with much needed facilities, and provide accommodation for the necessary support services. I feel it should be designed to be capable of hosting national scientific meetings.

It may astonish those who know me to find that I believe that there is surprisingly little dichotomy in philosophy between the medical staff and those involved in management, regarding their desires for the future of our hospital. I feel, however, there is a mutual inability to recognise each other's problems. I might use the analogy of two people trying to cross a minefield from different points on its periphery. Try as we may to understand the problems of management, doctors have an overriding duty to treat patients to the highest attainable standard, to be their advocate in obtaining the resources to achieve that end, and to train the future generations of staff to standards which are internationally acceptable. Managers might reasonably point out that hospitals are the subject of scrutiny as part of general social critique which includes prisons (soon also to be offered trust status?) schools and industry. The assumption that hospitals embody the best of modern medicine — technology, intensive care and heroic surgery — is correctly under challenge. The detractors of the existing policy in hospitals will quote Roemer's law — the chief indicator for treatment in hospital is the existence of a hospital bed. There can be no future for the rebuilding of ward units on a decay basis, when much future emphasis will be on non-hospital care.

It pains me to state the following, but I believe it to be true. Medical opposition to reform, derived as it is from principled commitment to patient care, will carry decreasing weight in an era of third party funding, with cost control and accountability. I do not believe that our future is necessarily bleak if we have vision, courage and resolve. Our vision must go beyond bricks and mortar or even the colourful sketches of a new ward block. It must extend well beyond the boundaries

of this site. There is no good reason why our many and varied clinical talents cannot be exploited on other relevant sites dedicated to health care.

The differences between general practitioners and hospital specialists are very much less than their common interest. A description I heard some years ago, of a hospital consultant by a general practitioner, as a man who had spent seven years training to look up the wrong end of a telescope was as inappropriate then as it is now — our talents are different but complementary. If there is less room for the generalist as a hospital consultant — so be it; if the generalist practises elsewhere — let us join him. Can we not offer our colleagues hospital facilities and bring them on to our site — why should 'open access' be restricted to X-rays and laboratory tests?

We must consider the threats to our colleagues in the ineptly named non-teaching hospitals as being as great, if not greater than to ourselves. I am a whole-hearted supporter of the small hospital practising efficiently and with community support. Their clinical work can be superb but they function with the major hospitals as backstop, when the unexpected complication occurs that could lead to disaster. What must be fundamentally clear to all — politicians, Department of Health and Social Service, Area or Trust Board, University, Postgraduate Council, and the medical, nursing and paramedical professions, is that wide dispersion of resources in terms of expertise and equipment is totally nonsensical and totally unacceptable.

A population of 1·57 million is marginal from any economic viewpoint in the provision of regional services, but there are no alternative options which are acceptable. The constant comparisons with the third best fiscal performance by an English region are not only flawed, but exhibit intellectual dishonesty. Medicine and medical teaching in Ulster cannot survive international inspection if the imbalance of resources between the acute hospitals and the rest of the patient care system continues. The regional specialties have, and deserve to have, some protection from the present pogrom against hospital medicine, but at no time in the last twenty-five years have I observed just recognition of individual consultants practising as regional experts in their specialised fields of medicine.

Our image of tomorrow must therefore include closer co-operation between the peripheral hospitals, the general practitioners and the teaching hospitals. There are many who regret that the opportunity to form an administrative grouping of the teaching hospitals and the University during the 1972 re-organisation failed to come to fruition, particularly when the system of four area boards has been shown to be fundamentally flawed.

The image for tomorrow would also include an approach to planning which was imaginative — even visionary in its concept of patient and staff environment. It is I believe vital that we examine not only the more enlightened hospitals within the United Kingdom but also those in Europe and North America. The scale of investment demands that we exercise the same level of skill and foresight as our predecessors, who in a time scale of seven years planned and built the existing hospital, described at that time as revoultion in design.

If I may quote Prince Charles — "I believe it is most certainly possible to design features in such buildings that are positively healing — for instance, I believe that courtyards, colonnades and running water are healing features." It cannot be easy

to be healed in a soul-less concrete box with characterless windows, inhospitable corridors and purely functional wards. The spirit needs healing as well as the body.

Courage has never been in short supply in this hospital but perhaps it will require to be of a different quality. To change the working philosophies of a life-time will be a more difficult task for those members of the staff approaching my age than for the younger generation of doctors. Courage will be required if each and every person on this site is to recognise that the fundamental long term objectives of the hospital as a whole must supersede factional interests. Our present concept of ward units will have to change but the concept of functional teams must be nurtured. The clinical directorates should be essentially functional entities, physiological, not anatomical or historical in concept. We will need resolve to withstand the frustrations of fighting apparently lost causes, of seeing opportunities missed, but we must retain our principled commitment to patient care and our insistence that the hospital retains those fundamental components, developed by evolution not revolution, which are required for undergraduate, postgraduate, nursing and paramedical training to international standards.

Finally, it will require both resolve and patience to await the time when there is a more balanced view of hospital medicine and a happier climate pertains. The pendulum will, I am certain, swing back. Two years ago on this occasion as Chairman of Staff I said that what was required was a period of stability and I believed it to be vital at that time — it is now crucial.

"We trained hard . . . but it seemed that every time we were beginning to form up in teams, we would be re-organised. I was to learn later in life that we tend to meet any new situation by re-organising and a wonderful method it can be for creating the illusion of progress while producing confusion, inefficiency and demoralisation." This is not a quotation from any member of the consultant staff, but attributed to Caius Petronius in AD 65.

Surely all those involved, politically and otherwise, must recognise that a period of stability is now essential. The scale and frenetic pace of change has produced an atmosphere of anxiety which is incompatible with the studied consideration which all aspects of health care deserve. The new Royal Trust must resolve its *image for tomorrow.* It must carry every member of its staff with it on the way forward. It must be given real and not ephemeral freedoms and in turn those freedoms must be passed down to functional clinical directorates which will provide patient care, teaching and research to the highest attainable standard. If this can be achieved — each and every one on this site can say, as I do today, *"it is a privilege to serve."*

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Calendar of the Royal Hospital, Frederick Street.

CIRCA — THE NINETIES

A is the Abscess which, hid in the brain
our surgeons have tried for, trephining in vain.

B is the Bleeding the patient must stand
who submits to one eminent surgeon's command.

C is the 'Crowner' who winds up the job (1)
and deducts from the medical witness a bob.

D is for Dick with great gifts you'll agree: (2)
he can steal a post-mortem or cure a D.T.

E is the Extern where pupils get cheek
from the bloated subscribers of twopence a week.

F is for Fegan renowned in his art, (3)
whose motto is "Volkmann" and rest to the part.

G is the Growl of the workmen's committee:
their existence at all is a h – ll of a pity.

H the Hypertrophied damnable cheek
that the resident puts on when in just a week.

I is for Isaac that masterly purge:
with col. and hydrarg. your liver he'll purge.

J is for Johnny ('tis Patrick I mean),
whose writing unique in the extern's oft seen.

K is the Kitchen, the haunt of the pup:
if caught by the super. his little game's up.

L is for Lindsay our boss ausculator: (4)
at spotting a murmur there's no one is nater.

M is for Mitchell who's sure to do well: (5)
he never consigns a subscriber to h – ll.

N is for Nelson to see him you must (6)
produce your red ticket or else lick the dust.

O's the Observant, intelligent student
exposing the patient just more than is prudent.

P is the Pupils whose chiefest delight
is chucking subscribers on Saturday night.

Q for the Quakers, that peaceable race, (7)
who are shocked by the blasphemous cries from the place.

R is for Richard the good man of Ross: (8)
at writing prescriptions he's easily boss.

S is for Sinclair, Professor profound, (9)
if once set a-going he'll talk the day round.

T is the Theatre, bossed by McKay,
whom taenia hath troubled for many a day.

U's Unity ruling our Visiting Staff:
when one makes a mistake how the other dons laugh.

V is the Voice of the 2nd subscriber
denouncing the pup, as a champagne imbiber.

W's our Whitla, who taketh the bun, (10)
writer, preacher and medico rolled into one.

X is the eXordium on conduct and morals
the colonel delivers when settling up quarrels. (11)

Y's for the Yarns which we spin to the Board
and when told in the parlour are often encored.

Z is the Zeal we all show for the place
that through us it never may suffer disgrace.

ANON.

