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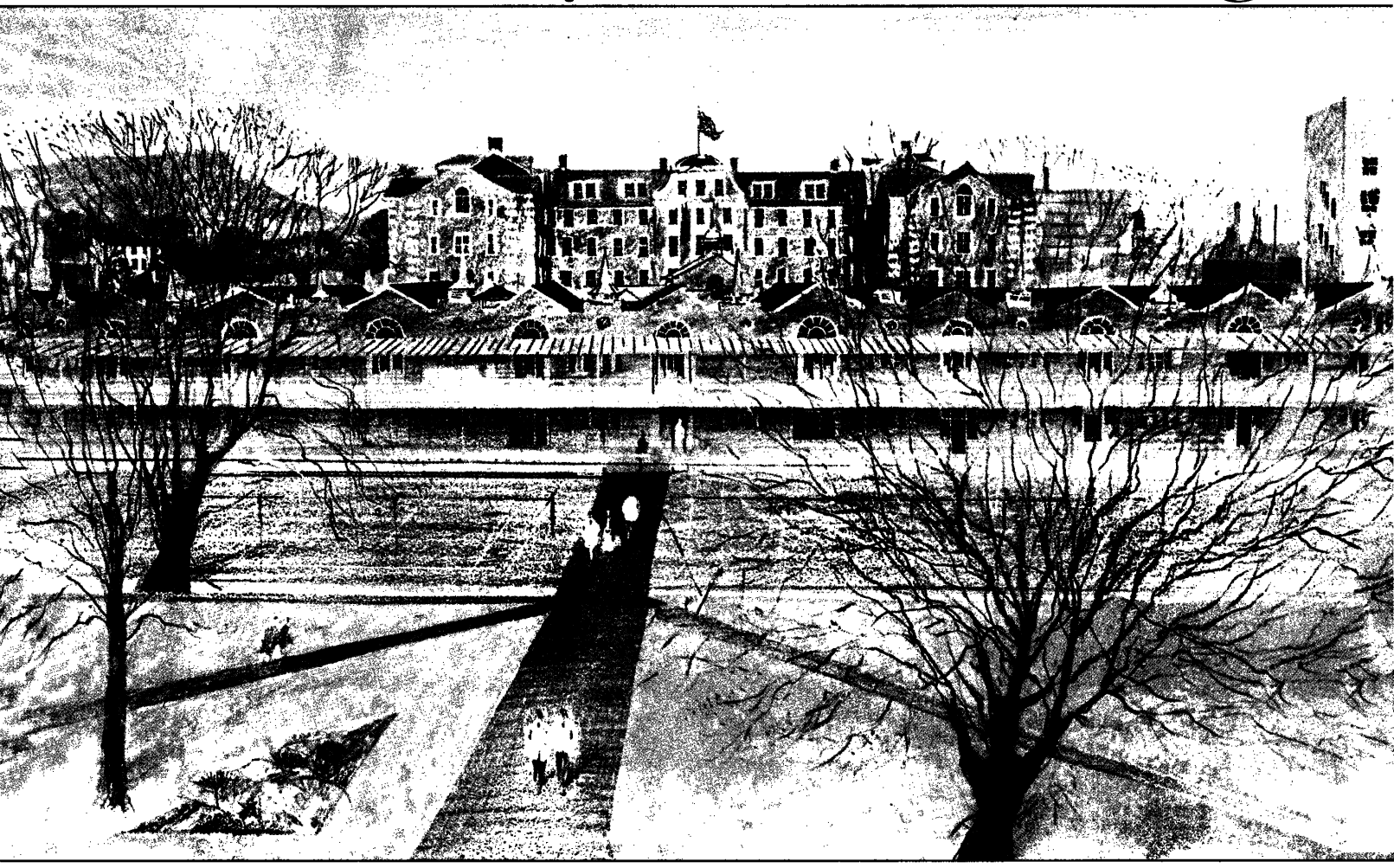

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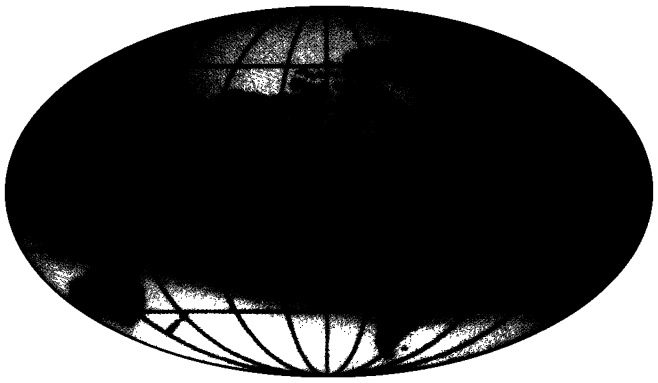

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The Ulster Medical Journal, Volume 66, No. 1, pp. 1-8, May 1997.

Screening for colorectal cancer

W J Campbell, R J Moorehead

Accepted 20 December 1996

SUMMARY

Colorectal carcinoma represents a major cause of cancer deaths in the United Kingdom. Tumours detected at an early or even premalignant stage have a better prognosis. In this review we consider the argument for screening for colorectal carcinomas and discuss the means available and the implications of implementing screening programmes using some of these methods. A suggestion is made for the more rational use of limited resources to target those at greatest risk.