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1. The Coroner.
2. Male nurses.
3. Sir John Fegan (senior surgeon).
4. Professor J A Lindsay — Professor of medicine.
5. A B Mitchell — surgeon.
6. Nelson — Ophthalmic surgeon — always called Garibaldi.
7. The Quakers meetinghouse was next door to the hospital in Frederick Street — it is still there.
8. Dr Dick Ross — a physician.
9. Thomas Sinclair — Professor of surgery.
10. Sir William Whitla — Professor of pharmacology.
11. Colonel Deane — late IMS.

The Ulster Medical Journal, Volume 62, No. 1, pp. 89 – 90, April 1993.

A Royal Victoria Hospital Alphabet
1930

A is for Andy of cystoscope fame:
in far Minnesota they've heard of his name.

B is for Bertie the Royal's best-dressed man:
as a teacher of medicine excel him who can.

C is for Calvert who'll debate half the night
until he is sure he has diagnosed right.

D is for Diana — how weary her moan —
she wonders if Calvert will ever go home.

E is the Extern, Bill Hamilton's pride:
no wily Münchausen takes him for a ride.

F is for Fraser who keeps Andy right:
he never at the cherry takes more than one bite.

G George McFadden, unruffled, polite:
he walks to the Royal when you call him at night.

H is for Houston, Sir Thomas the knight,
who wars with bacilli from dusk to daylight.

I is for Irwin, that is S.T. or Sam,
a popular surgeon, a likeable man.

J is John Morrow, the senior physician:
on soda and gentian he's built his position.

K Tommy Kirk, students gather to hear him
proclaiming the virtues of normal horse serum.

L is for Lowry, the women's professor,
balloonist and tenter and father confessor.

M is for Malcolm, the elegant Harry,
so eager to work, so willing to tarry.

N for the Nurses — Miss Mussen and all:
without them the whole place would crumble and fall.

O is the Ophthalmological cast:
James Craig, Henry Hanna, Fred Jefferson last.

P Percy Crymble, once Symington's student,
an applied anatomical surgeon most prudent.

Q QRST waves are hard to explain
could it be their inventor was Jack McIlwaine?.

R John Charles Rankin who worked with X-rays
not long after Röentgen discovered their ways.

S is for Stevenson skilled in dissection:
at cholecystectomy he is perfection.

T for the Turk, physician and wit:
he knows all the causes of coughing and spit.

U for the Unsung whose names you recall:
this alphabet hasn't got room for them all.

V Victor Fielden whose various skills
include anaesthetics, emulsions and pills.

W W.W.D. —
an echo of Osler, his students agree.

X is the X-ray department where Beath
reveals to the eye what is hidden beneath.

Y is the student who follows them round:
his name in the pass list is sure to be found.

Z is the Zeal of the housemen, their fate
is the monthly reward of three pounds six and eight.

ANON.

A Andrew Fullerton, professor of surgery and friend of the Mayo brothers of Rochester, Minnesota. He recalled that friendship when he received the honorary FACS.

B Robert Marshall, physician in charge of outpatients.

C C A Calvert, surgical registrar who pondered long over acute abdomens at night and aroused the impatience of

D Sister Dynes, night superintendent.

E Wm J Hamilton who so much despised medicine that he avoided a spell as house physician during his year in RVH.

F Ian Fraser, surgical registrar with Professor Fullerton — never undecided about what to do next.

G George D F McFadden — a surgical registrar. He was accustomed to walk to the hospital from College Gardens even at midnight.

H Sir Thomas Houston, physician, haematologist etc, who did most of his laboratory work in the small hours.

I S T Irwin, surgeon wards 15 and 16.

J J S Morrow, physician wards 1 & 2 where mist sod.et gent., a bitter tonic, was much used.

K T S Kirk, surgeon wards 9 & 10, advocate of urea in wounds, normal cow and horse serum and subcutaneous oxygen and other idiosyncracies.

L C G Lowry, professor of obstetrics, and gynaecologist. Balloons and laminaria tents were methods used to dilate the cervix.

M H P Malcolm, surgeon in charge of out-patients.

N Miss Mussen, was matron of the RVH.

O is self-explanatory.

P P T Crymble, surgeon in charge of outpatients. He had worked earlier in the Anatomy Department with Symington and had written sections on the peritoneum in Quain's Textbook of Anatomy.

Q J E McIlwaine, professor of materia medica and therapeutics, and physician to wards 7 and 8: pioneer in electrocardiography.

R John Charles Rankin, physician at large, pioneer in radiology.

S Howard Stevenson, surgeon wards 13 and 14 — rapid operator especially on gall bladder.

T S I Turkington, physician in charge of outpatients, and specialist in diseases of the chest by preference.

U

V Victor Fielden, teacher of anaesthetics and pharmacy.

W W W D Thomson, professor of medicine, followed Osler's text-book in systematic lectures.

X R M Beath was radiologist.

Y and Z — enough said. £3.6s.8d. = £3.33p.

The Ulster Medical Journal, Volume 62, No. 1, pp. 91 – 92, April 1993.

An Alphabet of the Royal
1960

A A's the Aorta that all must rely on:
if Reggie's in doubt he slips in some nylon.

B is for Brown with his rag and his bottle:
I am told that at Stormont there are some he would throttle.

C is for Craig — not tall or good looking:
golf not too bad but a habit of hooking.

D is for Desmond of blood sugar fame:
I am told with his books he has made a great name.

E is for Ernest, bald and sunburned:
his motto is always 'leave no stone unturned'.

F is for Frankie, I mean Frankie P.,
who knows all the heart waves from P through to T.

G is George Johnston, a surgeon with skill:
the 'gun' now has made his mortality — nil.

H is for Harley — his skill with the pill
keeps pregnancies down to virtually nil.

I is for Irwin, a strong silent man
who for vascular disease does the best that he can.

J is Jack Pinkerton — a midwife No. 1:
occasionally here when not chasing the sun.

K is for Kennedy — this time it is Joe:
if you can't pass your water he'll soon make it flow.

L is for Logan for years nicknamed Bunny:
his political views are serious — not funny.

M is for McKeown — the lady professor:
a friend to us all, her students all bless her.

N is for Nevin professor genetic
who says it's our genes that make us phrenetic.

O is for Osterberg, expert with bones:
a true successor to Sir Robert Jones.

P is for Froggatt — his first name is Peter:
the dean for three years — his hair could be neater.

Q Q's are the queer ones — I mean mental — not sex:
they're odd in their ways — yet morals not lax.

R is for Douglas — the Scottish Rob Roy:
up to date he has proven he's the 'broth of a boy'.

S is for Swallow, whose tapping of keys
leaves hardly a moment to tap scraggy knees.

T is Tom Smiley — he'll chop out a lung,
if he's not on his farm busy spreading the dung.

U U's the Unknown who writes all this drivel
and signs it 'anon' fearing action for libel.

V is the Vagus, poor innocent nerve
which Terence attacks with his usual verve.

W is Willoughby the Methody chap:
I hear the colons fall into his lap.

X are the X-rays now taken with care:
there'll be no overdosage if our Teddy is there.

Y Y's are the Young men who daily report
that they do the work when their chiefs are at court.

Z is the plasty that Norman produces:
a knife and some forceps are all that he uses.

ANON.

A Reggie Livingston.
B Maurice Brown.
C David Craig.
D Desmond Montgomery.
E Ernest Morrison.
F Frank Pantridge.
G George Johnston.
H Graham Harley.
I J W S Irwin.
J Professor Pinkerton.
K Joe Kennedy.
L J S Logan.
M Professor Florence McKeown.
N Professor Norman Nevin.
O Paul Osterberg.
P Peter Froggatt.
Q
R Professor Douglas Roy.
S Michael Swallow.
T Tom Smiley.
U
V Terence Kennedy.
W Willoughby Wilson.
X Teddy McIlrath.
Y
Z Norman Hughes.

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Historical note

The centenary of Ivy Cottage, Belfast City Hospital

J K Houston, J F O'Sullivan

Accepted 19 January 1993.

Pregnant women have been delivered in the Belfast City Hospital since 1842. These first patients were destitute inmates of the Workhouse. Over a number of years many reports of maternal deaths due to puerperal sepsis had been presented to the Board of Governors. At a meeting in August 1892 the members agreed to build a new hospital for maternity patients. This unit consisted of three wards, each containing ten beds, two rooms for resident nurses, a kitchen and "all necessary accommodation". The hospital, named Ivy Cottage, was opened in May 1893.[1]

Dr Robert Hall, Visiting Medical Officer, urged the Guardians to employ nursing staff exclusively for the new hospital. This was agreed. The unit was staffed by one sister and two nurses — one for day duty and one for night duty. Sister Douglas was appointed at a salary of £26.00 annually until her retirement in 1933 at the age of 72 years. She then lived with many other retired nurses in Gardner Robb Hospital until her death in 1948.