INTRODUCTION

It is a humbling fact that, despite advances in medical knowledge and improved anaesthetic and surgical techniques, mortality rates for patients diagnosed as having colorectal cancer have changed little in the past three decades.[1] This reflects the advanced stage at time of diagnosis in many cases. It is accepted that the prognosis is dependent on the age of the patient, the differentiation of the tumour and the depth of invasion at the time of diagnosis.[2] Tumours which are restricted to the bowel wall (Dukes' A) are associated with a five year survival of 80%. These however account for less than 10% of colorectal lesions.[3,4] The low occurrence of early tumours represents a failure to prevent colorectal carcinomas. Prevention may be primary, where aetiological factors are recognised and avoided, or secondary, where the disease is detected sooner through screenings.[5]

There is now evidence that animal fats have a role in the aetiology of colorectal carcinoma, while a high intake of vegetable fibre is believed to protect against tumour development.[6,7] To implement primary prevention would require re-education of the population, with major changes in dietary habits and benefits would not become apparent for many years.

Before screening can be considered as a means of secondary prevention the disease must fulfil certain criteria:

a) the disease must have serious consequences in the population

b) an acceptable treatment must be available

c) prognosis must be improved by early detection

d) the incidence of the disease must be high enough to justify the cost of screening

e) an acceptable screening test must be available; this should be cheap, reliable, have a high degree of sensitivity and specificity and be acceptable to the population being screened.[5,8]

Colorectal cancer fulfils many of these criteria. It is the second leading cause of cancer deaths in the United States of America and Great Britain. Over 20,000 new cases were diagnosed in England and Wales in 1983, and 1,138 cases were diagnosed in Northern Ireland during 1991-92 giving an incidence of 35.8/100,000 of the population.[9,10,11]

As has been mentioned earlier, prognosis is improved if tumours are detected when restricted to the mucosa. It is now accepted that most carcinomas develop from adenomatous polyps as suggested by Morson and colleagues.[12] In theory colorectal cancer could be prevented by the

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detection of adenomatous polyps in the premalignant phase. Many of these are amenable to endoscopic removal, increasing the acceptability of the treatment available.

At present the criterion which colorectal cancer fails to fulfil is the availability of an acceptable screening test. The methods available to the clinician include:

i) questionnaire
ii) digital examination
iii) rigid sigmoidoscopy
iv) flexible sigmoidoscopy
v) double contrast barium enema (DCBE)
vi) colonscopy
vii) faecal occult blood testing (FOBT)

Each of these has varying sensitivity and specificity and, as the investigations become more invasive, increasing morbidity and mortality.

QUESTIONNAIRE

Several studies have been undertaken to investigate the efficiency of a questionnaire in detecting colorectal neoplasia.[13, 14, 15] In using questionnaires it is possible to detect only those patients who are symptomatic and here one must assume that lesions will cause symptoms at an early premalignant stage of the disease. This is not supported by the presentation of colorectal neoplasia with up to 25% of those with colorectal carcinoma having disseminated disease at the time of diagnosis.[16, 17] In addition the high incidence of colonic symptoms in normal individuals or individuals with benign disease makes the specificity of questionnaires unacceptably low.[13, 14]

DIGITAL EXAMINATION

Digital examination while being cheap and easily performed fails both in acceptability and sensitivity, with approximately 10% of colonic neoplasia occurring within 10 cm of the anal margin.[18, 19]

RIGID SIGMOIDOSCOPY

Theoretically up to 25-40% of colorectal tumours should be visible with a rigid sigmoidoscope (i.e. up to 25 cms).[21, 22] In practice the instrument is rarely inserted to 25 cms and the view is often obscured by faeces.[19, 23] Screening programmes using rigid sigmoidoscopy have detected tumours in less than 0.2% of those screened.[24] The University of Minnesota Cancer Detection Center has shown the benefits of rigid proctosigmoidoscopy claiming an 85% reduction in the statistically anticipated adenocarcinomas in those undergoing the examination routinely.[25] However the costs of such a screening programme are prohibitive with figures from the United States suggesting that only one tumour is detected per $70,000 expended.[2]

FLEXIBLE SIGMOIDOSCOPY

Flexible sigmoidoscopy has many advantages over rigid sigmoidoscopy. Up to 60 cms of rectum and colon can be examined, with 50-70% of polyps said to occur within this length of colon.[20] The examination is said to cause less discomfort than rigid sigmoidoscopy and can be performed with a minimum of bowel preparation. Interestingly two studies have shown no difference in detection of polyps when using a 35 cms scope compared with the 60 cms instrument.[27, 28] In spite of these advantages compliance has been poor in screening programmes using the flexible scope.[31] The positive predictive value is low; between 2-6% of asymptomatic patients screened were found to have adenomas >1 cm in diameter.[29, 30]

The disadvantages of flexible sigmoidoscopy are the need for training of the endoscopist, the capital outlay in providing the service and the time required. It must also be noted when using both flexible and rigid sigmoidoscopy that in recent years several reports have documented an increased incidence of right sided colonic tumours. This so called "shift to the right" will reduce the number of tumours within reach of the sigmoidoscope and may reduce the efficacy of this as a method of screening.[32, 33]

COLONOSCOPY

Colonoscopy provides the best opportunity for evaluating the colonic mucosa, with sensitivities and specificities of over 95% being achieved. It may also be a therapeutic procedure enabling pedunculated polyps to be removed. Its use as a population screening test is prohibited by time, expense and expertise required to perform the examination, with even an experienced endoscopist failing to reach the caecum in as many as 20% of examinations. Being more invasive it is associated with a higher complication rate with the risk of perforation reported as 1 in 500- 1 in 10,000.[24, 34, 36] Perforation is associated with a mortality of 5-10%.[36] It cannot be recommended for screening on a population basis

but should be the method of choice in the high risk groups.

BARIUM ENEMA

Barium enema has the advantage of permitting visualisation of the colon and rectum at a lower cost and with lower morbidity and mortality than colonoscopy. Criticisms of this as a population screening method include the cost, the lack of any therapeutic potential and the lower sensitivities and specificities when compared to colonoscopy. Double contrast barium enema can detect up to 90% of cancers or polyps over 1 cm in diameter.[35] Single contrast enema should be condemned as a screening test achieving sensitivities of only 0.41 for polyps and 0.7 for cancers.[37]

It must also be considered in the cost of the examination that should it prove positive then endoscopy may be required if polypectomy is considered. Barium enema alone is also an inadequate examination of the colorectum and should be combined with at least rigid sigmoidoscopy to improve visualisation of the rectosigmoid junction.

FAECAL OCCULT BLOOD TESTING

FOBT is often used as a preliminary diagnostic test in those presenting with non-specific abdominal symptoms. It is also used in elderly patients in whom it is considered advisable to avoid more invasive tests if possible.

The basis of the test is not the detection of blood in the stool but rather the detection of an elevated faecal blood level. It has been calculated that the median daily blood loss into the gut for normal subjects is 0.6-1.2 ml/day which is equivalent to a faecal haemoglobin concentration of <2 mg/g of faeces[20, 38, 39]

Bleeding from colorectal cancers has been shown to range from 0 to 75 ml/day with a median loss of 1.2 ml/day being recorded.[38, 39, 40]

The basis of most chemical tests is the oxidation of phenolic compounds by the addition of hydrogen peroxide. This is catalysed by haematin, a breakdown of haemoglobin in the gastro-intestinal tract. Compounds such as benzidine, orthotolidine or most commonly guaiac react with hydrogen peroxidase to give a colour change. To avoid false positives from substances similar to haematin (e.g. animal haemoglobin) it is recommended that a meat free, high fibre diet is taken for three days prior to testing. Other foods such as turnips, horseradish, salmon and sardines are also to be avoided.

The test is repeated over three consecutive days to account for variable blood loss. Stoehlein and colleagues report that a blood loss of greater than 10 ml per day will result in a positive FOBT in 90% of cases, while Hardcastle suggested a loss of 20 ml per day will result in a positive result in 89-90% of cases[20, 41] The sensitivity of the test can be further increased by prolonging the duration of the test from 3-6 days and by rehydrating the slides of faeces before testing.[42, 43, 44] However the decrease in false negative rate results in an increase in false positive rate, and with this a fall in the positive predictive value.

There are however problems with the test, in that in order for the reaction to occur degradation of haemoglobin is required. If, in the case of left sided lesions the blood has not been degraded then the test may negative, while in caecal lesions excessive degradation may occur, destroying the haematin required to catalyse the reaction, thus resulting in a negative FOBT. It is recognised for these reasons that caecal and rectal tumours may not be detected by FOBT.[45, 46] Attempts to eliminate the effects of diet have been made with the Haemoquant test designed to detect the conversion of haem to fluorescent porphyrins thus eliminating the effects of dietary peroxidases. It has the added advantage of being a quantitative test, permitting an estimation of the origin of the blood loss to be made since the total amount of haemoglobin and degraded haemoglobin can be measured.[47]

Immunological tests detecting human haemoglobin only have been developed. These are extremely sensitive, detecting haemoglobin in a concentration of 0.3 mg/g of faeces.[48] Such tests have increased detection of blood in the stool by up to 25% in comparison with the Haemoccult test. These tests are however more expensive and difficult to perform.[50, 51, 52] A combination test with the immunological component being performed only if the chemical test proves positive has been suggested.[49]

To determine if FOBT is of benefit five major controlled trials have been undertaken.[53, 54, 55, 56, 57, 58, 59, 60] To eliminate problems with length bias (i.e. better differentiated tumours are present in the community longer and are therefore more likely to be detected by screening), lead time bias

TABLE I

Summary of five major trials of Faecal Occult Blood Test for screening for colorectal carcinoma.

Study	*Size*	*Compliance*	*Positive Test*	*Positive Predictive Value*	
Minnesota	46,000	80% 1st year 70% later	1.8-3.5%	Invasive Ca. Polyps	29% 8%
Memorial Sloan Kettering	>20,000	74%	2.4%		12% 38%
Danish Study	60,000 41%	67%	1.1%		17%
Swedish Study	27,700	66%	1.9-5.8%		
Nottingham Study	100,000	52%	2.3%		11% 23%

(i.e. prolongation of survival is attributed to earlier diagnosis with death occurring at the same time) and selection bias (i.e. well motivated, health conscious, individuals are more likely to participate in screening programmes) it is necessary to compare morbidity and mortality of a group offered the screening test with an age sex matched group who are not screened.

The results are summarised in Table I. At best compliance is of the order of 70% falling as low as 52% in the early stages of the Nottingham trial.[8] Results regarding survival advantage are becoming available. The percentage of Dukes' A tumours in the screened groups is higher than in the control groups and as one would anticipate a survival advantage is being demonstrated in the screen-detected groups with Dukes' A and B tumours.[61,62]

This is not the only criterion on which the feasibility of performing screening will be assessed. The cost of implementing such a programme is a major factor. Offering the screening test to those aged 50-65 years and assuming a positive FOB rate of 2% would result in approximately 1,250 colonoscopy examinations per million of the population assuming the percentage of those aged 50-65 remains constant. The cost would then increase as positive examinations required further endoscopy.