Few records of the work of the unit are available. The earliest report to the Guardians included the period from September 1898 — September 1890, during which time 251 patients had been delivered. There were three maternal deaths, five stillbirths and three infant deaths. One patient had several eclamptic fits. After delivery, mothers were carried in a 'stretcher' of blankets to the convalescent wards.

When Jubilee Maternity Hospital opened in 1935, Ivy Cottage was converted into a 'septic ward' (Jubilee IV) in which all women with puerperal sepsis were nursed. The number of beds was reduced to 20. The Sister in charge, Miss A Harron, was paid £75.00 annually. During 1945, there was a serious outbreak of gastroenteritis among the babies in the Jubilee Hospital so the entire hospital was closed and all the patients transferred to Purdysburn Fever Hospital. In that year, Dr Muriel Frazer was appointed to the staff as a Visiting Medical Officer to help with the increased clinical work.

In 1948, Jubilee IV (the old Ivy Cottage) re-opened as a neonatal unit. It now contained an operating theatre, various nurseries and facilities for mothers to remain with their sick babies. In 1958 it was designated as the Regional Surgical Neonatal Unit for Northern Ireland. Dr Frazer remained, unassisted, in charge of the unit until her retirement in 1976.

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J F O'Sullivan, MB, FRCS, FRCOG, Consultant Obstetrician.

Ivy Cottage (now Jubilee Hospital neonatal nursery). Photograph taken in 1930 when it was the maternity hospital.

In 1977, the neonatal unit was once more re-organised with more modern facilities for intensive care, special care and intermediate care of both premature and sick infants. Prior to that time, premature babies had been cared for in another part of the hospital. Dr M Reid was appointed as Consultant Neonatologist. He was later joined by two colleagues, Drs G McClure and H Halliday, all three doctors also sharing duties in the nursery at the Royal Maternity Hospital. In 1978, the unit was named 'The Muriel J Frazer Neonatal Unit' in honour of its first neonatologist.

Approximately 25% of babies admitted to the nursery are referred from other hospitals. In 1984, the neonatal death rate was 6·3 per 1,000 — the lowest ever recorded in this hospital. With improved facilities becoming available, a further reduction in the neonatal death rate is anticipated.

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Case report

Stevens-Johnson syndrome associated with methotrexate treatment for non-Hodgkin's lymphoma

R J G Cuthbert, J I O Craig, C A Ludlam

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In recent years methotrexate has been used increasingly in combination chemotherapeutic regimens for the treatment of aggressive non-Hodgkin's lymphoma.[1] Its principal toxic effects are bone marrow suppression, gastrointestinal mucositis, hepatitis, renal impairment, and erythematous rashes. The Stevens-Johnson syndrome has been reported previously in two children receiving high-dose methotrexate with leucovorin rescue for treatment of acute lymphoblastic leukaemia.[2] The syndrome is characterized by severe erythema multiforme associated with orogenital mucosal ulceration, and may be complicated by severe systemic upset and hepatic, renal and neurological disturbances.[3] We report a case of near-fatal Stevens-Johnson syndrome following intermediate dose methotrexate and leucovorin rescue in a patient receiving combination chemotherapy for diffuse large cell non-Hodgkin's lymphoma.

CASE REPORT. A 54-year-old man presented with cervical lymphadenopathy and an abdominal mass. Cervical lymph node biopsy demonstrated a diffuse large cell non-Hodgkin's lymphoma.[4] Extensive involvement of mesenteric lymph nodes was demonstrated by CT scanning. He was treated with BCHOP-M chemotherapy intravenously: bleomycin 10 mg, cyclophosphamide 1·4 g, doxorubicin 76 mg and vincristine 2 mg on day 1; followed by oral prednisolone 40 mg daily on days 1 – 5 and intravenous methotrexate 380 mg on day 15, and leucovorin 30 mg orally six-hourly for four doses on day 16.

On days 22 – 24 he developed a fever, a generalised erythematous itchy rash, and severe mucosal ulceration of the orpharynx, glans penis, and anus. He had epidermal ulceration of the scrotum, perineum, and upper medial aspect of the thighs. On days 25 – 30 the rash became confluent over the whole body surface and began to blister over the trunk, palms and soles, gradually resolving over days 33 – 40.

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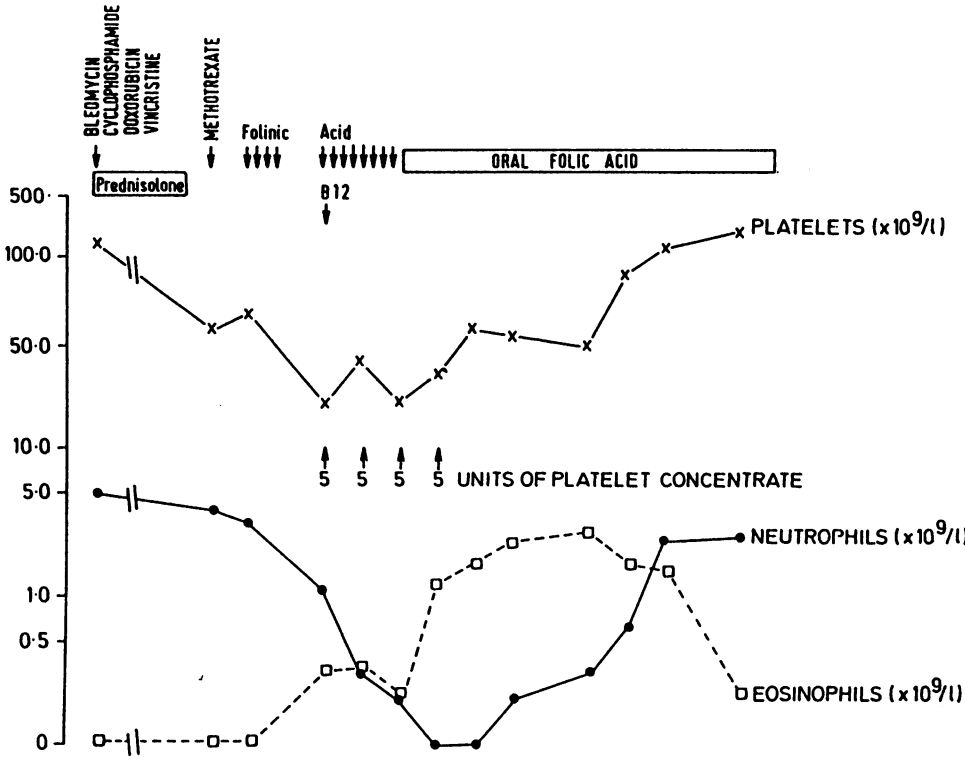

Figure. Neutrophil, eosinophil and platelet counts following methotrexate and leucovorin rescue. The haemoglobin fell gradually from 15·4g/dl on day 1 to 9·2g/dl on day 21, rising to 9·6g/dl on day 30. Blood transfusion was not required.

On day 18 he had been found to have pancytopenia associated with eosinophilia (Figure). The bone marrow was hypocellular with gross megaloblastic changes and no evidence of lymphomatous infiltration. He was given further doses of leucovorin intravenously (30mg six-hourly for 48 hours) followed by oral folic acid (15mg daily for 10 days), and hydroxocobalamin 1mg intravenously. The peripheral blood count gradually improved over days 20 – 24, but the eosinophilia persisted until day 29 and then gradually resolved. The period of pancytopenia was complicated by bleeding from the ulcerated oropharyngeal mucosa and a purpuric rash on the lower limbs. *Staphylococcus aureus, Escherischia coli,* and *Klebsiella pneumoniae* were isolated from the skin, throat, sputum and blood. He required support with platelet transfusions and intravenous antibiotics. During the acute illness he had reversible renal and hepatocellular damage, but ultrasound scan showed no evidence of ureteric or biliary obstruction.

By day 40 his temperature was normal and there was complete resolution of the rash, complete healing of the orogenital ulceration, and normal liver, renal, and bone marrow function. Subsequently he received five further pulses of BCHOP without methotrexate, and had no recurrence of the Stevens-Johnson syndrome. His non-Hodgkin's lymphoma remains in complete remission 36 months after completion of chemotherapy.