Due to a lack of controlled trials it has been necessary to resort to an elaborate mathematical model. A number of screening strategies have been considered incorporating a combination of procedures e.g. FOBT and sigmoidoscopy, FOBT and DCBE and FOBT and colonoscopy. The decrease in probability of developing colorectal cancer, increase in life expectancy and cost have been calculated.[63,64,65] The authors stress that each strategy must be compared in terms of efficiency, cost and inconvenience. The results suggest that annual FOBT might reduce mortality by 30% while annual colonoscopy could reduce mortality by 85%.[66] It is also suggested that annual FOBT combined with either 5 yearly DCBE or colonoscopy preserves 70-90% of the effectiveness of annual colonoscopic examination while reducing costs by 80%.[66]

The dilemma with which we are faced is that while preliminary results from controlled trials and mathematical models suggest that screening may be effective the cost of performing such a screening programme would be enormous. The numbers requiring endoscopy/DCBE following positive FOBT would necessitate a major expansion in the existing services.

A more rational use of limited resources would be the targeting of those at greatest risk. This would include those with a genetic predisposition

to cancer, and those with a long standing history of colitis.

Familial adenomatous polyposis which encompasses the diseases familial polyposis coli and Gardner's syndrome is an autosomal dominant condition characterised by the development of more than 100 adenomatous polyps in the colon and rectum. If not treated appropriately malignant change inevitably develops in one or more of these polyps. The genetic defect has been localised to chromosome 5. This has permitted genetic screening of those at risk, initially by linkage analysis but more recently by direct sequencing of the gene and mutation analysis. Northern Ireland has a high prevalence of familial adenomatous polyposis with an estimated 93 from 26 families having a 1 in 2 risk of having inherited the gene with a further 49 with a risk of 1 in 4.[67] Prior to DNA analysis, screening of those at risk was performed by regular sigmoidoscopic examination of the rectum. Such is the accuracy of DNA analysis that many of those at risk can either be eliminated or have the frequency of the endoscopic examinations greatly reduced. Colonoscopy can be reserved for those at greatest risk to monitor the colon and determine the optimum time for surgical intervention.

In contrast to FAP, hereditary non-polyposis colorectal cancer (HNPCC) lacks a readily identifiable premalignant marker of the disease. The diagnosis is dependent on an accurate family history which often is not available. The penetrance of the gene is 70-80%. These factors may make it difficult to label a family as an HNPCC kindred with confidence. HNPCC families are said to account for 2-5% of all colorectal tumours, although published data would suggest that in Northern Ireland the incidence is at the lower end of the spectrum.[68] To date 4 genes have been implicated in HNPCC, thus making DNA analysis more difficult.[68] Unlike FAP in which DNA analysis is well established the mainstay of screening HNPCC families remains identification of families at risk followed by regular visualisation of the colon. It is recommended that HNPCC kindred members undergo 3-yearly colonoscopy beginning at 25 years of age although some would suggest that this should be increased to annual examination after 35 years of age.[69, 70]

There are also a number of families who while failing to fulfil the strict criteria for an HNPCC kindred undoubtedly have an increased risk (see Tables II and III). We would recommend that patients in whom the life time risk is increased to greater than 1 in 10 be included in the screening programme.

The final group with an increased risk of developing colorectal carcinoma are those with a longstanding history of colitis. The association between ulcerative colitis and carcinoma is well established in those with a pancolitis, poor control, and disease ongoing for greater than 10 years. Gyde and colleagues reported an 8-fold increase

TABLE II

Amsterdam criteria for diagnosis of Hereditary Non-polyposis Colorectal Cancer (HNPCC) kindreds

i) Three or more relatives with histologically verified colorectal cancer, one of them being a first degree relative of the other two.

ii) At least two consecutive generations should be affected.

iii) In one of the relatives colorectal cancer should be diagnosed at under 50 years of age.

(Vassen H F, Mecklin J-P, Meera Khan P, Lynch H T. The international collaborative group on hereditary non-polyposis colorectal cancer (ICG-HNPCC) Dis Colon Rectum 1991; 34: 424-5)

TABLE III

Cancer risk in first degree relatives of patients with colorectal carcinoma

Population risk	1 in 50
One relative affected (any age)	1 in 17
One first degree & one second degree	1 in 12
One relative under 45 affected	1 in 10
Two first degree relatives affected	1 in 6
Dominant pedigree	1 in 2

in risk of developing colorectal cancer in a group of over 200 patients with ulcerative colitis when compared with the general public. Within this group those with extensive colitis had a 19-fold increase in risk of developing malignancy.[71]

We believe screening of these high-risk groups represents the best use of limited resources. Implementation of a population screening programme using FOBT would require an enormous expansion of endoscopy services for a very low yield in terms of significant pathology detected per thousand patients screened. Colonoscopy of high-risk groups would require minimal expansion of existing endoscopy services and has the potential for identifying up to 10% of colorectal carcinomata at an early stage, or indeed preventing their development by detection of premalignant adenomas.

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The Belfast Cord Blood Bank

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SUMMARY

The first cord blood bank in the British Isles was established in Belfast in June 1993. Cord blood (CB) is rich in haematopoietic progenitor cells and has been used successfully as a substitute for bone marrow transplants in over 200 patients world-wide. Most have received CB from a histocompatible sibling, but reports include several unrelated HLA matched transplants. In addition to the cryopreservation of 400 units of donated CB in the Cord Blood Bank, we have stored eight CB collections from siblings of children with leukaemia in Northern Ireland. A pilot study in collaboration with the maternity unit in the Mater Infirmorum Hospital confirmed the feasibility of a CB banking programme and highlighted many issues relating to Good Manufacturing Practice (GMP). The authors describe experience of collecting 824 units of CB over three years and discuss a few of the wider implications of this innovation in the management of patients requiring myeloablative therapy.

INTRODUCTION

Umbilical Cord Blood (CB) is a source of haematopoietic stem cells which can be used as an alternative to bone marrow for transplantation.[1] Since the first report of a successful CB transplant[2] more than 200 children and adults with congenital or malignant diseases have received histocompatible CB from a sibling or stored unrelated HLA-matched CB. The Belfast Cord Blood Bank is based within the Northern Ireland Blood Transfusion Service (NIBTS) and consists of dedicated sibling donations for specified patients and unrelated donations for general use.

SIBLING DONATIONS

There is general agreement among haematologists and oncologists that cord blood from a sibling must be cryopreserved if an older child in the family is known to suffer from a disease which is normally treated with bone marrow transplantation.[3] Many CB transplants carried out to date have used sibling collections. We have received requests from the paediatric haematologist for collection of CB from siblings of nine patients with leukaemia when their mothers have become pregnant. Such sibling collections can be arranged in any hospital where delivery is scheduled. The obstetrician in charge is contacted and at least two midwives are trained in the collection procedure, with emphasis on the importance of sterile techniques and accurate documentation. To date, nine sibling collections have been cryopreserved from eight pregnancies (one mother had twins). So far it has not been deemed clinically necessary to use any of the stored units for transplant.

UNRELATED DONATIONS: INFORMED CONSENT

Information is provided to pregnant women by midwives and obstetricians towards the end of pregnancy. In consenting to CB banking, the mother agrees that the collection will not be reserved for any member of her family. At antenatal clinics, mothers are given a leaflet which explains the Cord Blood Bank and the use of CB as an alternative to donated bone marrow in medical treatment. The obstetrician or midwife discusses the programme with the mother,

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answering any queries. The leaflet contains a consent form: the mother gives her written consent to the collection of CB post-partum and consents to provide blood samples for all mandatory tests. The mother is assured that blood is not taken from the baby.

COLLECTION OF CORD BLOOD

Normal obstetric practice is not altered in any way for purposes of CB collection. The obstetrician is in charge of the collection procedure and the actual collection is performed by midwives with the placenta *in utero*. Midwives are trained by a member of NIBTS staff. After delivery, the cord is clamped and cut, and using appropriate aseptic techniques the umbilical vein is punctured. We use standard blood collection sets incorporating a bag containing anticoagulant, sterile tubing and a needle which is used to pierce the umbilical vein; blood is allowed to drain into the bag under gravity.

In addition to sterile collection of the CB, a small sample is milked from the cord into a tube for use as an archive serum sample. A venous sample is collected from the mother for microbiology tests.

Midwives complete forms to provide the mother's details and those of the birth. Thorough documentation of the CB donation is meticulously carried out during collection and processing of samples. Unique barcode labels are affixed to all samples and to the CB pack. These labels are specific for each collection and are an integral part of the documentation system for the CB donations. Any labels that remain unused are returned to NIBTS with the collection.

PROCESSING OF CORD BLOOD COLLECTIONS

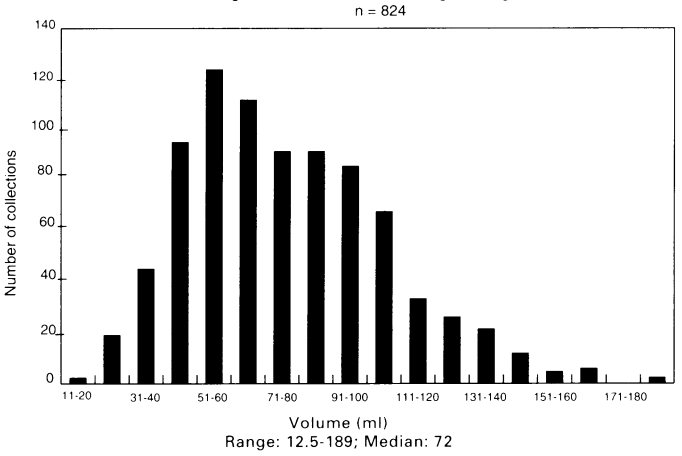
CB is transported each morning from maternity units to NIBTS under the strictly controlled conditions which we use for blood and blood products. At NIBTS all details are recorded and 3 ml CB is removed under sterile conditions from the blood pack using a needle and syringe. This sample is used for ABO and Rhesus grouping, HLA typing, bacterial cultures and nucleated cell counts.

The remaining CB in the pack is mixed with an equal volume of cryodiluent prior to freezing. The cryodiluent consists of sterile dimethyl sulphoxide (DMSO) and albumin in a ratio of 1:4; this protects the integrity of the stem cells. DMSO is exothermic and care is taken to add chilled cryodiluent slowly to CB with continuous mixing. The final mixture for freezing is double the volume of the CB and contains DMSO at a concentration of 10%. The CB/cryodiluent mixture in a freezing bag is placed between metal plates and frozen in a controlled rate freezer to a temperature of -100°C. Subsequently, the frozen packs are transferred to liquid nitrogen tanks where they are stored in the vapour phase.

RESULTS

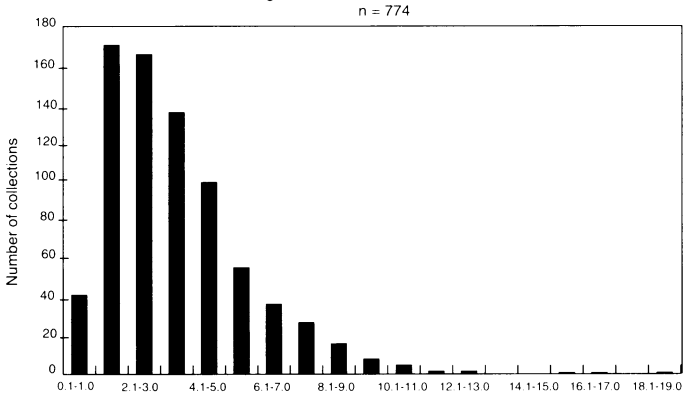
A total of 824 units of CB were collected, of which 186 are available for unrelated transplantation and the remaining collections are used for validation, quality assurance procedures and development of improved techniques for storage. There is a wide range in the volume collected (12.5 to 189ml) with a median of 72ml (Fig. 1). The range in mononuclear cell (MNC) numbers was 0.3 to 18.1 x 10^8/unit with a median MNC of 3.1 x 10^8/unit (Fig. 2). Total nucleated cell numbers were also assessed: the range was 0.1 to 33 x 10^8/unit, with a median of 7.1 x 10^8/unit (Fig. 3).