DISCUSSION

Although dermatological complications of methotrexate therapy appear to be relatively rare, they may be serious when they do occur. Bullous skin reactions have been reported in high-dose methotrexate regimens used in the treatment of non-Hodgkin's lymphomas,[5] and the Stevens-Johnson syndrome in two patients treated for childhood acute lymphoblastic leukaemia.[2]

This case demonstrates that the Stevens-Johnson syndrome can occur following intermediate dose methotrexate with leucovorin rescue in aggressive non-Hodgkin's lymphoma. In any severe drug reaction in patients receiving multiple agents, a cause-effect relationship can only be proven by selective re-challenge. The reaction in our patient was temporarily related to methotrexate administration, and did not recur when the patient received five further pulses of BCHOP without methotrexate. The syndrome was not present before the initiation of chemotherapy, suggesting that it was not part of the presenting features of his lymphoma. He did have evidence of infection manifested by triple organism septicaemia, but this occurred after the onset of the mucocutaneous reaction, and was therefore more likely a complication than the cause. These arguments provide strong support for a causal relationship between the Stevens-Johnson syndrome and methotrexate administration in this case.

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Case report

Anaplastic carcinoma of the paranasal sinuses presenting as a nasal polyp

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Nasal polyps are benign oedematous outgrowths of respiratory mucosa which frequently present to the clinician as a cause of nasal obstruction. Though nasal and sinus polyps are not true neoplasms, long-standing inflammation can lead to metaplastic changes on the surface of the mucosa, and occasionally even to carcinoma. We report a case who presented with typical findings of nasal polyposis, but was eventually found to have a malignant neoplasm of the paranasal sinuses.

CASE REPORT. A 47-year-old farmer presented to the ear, nose and throat department of another hospital with a history of increasing left-sided nasal obstruction of seven months' duration. He also suffered from intermittent epistaxis. Clinical examination revealed a smooth greyish pink polyp filling the left nasal cavity. The mass was not visible on post nasal examination. Conventional radiographic examination of the sinuses showed a soft tissue density occupying the left nasal cavity and mild haziness of the left maxillary antrum. A diagnosis of chronic maxillary sinusitis with a sinonasal polyp was made and he was placed on the waiting list for surgery.

He returned six weeks later complaining of left-sided facial pain and puffiness of his left eye. He had also noticed an enlarging swelling over the left side of his nose and face. Examination showed the polyp to have increased in size and it was now protruding through the left nostril. A smooth, tender and hard swelling had deformed the left side of the bony nasal pyramid and had obliterated the left nasofacial fold. The mass was still not visible on post nasal examination. CT scanning of the sinonasal complex showed a lobulated soft tissue mass filling the left nasal cavity and ethmoid labyrinth and involving the medial walls of the left maxilla and orbit.

Under a general anaesthetic the tumour was partially removed intranasally and a left intranasal ethmoidectomy performed, but curative surgery was not attempted. The tumour had eroded the medial wall of the maxilla, creating a

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natural antrostomy. Bleeding was controlled by a Brighton balloon and gauze packs, which were removed on the third day. He was referred for radiotherapy.

DISCUSSION

Badib et al[1] and Batsakis[2] state that nasal and paranasal carcinoma presents as chronic sinusitis or nasal polyps in approximately 15% of cases. Busuttil[3] in a study of 1720 patients with nasal polyps reported carcinoma *in situ* in 1·8% of cases, while Mera[4] in a ten year study of nasal and sinus polyps found frank carcinoma in 1·2%. These findings suggest a relationship between carcinoma of the nose and paranasal sinuses and chronic sinusitis and nasal polyps.

Among the epithelial neoplasms of the nose and paranasal sinuses, inverted papillomas are usually associated with a high recurrence rate, and occasionally with malignant transformation. Nasal polyps are considered to be benign mucosal outgrowths, and reports of their conversion to an invasive carcinoma are very infrequent. Maran and Stell[5] are of the opinion that malignant degeneration of true sino-nasal polyps does not occur but polyps can arise secondary to malignant disease in the nose and paranasal sinuses.

Hasegawa et al[6] described a case of a 49 year old man who presented with a long-standing history of nasal obstruction and a huge polyp in the right nostril. Though CT scanning showed changes consistent with chronic sinusitis and polyposis, histopathological examination of the excised polyp revealed an invasive carcinoma. Initially, conventional radiographs in our patient also suggested chronic sinusitis, though CT scanning a short time later demonstrated an invasive tumour, with bone destruction. Normal sinus radiographs cannot definitely exclude malignancy.

Batsakis[2] feels that though nasal and sinus polyps are not true neoplasms, long-standing inflammation can lead to metaplastic changes on the mucosal surface and eventually to dysplasia and carcinoma *in situ.* Smith et al[7] and Klenhoff and Goodman[8] have reported atypical mesenchymal cells in inflammatory nasal and sinus polyps. Mera[4] cites Barnes as suggesting that the findings of stromal atypia, epithelial aberrations or granulomata may hint at a tendency towards malignant degeneration.

There are many who recommend histological examination of all surgically excised polyps. When one considers that 10–20 polyps may be removed from one patient, this would create a heavy work load for the laboratory. All solitary or suspicious polyps should be submitted for histology, which may help to identify epithelial changes at an early stage and possibly demonstrate the true incidence of malignant transformation.

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Case report

Traumatic carotico-cavernous fistula presenting as delayed epilepsy

Anne Begley, Kathleen E Bell, D P Byrnes, C S McKinstry

Accepted 2 February 1993.

Carotico-cavernous fistula typically presents as a pulsatile proptosis with chemosis, diplopia and a bruit. It is a recognised complication of facial trauma as well as head injury,[1] and it has been reported after closed head injury (particularly deceleration types),[2] basal skull fracture, mid facial fractures and surgery, and isolated mandibular fracture.[3-7]

CASE REPORT. A 22-year-old man was transferred from a peripheral hospital to the neurosurgery department following a car accident in which he had been a front seat passenger. Prior to transfer he had been assessed on the Glasgow coma scale at 7/14 (he did not open his eyes, made incomprehensible sounds, but localised to painful stimuli) and had undergone endotracheal intubation. There were bilateral periorbital haematomas, his pupils were small but reacting. Blood obscured the right tympanic membrane. The maxillary bone was mobile, and there was transient CSF rhinorrhoea.

X-rays showed fractures of the middle third of the face in the naso-ethmoidal region and separation of the fronto-zygomatic suture on the right. On the left the fractures extended through the floor and lateral wall of the maxillary antrum. CT scan revealed left fronto-basal contusion with associated cerebral oedema and small ventricles.

He was paralysed and artificially ventilated in the intensive care unit, and the intracranial pressure monitored. Over the following three days his sedation was reduced and at extubation his Glasgow coma scale was assessed at 13/14 (speech was confused). Further assessment of the facial injuries showed minimal displacement and limited mobility of the fractures and the occlusion of the teeth was good. Surgical intervention was therefore not warranted. Neurological examination revealed anosmia, and reduced hearing in the right ear. There was mild diplopia. Recovery continued and he was discharged from hospital three weeks after the accident. At review he remained well and reported that the diplopia had completely resolved, but that he noticed a slight buzzing in the right ear.

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Kathleen E Bell, FRCR, Consultant Neuroradiologist.
D P Byrnes, FRCI, FRCSEd, Consultant Neurosurgeon.
C S McKinstry, FRCR, Consultant Neuroradiologist.

Correspondence to Dr Begley.

Thirteen months following the injury he presented to the accident and emergency department of another hospital having had an epileptic seizure during sleep. He suffered no obvious neurological deficit at that time and was commenced on carbamazepine. CT scan showed a well-defined area of low attenuation in the left frontal lobe in keeping with the previous contusion. There was also a vascular abnormality, which with enhancement showed enlarged vessels over the right cerebral hemisphere particularly marked in the region of the right middle cerebral artery (Fig 1).

A systolic bruit was audible over the right eye, and in the right and left frontal and temporal regions. There was mild asymmetry of the orbits, the right eye being more prominent than the left but there was no palpable pulsation, no chemosis, and fundoscopy was normal. Visual acuity had not deteriorated and ocular movements were full. Audiometry revealed decreased hearing in the right ear and he again described a constant buzzing noise in this ear. He had also been aware at times of a pulsatile noise in the head.

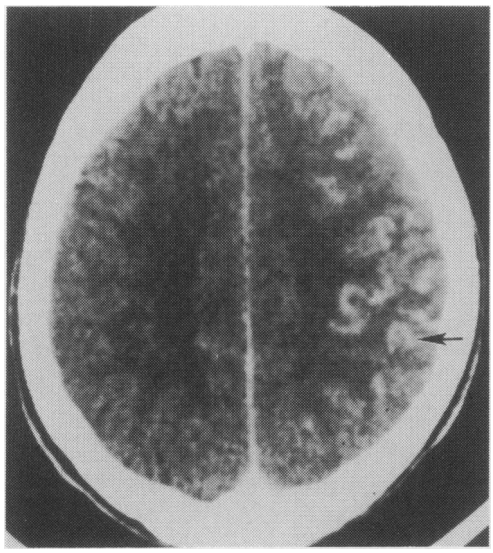

Fig 1. CT scan following intravenous contrast showing dilated vessels in right cerebral hemisphere (short arrow).