Figure 1: Volume of CB excluding anticoagulant
n = 824

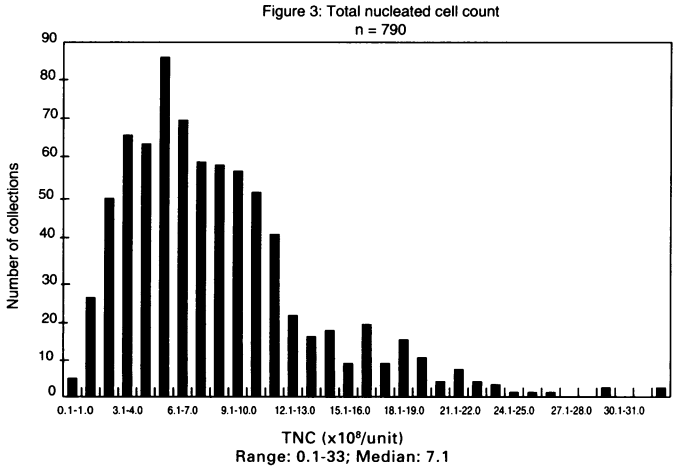


Range: 12.5-189; Median: 72

Figure 2: Total mononuclear cell count
n = 774



Range: 0.3-18.1; Median: 3.1



Microbiological screening for mandatory tests include Hepatitis B, Hepatitis C, HIV and syphilis; no positive results were obtained in the 186 collections for which consent for banking was obtained. The bacteriological contamination rate was significant (12.8%) during the early stages of the programme with a brief period when the infection rate was greater than 20%. There was a marked reduction in contamination (4.2%) after midwives were trained in sterile procedures. The organisms cultured were *streptococci, staphylococci* (including coagulase negative strains), *bacteroides, enterococcus faecalis* and *proprionibacterium spp.*

STORAGE AND RETRIEVAL OF CB COLLECTIONS

Documentation is necessary when dealing with blood and blood products and the routine procedures used in NIBTS are extended to CB banking. Identification and accrual of all information relating to tests and subsequent results of HLA typing can be collated for each specimen. Each collection is labelled with a unique barcode number, date of freezing and volume. The special labels must withstand the freezing procedure and are licensed for use in liquid nitrogen tanks. Archive information includes the position of each bag and sample so that rapid and accurate retrieval is assured.

DISCUSSION

CB has a higher concentration of haematopoietic progenitor cells than bone marrow[4]. Furthermore, partially mismatched CB can be used successfully[5] and the incidence of graft-versus-host-disease appears to be infrequent. This is attributed to the immunological naivety of cells in CB. It has been estimated that approximately 40% only of patients who require bone marrow transplantation receive it. Several factors such as a lack of identical HLA matched donors, inability to trace volunteers on the bone marrow donor panel and relapse of disease during the delay in identifying and testing suitable donors have been recognised by clinicians as unsatisfactory[6]. An "off-the-shelf" supply of cryopreserved ("banked") CB will increase the availability of stem cell transplants for patients who require it as part of their management. This is confirmed by the experience in the USA where recent figures indicate that approximately 25% of all unrelated stem cell transplants are from cord blood (Rubinstein, personal communication).

The European Organisation for Cord Blood Banking proposes to collect and store 20,000 CB units in Europe in the next 2-3 years and this will enable us to evaluate the clinical outcome of such a programme[1]. The Belfast Cord Blood Bank is part of this collaborative venture and one of the authors (Chitra Bharucha) is co-ordinator for standardisation of CB banking in Europe. The aim is to store 1000-3000 units of CB in each of the participating centres and to share HLA data with access to compatible units. In the meantime, all the centres are developing techniques for volume reduction of CB for storage without compromising viability of stem cells because of the considerable resource implications associated with liquid nitrogen storage of such a large number of blood bags.

There is no standardisation of processing procedures or tests performed in different centres. Reported results indicate that there is correlation between speed of engraftment and "white cell count" (WBC), "total nucleated cell count" (TNC), "mononuclear cell count" (MNC), CD34 cell count and haemopoietic progenitor colony count. However, these parameters do not provide a uniform accurate determination of stem cell content because of the variation in techniques. Therefore, analyses of clinical results show a wide variation in the optimum CB collection, with one study[5] concluding that a minimum of 1×10^6 TNC/kg is required for engraftment and another study cites 3.7×10^7 nucleated cell dosekg. (Eliane Gluckman, personal communication).

A pilot study initiated in NIBTS in 1993[7] established the feasibility of the collection procedures and banking programme, and highlighted issues of good manufacturing practice (GMP) which have been incorporated into our routine procedures. The wide range in volume

and mononuclear cells is well recognised[8] and the obstetric factors influencing their recovery have been analysed[9]. The superior engraftment potential and good correlation between volume and MNC concentration make it possible to identify a minimum volume for storage. There are approximately 20,000 deliveries per annum in Northern Ireland. At present, it is necessary to be selective for CB banking and two maternity units have been targeted for training in procedures which comply with GMP requirements. We process and cryopreserve CB collections which are greater than 70ml in volume and have been transported to NIBTS within 48 hours of delivery.