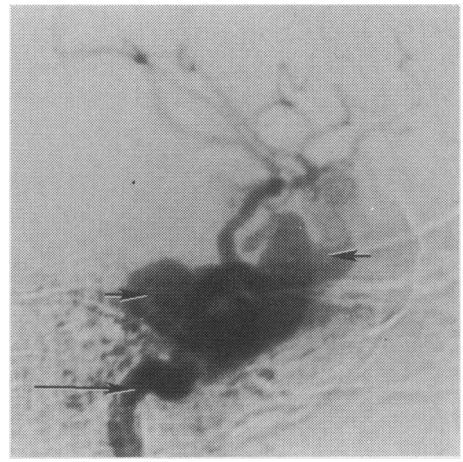

Fig 2. Right carotid arteriogram, lateral view. Contrast passing from right internal carotid artery (long arrow) to venous sinuses (short arrows).

On arteriography contrast passed directly from the right internal carotid artery into the cavernous sinus, and then into the petrosal sinus and some dilated superficial veins (Fig 2). There was incomplete filling of the ophthalmic veins which probably accounted for the absence of the classical clinical findings of a carotico-cavernous fistula (pulsating exophthalmos, chemosis and optic disc changes). There was good cross-circulation from the left internal carotid artery through the circle of Willis. The right internal carotid was therefore occluded using two detachable balloons which were placed as close to the fistula as possible.

DISCUSSION

This fistula only came to attention following an epileptic seizure 13 months after

the accident. Post-traumatic epilepsy following head injury and maxillofacial trauma is well recognised.[8] Late epilepsy, defined as a seizure occurring after the first week, may occur for the first time some years after the head injury. Over 50% of those destined to develop late epilepsy will do so within the first year. Factors predisposing to late post-traumatic epilepsy include post-traumatic amnesia of more than 24 hours, intra-cranial haemorrhage, the occurrence of early epileptic seizures, dural damage and depressed fracture.

Epilepsy is also a presenting feature of other intra-cranial lesions such as tumours or arteriovenous malformations. We have found no other cases of carotico-cavernous fistula presenting with an epileptic seizure. Kanno et al,[9] reported a case where a carotico-cavernous fistula presented with subarachnoid haemorrhage five years after a traumatic event. The epileptic seizure in this case was probably post-traumatic in origin, and the carotico-cavernous fistula discovered fortuitously on the repeat CT scan.

The cavernous sinus lies lateral to the pituitary fossa and medial to the sphenoid bone, and tapers anteriorly to the superior orbital fissure. The carotid artery is mobile within the sinus but it is tethered at its entrance and exit. The IIIrd, IVth and Vth cranial nerves as well as the ophthalmic and maxillary divisions of the Vth cranial nerve pass through the sinus. It receives the superior and inferior ophthalmic veins, the central retinal vein, and the middle cerebral veins, and is drained by the superior and inferior petrosal sinuses, which in turn drain into the internal jugular vein. A carotico-cavernous fistula allows shunting of blood from the high pressure internal carotid artery to a low pressure system, usually resulting in engorgement of the ophthalmic venous system with congestion and oedema of the orbital tissues. In this case none of the ophthalmic features were present, and there must have been an anomalous venous drainage of the area which favoured blood flow to the petrosal sinus and superficial veins rather than to the ophthalmic venous system. The apparent prominence of the right eye was more probably due to a mild enophthalmos on the left side secondary to the facial fractures.

The aims of treatment are to correct the orbital signs and symptoms, to prevent neurological damage due to pressure effects within the cavernous sinus, and to avoid subarachnoid haemorrhage or catastrophic epistaxis.[10] Observation alone may be considered for a spontaneous fistula in an older patient, but traumatic fistulas are actively managed. Treatment options have included ligation of the internal carotid artery, with or without muscle embolisation and direct surgical closure of the fistula. The use of the detachable intravascular balloon has now become the treatment of choice.[11, 12]

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Case report

Absence of the odontoid process with atlanto-axial subluxation; anaesthetic aspects

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Anaesthesia in patients with an unstable atlanto-axial joint is fraught with hazards.[1] Manipulation of the neck during intubation may lead to considerable subluxation in both flexion and extension movements, with pressure from the vertebral body and the odontoid peg. This can significantly reduce the sagittal diameter of the cervical cord, with the possibility of transient or even permanent neurological damage. The case reported is unusual in that in addition to atlanto-axial subluxation the odontoid process was completely absent.

CASE HISTORY. A 28-year-old man previously diagnosed as having ankylosing spondylitis was to have general anaesthesia for dental extractions. He gave a 12-year history of bilateral temporo-mandibular joint ankylosis requiring three surgical procedures under general anaesthesia, the most recent in 1987 involving gap arthroplasty with insertion of silastic blocks. Postoperative mouth opening was 20 mm. All surgical procedures required blind naso-tracheal intubation as mouth opening was insufficient to allow laryngoscopy. He gave a 10-year history of back pain, was HLA B–27 positive but X-rays of his thoraco-lumbar spine were normal. No cardiovascular or respiratory abnormality was detected.

Anaesthesia was induced using thiopentone 300 mg with gallamine 20 mg and alfentanil 1 mg. Gentle manual ventilation was commenced using 1% halothane in 66% nitrous oxide in oxygen. Otrivine nasal drops were instilled into both nostrils and blind naso-tracheal intubation was easily performed using a 9 mm cuffed endotracheal tube. Extubation was carried out whilst deeply anaesthetised.

Prior to anaesthesia the dental house surgeon had ordered a lateral X-ray of the upper airway, but this was not considered helpful as it really was a lateral view of the cervical spine. Some days postoperatively a radiologist noted that there was marked atlanto-axial subluxation. In follow-up, plain films of the lateral cervical spine in flexion, extension and neutral positions demonstrated considerable

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atlanto-axial instability (Figs 1 and 2). The odontoid peg was absent. In the neutral and extension positions there was posterior subluxation of C_1 and C_2 on the rest of the cervical spine. This was of the order of 5 mm and was further increased in the extension position to almost 7 mm. The flexion view demonstrated about 5 mm forward slip of the atlas on the axis and the rest of the cervical spine. There was evidence of both anterior and posterior subluxation of the atlanto-axial joint, but there were no distinct neurological sequelae.

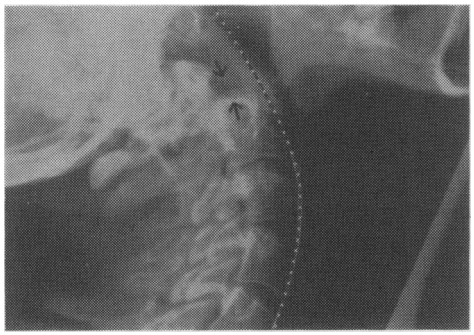

Fig 1. Lateral view of the cervical spine in extension. The dotted line shows the anterior border of the cervical spine. The odontoid process should extend upwards from C_2 to between the two arrows so preventing the backward subluxation of C_1 on C_2.

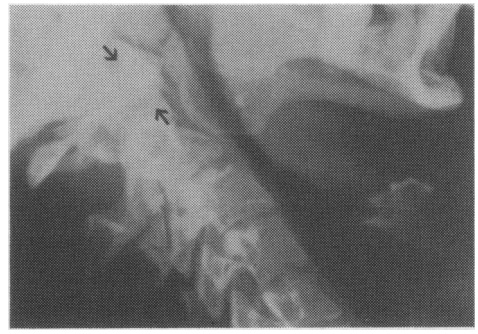

Fig 2. Lateral view of the cervical spine in flexion. The odontoid process should be between the two arrows.

DISCUSSION

Anaesthesia had been carried out on this patient on four occasions, each requiring blind naso-tracheal intubation, without any abnormality of the atlanto-axial joint being suspected. He had been suspected of developing ankylosing spondylitis on the basis of a long history of back pain, temporo-mandibular joint ankylosis, and he was positive for HLA B–27. The radiological findings in his cervical spine were attributed to ankylosing spondylitis, but it is more likely that they are a result of a fall in childhood, when he sustained severe head and neck trauma, resulting in bilateral mandibular condyle fractures. This caused subsequent temporo-mandibular joint ankylosis and retrognathism, requiring many attendances at hospital for reparative surgery. Presumably he had also fractured his odontoid peg at the time of the accident, and aseptic necrosis or failure of the peg to develop ensued.