The fact that a significant number of CB stem cells are pluripotent haematopoietic cells makes genetic modification and *ex vivo* expansion possible areas of enormous potential for gene therapy in the future. Commercial companies have been quick in recognising future possibilities, and several companies, at least one of them in Ireland, have begun to exploit patients by offering to store CB indefinitely for an annual fee. This is highly undesirable. Furthermore, there is increasing recognition by the Department of Health and Social Services that CB banking must not be allowed to develop in an unplanned and haphazard manner all over the UK. We are hopeful that funding and procedures for planned further development and extension of the Belfast Cord Blood Bank will be implemented soon.

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Nosological Inaccuracies in Death Certification in Northern Ireland

A comparative study between hospital doctors and general practitioners

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SUMMARY

We aimed to audit nosological inaccuracies in death certification in Northern Ireland and to compare performance of hospital doctors and general practitioners. Nosology is the branch of medicine which treats of the classification of diseases. 1138 deaths were registered in Northern Ireland in a 4-week period commencing 3/10/94. 195 of these were either registered by HM Coroners (HMC) or required further investigation by their staff; these cases were excluded from the study. The remaining 943 were analysed for wording and formulation inaccuracies according to the revised notes (1974), Northern Ireland Medical Certificate of Cause of Death. These are issued in book form by the Registrar of Births and Deaths. The commonest inaccuracies in death certification occur in the areas of poor terminology, sequence errors and unqualified mode. One or more inaccuracies were found in 317 (33.6%) of cases. In 13 of these (4%) cases, the inaccuracies were serious enough to warrant referral by the Registrar of Deaths to HM Coroner. The numbers of general practitioners and hospital doctors were recorded, with general practitioners being responsible for 122 (38%) and hospital doctors being responsible for 195 (62%) of inaccuracies.

Conclusions:

Many of these inaccuracies could have been avoided by adherence to simple guidelines which are readily available in the death certification booklet (G.R.O. 20). In Northern Ireland there is also undergraduate teaching on the importance of death certification and the avoidance of undesirable terminology. However, this seems to have had little effect on doctors' abilities to perform this vital task.

INTRODUCTION

Death certification is a vital function of medical practice. Its poor implementation leads to erroneous health statistics, inaccurate data of disease prevalence and, perhaps, uneven allocation of scarce resources as a consequence of imprecise assessments of disease patterns. Distress to relatives can also be caused by use of the phrase "cerebro-vascular *accident*" – the last word often being confused with traumatic death at a time of emotional stress. In other areas mistakes made are not only semantic but conceptual, hence our preference for the word nosological.

Lack of referral to the coroner of relevant cases is another problem which has been highlighted in this and other studies.[1,2] A study from Rotherham, England[3] reported that the inaccuracies found could have been avoided by adhering to the notes for medical practitioners. In Northern Ireland similar information is contained in booklets of death certificates (G.R.O.20) and we concur with

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the view that most of the errors could have been avoided. In Northern Ireland all medical students graduating from Queen's University in Belfast are taught the subject of forensic medicine in the third academic year. This course includes the topic of death certification and the avoidance of undesirable terms. This seems to have had little effect on either hospital doctors or general practitioners in the performance of this vital task. In many cases there seems to be a fundamental misunderstanding of the purpose of death certification. Since August 1995, the Coroner for Greater Belfast and a consultant forensic pathologist jointly have given a refresher course to newly qualified doctors on the importance of death certification. It will be interesting to see if this has any impact on the death registration patterns in Northern Ireland in the future, though a recent study[4] suggests that this may not be the obvious answer.

METHODS

The General Register Office in Belfast receives the registration returns for all deaths in the Province from the local Registrar's offices throughout Northern Ireland. A four week period in 1994 commencing 3 October was randomly chosen. During this period a total of 1138 registered deaths were recorded and each of these was examined from the original certificates. Some of these registered deaths (195 in number) had been investigated or registered by HM Coroners and were therefore excluded from this study.

Of the remaining 943 deaths, 460 were registered by general practitioners and 483 by hospital doctors of various grades. It was not possible to confirm the grade of the hospital doctor, because this information was seldom available on the death certificate. Deaths occurring in hospital were certified by hospital doctors in this study. Also, it was not possible to ascertain if the certificate was signed by a general practitioner except by assuming that if the death occurred in the community, the signatory on the death certificate was a general practitioner.

RESULTS

Of the 943 death certificates examined in this study 626 (66.4%) were acceptable. 338 (54%) of these certificates were completed by general practitioners and 288 (46%) by hospital doctors. Further subcategorisation of hospital doctors was a difficult task as many signatures were illegible, qualifications poorly if at all documented and the residence of the doctor often left blank. This often made the Registrar's task more difficult when enquiring about serious inaccuracies. However, in all cases, the place of death of the deceased was documented allowing the differentiation into hospital doctors and general practitioners.

TABLE

Inaccuracies in the causes of death showing type and number of cases

Type of inaccuracy	GP	Hosp.	GP + Hosp.	% of Total
Mode of dying	13	36	49	5.2
Poor terminology	55	94	149	15.8
Clinical term or symptom	8	26	34	3.6
Sequence error	38	31	69	7.3
Non-existent terminology	2	1	3	0.3
Referred to Coroner:	6	7	13	1.4
• Trauma	2	1	3	
• Industrial lung disease	4	2	6	
• Underlying cause of death unknown	0	4	4	
Total	122	195	317	33.6

One inaccuracy was identified in 317 (33.6%) of cases registered. More than one inaccuracy was identified in 81 (8.6%) cases. (See Table 1). Thirteen cases, 1.4% of the total, were sufficiently serious to warrant referral to the Coroner. This figure is a gross understatement because there are several enquiries from the Registrar of Births & Deaths staff that each Coroner's office handles on the telephone; however, a formal record of these is not maintained. In the 13 cases mentioned above, one certificate referred to "old fracture of left hip" as the underlying cause of death. In one case the immediate cause of death was given as "intracerebral haemorrhage" without qualification. In another the underlying cause of death was given as "pressure sores" following on a period of immobility. In two cases the certificates did not exclude trauma as the underlying cause of death; in six cases the certificates did not exclude industrial lung disease. In the remaining four cases, use of ambiguous terms such as "chest infection," "aspiration pneumonia" (unqualified) "cardiac failure" (unqualified) and "aspiration pneumonia due to bowel obstruction" led to referral to the Coroner.