The first case of odontoid hypoplasia was reported by Roberts[2] in 1933. Up until 1962 only 22 cases were reported in the literature when Gwinn and Smith reported the first case of acquired absence of the odontoid process.[3] Agenesis or absence of the odontoid process is a rare anomaly whereby no extension of the odontoid process above the body of the axis is present. It may be congenital or, more rarely acquired. When congenital, it may be an isolated anomaly or associated with the mucopolysaccharidoses and other syndromes.[4] When acquired, it is believed to result from aseptic necrosis following trauma, or it may be secondary to cervical infection such as tuberculosis. It has also been seen in severe cases of rheumatoid arthritis.

This degree of instability of the atlanto-axial joint would be likely to cause significant neurological impairment were it not for the absence of the odontoid process, so that the cervical cord is not subject to pressure when the subluxation occurs. This case is particularly interesting because the patient had undergone four blind naso-tracheal intubations before absence of the odontoid peg and atlanto-axial instability were noted. The instability caused by the absence of the odontoid process is relatively mild and only in the most severe cases is surgical fusion of the atlanto-axial joint necessary. Despite the lack of neurological sequelae during neck movement in this case, we would consider it prudent to intubate such cases in future using fibre optic laryngoscopy, provided that the problem is identified in the first place.

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Case report

Birth following replacement of frozen – thawed embryos in an *in vitro* fertilization programme

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Ovulation induction is used routinely in all *in vitro* fertilization (IVF) programmes[1] and as a result large numbers of oocytes, often up to 15, may be retrieved in one cycle. To avoid multiple pregnancies, no more than three embryos are transferred to the uterus at one time, so that a number of embryos may be unused in each treatment. These supernumerary embryos have been successfully cryopreserved for later use.[2-4]

Cryopreservation reduces the cost and risk to the patient as no further superovulation or oocyte recovery is necessary in the cycle during which the freeze – thawed embryos are replaced. In addition, it allows the possibility of embryo replacement during a natural cycle subsequent to that in which the oocytes were recovered. This avoids hormone induced changes in the endometrium which may render it antagonistic to implantation.[5] Thus, the introduction of cryopreservation to an IVF programme should complement it and improve its efficiency. We report the first successful pregnancy achieved in Northern Ireland following the replacement of frozen – thawed embryos.

CASE REPORT. A 30-year-old married woman presented to the sub-fertility clinic, Royal Maternity Hospital, Belfast, with a history of infertility over the previous nine years. She was admitted to the *in vitro* fertilization programme in May 1990 and given superovulation therapy. Six oocytes were recovered by follicular aspiration using a needle which was passed via the vagina into the ovary under ultrasonic guidance. The oocytes were inseminated with spermatozoa from her husband, whose semen had a normal profile according to WHO criteria.[6] The next morning five of the oocytes had fertilized, each showing two pronuclei. Eighteen hours after insemination three of these embryos were placed in the patient's uterine cavity using a fine catheter which was passed through the cervix.

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Two of these embryos were at the six cell stage and of 'A' quality which meant that all the blastomeres were of regular shape and equal size. The other embryo had four cells, graded 'B' quality because it had slightly irregular blastomeres. The remaining two embryos were available for freezing. One had cleaved to form four grade 'B' blastomeres and the other also had four blastomeres but graded 'B' to 'C' quality because it had irregular blastomeres and some fragmentation.

Embryo freezing method

To freeze the embryos they were placed in phosphate-buffered saline (PBS; Gibco, Paisley, Scotland) supplemented with 17% human albumin (Albuminar 20; Armour Pharmaceutical Co Ltd, Eastbourne, England). They were then passed to a further PBS solution containing 1·5 M 1·2-propanediol (PROH; Sigma Chemicals Ltd, St Louis, Missouri, USA) for up to 10 minutes and then transferred to the actual freezing solution of serum supplemented plus 1·5 M PROH and PBS 0·1 M sucrose (Sigma) for up to 10 minutes.[4] During exposure to this final solution, embryos were individually loaded into crystal straws (Rocket, London, England). The straws were cooled and frozen in a controlled rate freezer (Kryo 10.16, Planar Products, Sunbury-on-Thames, England) with the cooling rates within each temperature range chosen to give the embryo maximum protection against trauma occurring at that temperature.

The fresh embryo transfer did not result in pregnancy, and in October 1991 the patient requested that her two frozen stored embryos be thawed and replaced.

Embryo thawing and replacement

The thawed embryos were replaced in a subsequent natural menstrual cycle. The age of the embryos was three days post-ovulation at the time of freezing and thawing was timed to allow their transfer to synchronise with the post-ovulatory age of the endometrium. It has been shown that the most favourable 'window' of endometrial receptivity is between days 17 and 19.[7] The patient was scanned on days 13, 14 and 15 of her cycle to monitor the growth of the follicle within the ovary. On day 15 the follicle was seen to have ruptured and so embryo transfer was arranged for two days later. Thawing was undertaken rapidly (200–300°C min^{-1}), taking the embryos from liquid nitrogen temperatures of −180°C and warming them in a 37°C water bath. This prevents the growth of small intracellular ice crystals which might damage the blastomeres. Next, the embryos were rehydrated in a series of PBS solutions, each containing 0·2 M sucrose but with decreasing concentrations of the cryoprotectant, so that in the final solution there was no PROH present. The addition of sucrose controlled the degree of swelling during cryoprotectant removal by acting as a non-toxic counterforce.

Immediately after thawing one embryo was graded as a three 'B', because one of its four blastomeres had not survived the freezing and thawing processes, but 30 minutes later the embryo had cleaved in culture, forming five healthy cells. Only one blastomere of the other, poorer quality, embryo had survived. However, both embryos were transferred to the patient after 2½ hours in culture. Fifteen days later the patient had a positive pregnancy test and after a further week ultra-sound scan showed a single intrauterine pregnancy sac. Thereafter serial scans showed a healthy single fetus. The patient's antenatal care was undertaken at the

Royal Maternity Hospital and progressed satisfactorily until the patient had a spontaneous vaginal delivery of a healthy male infant weighing 3150 grams at term.

DISCUSSION

The first pregnancy to result from the transfer of a frozen–thawed embryo occurred in Australia in 1983.[8] Since then many different cryopreservation techniques have been employed and it is now common practice to freeze super-numerary embryos after GIFT and IVF if facilities and staff are available.

There are at least two prerequisites for a successful pregnancy in a freezing programme — embryo quality and endometrial suitability. The embryos most likely to survive the trauma of freezing and thawing are those of high quality, with all their blastomeres intact and with no signs of fragmenting.[9] The advantage of freezing embryos in early cleavage stages, when they have divided to form two, four or eight cells, is that these embryos have more blastomeres and can maintain their viability with 50% survival. In contrast, pronucleates which have not begun to divide need 100% cell survival to maintain their viability. Testart[10] reported high survival rates (88%) for pronuclear oocytes but with a progressive decline in survival with increasing cleavage divisions. Troup and colleagues claim that the number of embryos surviving when frozen–thawed at the pronucleate stage is not significantly higher than when frozen at earlier cleavage stages (60%) but the implantation rates of pronucleates are substantially greater (47%) than those of early cleavage embryos (14%).[11]

The frozen–thawed embryos may be replaced in a natural menstrual cycle without artificial regulation if, as in this case, the patient has a regular cycle (28 ± 1 days). If her periods are irregular, pituitary function is suppressed by the administration of a GNRH analogue and the ovaries are then stimulated by gonadotrophin injections. Studies have shown that pregnancy rates are similar whether in natural or simulated cycles.[12]

There are varying degrees of success in attaining pregnancies with frozen–thawed embryos in different IVF centres. Some larger and better staffed centres report pregnancy rates as high as 32%[13] and 47%,[11] whereas an overall success rate in the range of 3–6% has been suggested.[14] Another consideration is that a patient requesting replacement of frozen–thawed embryos is excluded from a further cycle on the IVF programme until the frozen embryo cycle is completed. As her chances of becoming pregnant with fresh embryos are greater (≃ 30%/cycle) than with frozen–thawed embryos, it may be in the patient's interest to opt for another cycle of IVF rather than using frozen embryos. This decision must be made by the couple.

Following the lead of Troup in Manchester,[11] there is an increasing preference to freeze only pronuclear oocytes and to give priority to the timing of the freezing procedure. Initial reports of this modified technique claim greater success and it is hoped that this improvement will allow cryopreservation of human embryos to achieve the very high success rates obtained in mouse embryos and thus fulfil its potential. Embryo freezing combined with IVF can improve conception rates per cycle for infertile couples, as it did for this couple, for the first time in Northern Ireland.

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Case report

Five cases of hepatitis A jaundice: diagnostic problems during an epidemic

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When an epidemic of an infectious disease affects a community there are bound to be patients with double diagnoses, even in childhood where such is the exception rather than the rule. When the epidemic is of hepatitis A, a number of diagnostic pitfalls can arise. The need for the hospital paediatrician to be aware of community events is essential, but should not lead to a hasty dismissal of other causes of jaundice. Five patients admitted recently to the Royal Hospital for Sick Children in Edinburgh highlight these difficulties.

CASE 1. A girl aged four years presented to the accident and emergency department with a one week history of cough, followed three days later by onset of intermittent fever, vomiting and malaise. On the day of presentation, her mother had noticed her to be jaundiced and her urine to be dark. There had been recent indirect contact with a case of infectious hepatitis. On examination, she was apyrexial with no hepatosplenomegaly and only mild right hypochondrial tenderness. After blood had been taken for full blood count, erythrocyte sedimentation rate, liver enzymes and hepatitis serology, she was discharged to the care of her family practitioner with a clinical diagnosis of infectious hepatitis. When blood results were available, showing a haemoglobin of 8·3 g/dl and 20% reticulocytes, she was immediately readmitted for observation and investigation of haemolysis. The direct Coombs test was negative but an anti-H1 antibody was detected, active at 4 and 20 degrees centigrade. Chest X-ray showed slight consolidation of the lingula. *Mycoplasma pneumoniae* infection was suspected and subsequent testing showed a four-fold rise in titres. Prednisolone (2 mg/kg/day) and folate (10 mg daily) were commenced for what was now thought to be an acute autoimmune haemolytic anaemia secondary to infection with *m.pneumoniae.* Haemoglobin and reticulocyte levels did not alter significantly in the next four days but, whilst on steroids eight days after presentation, the patient's jaundice deepened, accompanied by worsening anorexia, vomiting and diarrhoea. Steroid therapy was rapidly reduced and discontinued. Two weeks following admission, viral serology

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identified IgM to hepatitis A. One week later the jaundice had almost completely resolved and haemoglobin was rising again. This patient had therefore contracted both hepatitis A and *m. pneumoniae* infection complicated by autoimmune haemolytic anaemia.

CASE 2. A two year old boy, who had been diagnosed as suffering from stage IV neuroblastoma when aged six months, presented as an emergency one year after completing therapy. He had a short history of vomiting and diarrhoea which settled and was followed by reluctance to walk accompanied by general irritability. Intercurrent infection and disease recurrence were among the provisional diagnoses when he was admitted for investigation. Transaminases were mildly elevated but ultrasound scan of liver was normal. IgM to hepatitis A was identified. Clinically and radiologically, the difficulty in walking appeared to be due to avascular necrosis of the left femoral head. He was allowed home after several days of rest with a diagnosis of hepatitis A. Five days later he was readmitted with worsening malaise and irritability. Computerised tomography revealed an intracranial recurrence of the neuroblastoma. He was treated successfully with surgical excision and intensive chemotherapy and is again off treatment.

CASE 3. A seven year old girl developed headache and central abdominal pain and after four days was admitted to hospital. She had developed a petechial rash over her trunk and large bruises on her legs on the day of admission. On examination, there was mild jaundice and the liver was palpable 1 cm below the right costal margin. Blood tests showed a haemoglobin of 13·3 g/dl and platelet count of 3×10^9/l. Other coagulation indices, white cell count and differential were normal. The platelet count rose gradually to normal over the next four days. Serology showed IgM to hepatitis A. A diagnosis of hepatitis A infection with transient thrombocytopenia was made.

CASE 4. A 14 year old girl, who had been found to have elliptocytosis when aged four, was admitted after seven days of headache, cough and sore throat followed by generalised abdominal discomfort and jaundice. There had been no recent contact with anyone else with jaundice. On examination she was apyrexial and not anaemic, with minimal hepatomegaly but no splenomegaly. Consideration was given to an acute haemolytic crisis secondary to her hereditary elliptocytosis. Haemoglobin was in the normal range and there was no reticulocytosis. The blood film showed elliptocytes. IgM to hepatitis A was present. The diagnosis made was of infective jaundice without significant contribution from the elliptocytosis.

CASE 5. A ten year old boy had been diagnosed as suffering from acute lymphoblastic leukaemia eight years previously. Following remission, he had remained well until his admission, when he developed general malaise, severe headache and right hypochondrial pain. He had no pyrexia or hepatomegaly, and was referred by his general practitioner with a provisional diagnosis of recurrence of leukaemia in the meninges. On admission he was clearly icteric with mild tenderness in the right hypochondrium. He was found to have high titres of IgM to hepatitis A, and made a full recovery after a short stay in hospital.

DISCUSSION

During a hepatitis epidemic it is easy and tempting to label all jaundice as due to that infection. These five case histories demonstrate diagnostic dilemmas. In two, a diagnosis of infectious hepatitis was made too readily during an epidemic without careful evaluation of all the symptoms and signs. Two patients had dual pathology, although their haematological disorder was either transient (thrombocytopenia) or non-contributory (elliptocytosis). The final case demonstrates clearly the dangers of assuming that, once labelled, a child can only have one diagnosis. A number of different aetiologies for the many and varied clinical presentations of hepatitis A infection were involved in the five cases we have presented.[1, 2]

The first patient, who had hepatitis A and *m.pneumoniae* infection complicated by haemolytic anaemia, demonstrates the difficulty of diagnosing and treating several concurrent pathologies. Initially steroid therapy appeared to be appropriate for haemolytic anaemia, but could have been deleterious by exacerbating or prolonging the natural course of her infection. An extra confusion can arise since *m.pneumoniae* infection can be rarely complicated by a hepatic clinical picture, quite apart from the hepatitis A infection seen here.[3, 4]

The propensity of neuroblastoma to dissemination, and therefore its protean presenting symptoms and signs, together with coincidental infection by hepatitis A, served to delay the most important component of the diagnosis in the second case, that of recurrence of malignancy. Here double pathology and the assumption that the patient's symptoms could be attributed to the hepatitis A epidemic were both factors which delayed the crucial identification of an intracerebral mass.

The thrombocytopenic patient demonstrates that, of the many possible causes of a low platelet count, the great majority in childhood are acquired rather than hereditary. In paediatric practice idiopathic thrombocytopenic purpura and leukaemia constitute the two most frequent causes of significant thrombocytopenia, and the incidence of the two diseases are very similar. It is also common to find a moderate degree of thrombocytopenia ($60-100 \times 10^9/l$) in young children who have recently had an infection. Sometimes there is associated mild splenomegaly. Severe but transient thrombocytopenia of this level is not commonly reported in infectious hepatitis unless associated with disseminated intravascular coagulation.

Anaemia in elliptocytosis may be precipitated by infection. Despite her infection with hepatitis A, our patient's course was not complicated by any haemolytic component and the cause of her jaundice was therefore purely infective, although we had initially clinically considered her to have an acute haemolytic crisis. In the final patient, because of the previous diagnosis a very competent general practitioner misinterpreted the headache and malaise as a reflection of recurrent acute lymphoblastic leukaemia in the central nervous system. The rapid development of jaundice enabled the correct diagnosis to be made.

There have emerged two subgroups of difficulties associated with the assessment of children during an epidemic of hepatitis A. Either symptoms and signs may be conveniently attributed to a previous diagnosis (for example, elliptocytosis or

leukaemia) and the possibility of infection insufficiently considered, or hepatitis may be assumed to be the cause of any jaundice during an epidemic, with alternative or coincidental aetiologies being inappropriately excluded at an early stage. These cases demonstrate that the initial assessment of the child should be open-minded, with account being taken of past medical history and epidemiological setting but without allowing either to exert undue influence. Further investigations are obviously of benefit, with those necessary to identify the true diagnosis ranging from a reticulocyte count to computerised tomography.

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Book review

Essential management of obstetric emergencies. By Thomas F Baskett. (pp 263. £12.50). Clinical Press Limited, Bristol, 1991.

The delivery of healthy babies to healthy mothers is occurring with increased frequency. Tom Baskett's book however is a timely reminder that Mother Nature has changed little, and given the correct factors and environment can still deal lethal blows. The author, who carried out all of his undergraduate and much of his postgraduate education in Belfast has again addressed these problems in a concise, simple and practical manner.

The introduction of ultrasound and 'high tech' antenatal and intrapartum care has meant that emergencies are often predictable and can therefore be dealt with expeditiously to the ultimate benefit of mother and child.

The chapters on acute abdominal pain, antepartum haemorrhage, disseminated intravascular coagulation in pregnancy and those chapters dealing with mechanical problems in labour are excellent. However, I feel that to try to address antenatal care, preterm labour and labour dystocia in a book like this is perhaps overly ambitious and would be best expanded and dealt with in another volume.

The book concentrates on the management of a particular diagnosis rather than on the management of the symptoms. Perhaps it would have been more appropriate to have chapters on management of 'postpartum collapse' or 'pain' rather than on a specific diagnosis such as amniotic fluid embolus which assumes that all concerned know the diagnosis at the time of the emergency.

'Essential management of obstetric emergencies' by Thomas Baskett makes easy reading and would be a valuable companion to all obstetric junior staff.

JC DORNAN

leukaemia) and the possibility of infection insufficiently considered, or hepatitis may be assumed to be the cause of any jaundice during an epidemic, with alternative or coincidental aetiologies being inappropriately excluded at an early stage. These cases demonstrate that the initial assessment of the child should be open-minded, with account being taken of past medical history and epidemiological setting but without allowing either to exert undue influence. Further investigations are obviously of benefit, with those necessary to identify the true diagnosis ranging from a reticulocyte count to computerised tomography.

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Book review

Essential management of obstetric emergencies. By Thomas F Baskett. (pp 263. £12.50). Clinical Press Limited, Bristol, 1991.

The delivery of healthy babies to healthy mothers is occurring with increased frequency. Tom Baskett's book however is a timely reminder that Mother Nature has changed little, and given the correct factors and environment can still deal lethal blows. The author, who carried out all of his undergraduate and much of his postgraduate education in Belfast has again addressed these problems in a concise, simple and practical manner.

The introduction of ultrasound and 'high tech' antenatal and intrapartum care has meant that emergencies are often predictable and can therefore be dealt with expeditiously to the ultimate benefit of mother and child.

The chapters on acute abdominal pain, antepartum haemorrhage, disseminated intravascular coagulation in pregnancy and those chapters dealing with mechanical problems in labour are excellent. However, I feel that to try to address antenatal care, preterm labour and labour dystocia in a book like this is perhaps overly ambitious and would be best expanded and dealt with in another volume.

The book concentrates on the management of a particular diagnosis rather than on the management of the symptoms. Perhaps it would have been more appropriate to have chapters on management of 'postpartum collapse' or 'pain' rather than on a specific diagnosis such as amniotic fluid embolus which assumes that all concerned know the diagnosis at the time of the emergency.

'Essential management of obstetric emergencies' by Thomas Baskett makes easy reading and would be a valuable companion to all obstetric junior staff.

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Case report

Idiopathic pulmonary haemosiderosis and smoking

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Idiopathic pulmonary haemosiderosis is a rare condition usually affecting children and young adults, both male and female. It is characterised by intermittent episodes of pulmonary haemorrhage producing haemoptysis, iron deficiency anaemia and in its early stages a rise in KICO (transfer factor per unit of alveolar volume). Electron microscopic studies have demonstrated damage to the capillary wall resulting in the escape of red blood cells into the alveoli.[1] The iron thus released is converted into haemosiderin by pulmonary macrophages and cannot be used for haemoglobin synthesis. The condition should be distinguished from pulmonary haemorrhage secondary to Goodpasture's syndrome (glomerular nephritis and intra-pulmonary haemorrhage associated with cross-reactivity between glomerular and pulmonary basement membrane antibodies).

CASE REPORT. A 15-year-old boy, an "occasional" smoker of up to seven cigarettes daily, was admitted in April 1983. He had been short of breath on exertion for two months, with cough and haemoptysis. On the day of admission he was feverish and coughed up blood-stained sputum. His mucous membranes were pale and his temperature was 38·5°C. He had bilateral basal crackles on auscultation, and chest X-ray showed bilateral diffuse infiltration, especially in the left mid zone. A diagnosis of atypical pneumonia was made, he was treated with erythromycin, and improved clinically and radiologically.

Sputum culture for micro-organisms was negative, haemoglobin 6·7 g/dl with microcytic hypochromic indices, serum iron 1·9 mmol/l (normal 6–30), total iron binding capacity 54 mmol/l (normal 45–70). Tests of renal function, arterial blood gases and routine auto-antibody screening were normal. Atypical pneumonia screen (including *rickettsia, chlamydia, legionella* and *mycoplasma pneumonia*) was negative.

Eight days after admission a further sample of sputum showed macrophages laden with haemosiderin, but the significance of this was not at first recognised.

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His haemoptysis gradually ceased over the next few days and he was discharged on oral iron. His haemoglobin gradually returned to normal (15·4 g/dl). He had not been treated with corticosteroids, and did not smoke while in hospital.

Thereafter he remained well in spite of several episodes of haemoptysis and maintained his haemoglobin at normal levels. Eleven months after the initial presentation he had further brisk episodes of haemoptysis and his haemoglobin fell again to 6·7 g/dl. He admitted that six weeks previously he had started to smoke approximately 6 – 7 cigarettes daily. Chest X-ray again showed bilateral infiltrates, sputum contained large numbers of macrophages laden with haemosiderin, spirometry was normal, but serial measurements of single breath carbon monoxide transfer factor (TICO) ranged from 86 – 131% predicted, and the transfer factor corrected for the alveolar lung volume (KICO) 96 – 116% predicted. Antibasement membrane antibodies were not found and jejunal biopsy was normal. A diagnosis of idiopathic pulmonary haemosiderosis was now made. He was treated with prednisolone 20 mg daily and transfused with seven units of packed cells. His haemoglobin returned to normal and again he stopped smoking. He remained well on 5·0 – 7·5 mg prednisolone daily.

Eighteen months later, while still on prednisolone, he had further episodes of haemoptysis and his haemoglobin fell to 7·1 g/dl: he again admitted to having started smoking up to ten cigarettes daily six weeks before this deterioration. Prednisolone was increased to 20 mg daily and he was given a further three units of packed cells. He again stopped smoking and his haemoglobin returned to normal. Steroids were eventually withdrawn some 12 months later, (27 months after starting corticosteroids). Nine years after initial presentation, seven years after stopping smoking, and six years since corticosteroids were stopped, he remains clinically fit and healthy.

DISCUSSION

Idiopathic pulmonary haemosiderosis has been reported in association with mitral valve disease,[2] atrial myxoma,[3] rheumatoid arthritis,[4] and IgA gammopathy.[5] In Greece a definite rural distribution has been found and it was suggested that insecticides might be responsible.[6] Antibodies to cow's milk, and co-existing coeliac disease have also been described.[7] It is frequently fatal; in one series the median survival from diagnosis was only three years.[8] Massive pulmonary haemorrhage is a common terminal event. It has been suggested that the prognosis is better in young adults than in children.[9]

Given the clinical picture and radiological findings, macrophages laden with haemosiderin, the pulmonary physiology and negative antibasement membrane antibodies, the most likely diagnosis was idiopathic pulmonary haemosiderosis. Radioscintigraphy and lung biopsy were not routinely available in 1983 in this hospital. The variability in transfer factor and KICO probably reflect haemorrhage into the alveoli (all the measurements were performed by the same experienced observer). Considerable alveolar haemorrhage can occur without haemoptysis, unlike bronchial bleeding.

This case is of particular interest because at each time of presentation he was smoking cigarettes. It is unlikely that the remission which occurred was related to the treatment with erythromycin, but it may have been related to

cessation of smoking, or was perhaps spontaneous. He had two relapses, one of which occurred when he was on corticosteroids, and on each occasion he had commenced smoking about six weeks previously. His mother kept a diary and is absolutely certain of the accuracy of her observations and when he was smoking. Sadly both parents continue to smoke in spite of advice to the contrary.

Tobacco smoke has a profound effect both *in vitro* and *in vivo* on immune function. Lavage fluid from smokers yields more pulmonary alveolar macrophages than non-smokers and the cells in smokers demonstrate elevated metabolic rates, increased adherence, increased activity of lysozomal hydrolases and many ultra structural anomalies.[10] It is possible that smoking-induced alteration in macrophage function contributed to the relapses, but also inhalation of any irritant could have precipitated further alveolar haemorrhage in already "fragile" pulmonary capillaries.

Smoking is common in young adults. It would be wise to check the smoking habits of any young adult who develops this condition.

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