In 49 (5.2%) cases a mode of dying was stated without qualification. Examples included terms such as left ventricular failure, congestive cardiac failure, acute renal failure, chronic renal failure, respiratory failure and chronic brain failure.

In 149 (15.8%) cases poor terminology was used including many cases labelled "cerebrovascular accident", including the abbreviation CVA; one certificate used the term "CVAfi left hemiparesis". Cerebrovascular *accident* should not be used on a death certificate, even though it conveys a clear clinical event, because it is poor terminology and because the death is not accidental as is suggested by the phraseology; it is in effect a natural death. Others used terms such as "carcinomatosis", "disseminated malignancy" with no reference to the underlying malignant condition, even though "unknown" would have sufficed in those cases where the primary remained unidentified. Other examples of poor terminology were "debility", "lung neoplasm", "circulatory insufficiency", "aspiration pneumonia" (unqualified), "pulmonary oedema" (unqualified) and "septicaemia" (unqualified).

In 34 (3.6%) cases unqualified clinical terms were used including "atrial fibrillation", "chest infection", "anuria", "shortness of breath", "gangrenous feet", "severe haemoptysis", "stroke", "unstable angina", "atrial tachycardia", "heart block", "haemorrhage per rectum", "melacna" and "bleed from carotid artery." Some of these certificates contained more than one error, usually sequence error and unqualified mode. Three of the terms used were non-existent: "mamacarcinoma", "myocardial ileus" and "secondary carcinomatosis".

In 69 (7.3%) cases there was a sequence error. Often the underlying cause of death which should be either I(b) or I(c) was given as the immediate cause of death. A common example of this error is given below:

I (a) Myocardial infarction

I (b) Congestive heart failure.

In some instances it was difficult to follow the reasoning behind the statements made which bore no causal relationship e.g.:

I (a) Congestive heart failure

I (b) Dilated cardiomyopathy

I (c) Coronary artery disease

In other instances items in category I (c) should have been in category II i.e. other disease processes present contributing to the cause of death but not directly related to the main disease process:

I (a) Bronchopneumonia

I (b) Chronic obstructive airways disease

I (c) *Ischaemic heart disease*

DISCUSSION

This is the first study from Northern Ireland, where the law on death certification is slightly different from that in England and Wales.[5] Section 7 of the Coroners Act (Northern Ireland) 1959 Ch.15,[6] states: "Every medical practitioner, registrar of deaths or funeral undertaker and every occupier of a house or mobile dwelling and every person in charge of any institution or premises in which a deceased person was residing, who has reason to believe that the deceased person died, either directly or indirectly, as a result of violence or misadventure or by unfair means, or as a result of negligence or misconduct or malpractice on the part of others, or from any cause other than natural illness or disease for which he had been seen and treated by a registered medical practitioner within 28 days prior to his death, or in such circumstances as may require investigation

(including death as a result of the administration of an anaesthetic), shall immediately notify the Coroner within whose district the body of such deceased person is of the facts and circumstances relating to the death".

This information is reiterated on page 1 of the book on death certification.[7] Despite this, and despite a list of 82 indefinite or undesirable terms listed at the front of the same book, including terms like bedsore, debility, coma, renal failure, haemoptysis, haematemesis and cardiac and respiratory failure, these terms still regularly occur on death certificates. Slater[3] considered that the most likely explanation for many of the inaccuracies was inadequate medical education. In Northern Ireland, Queen's University Medical School teaches the subject of forensic medicine to third year students and this includes the subject of death certification. In addition a refresher course is given to recently qualified doctors by a consultant forensic pathologist and the Belfast Coroner just prior to the commencement of the pre-registration year. The majority of hospital doctors and general practitioners working in Northern Ireland are UK graduates, overseas/EU graduates forming a very small minority. We concur with Slater[3] that comprehension of the English language is not the problem. We think that the problems in death certification are more complex than the lack of medical education. The problem would appear to be one of attitude towards the writing of the death certificate and a failure to understand its significance. Very often the task of writing the death certificate is delegated to a junior clinician.[8] This practice still continues despite a report from the Royal College of Pathologists and the Royal College of Physicians which recommended that provisionally registered house-officers should not complete death certificates.[9] In Northern Ireland social mores demand that the funeral be held within three days, hence there is a certain amount of pressure on nursing and medical staff to complete the death certificate before the final result of the autopsy. Of the 943 death certificates examined in this study none used the information box (A) on the back of the death certificate form which asks if additional information may come to light for a more precise statistical clarification e.g. results of a post-mortem. If the deceased is the subject of a Coroner's investigation, a death certificate cannot be issued by a doctor; instead the Coroner will issue appropriate documentation.

In this study we verified the certifying doctor as a hospital doctor or general practitioner. This study showed that 460 (49%) of all deaths registered in this period were certified by general practitioners. Therefore there was no significant difference between the two groups regarding actual numbers of cases registered. However, general practitioners were responsible for less inaccuracies than hospital doctors (38% compared to 62%). This figure for general practitioners is much higher than a previous study[10] where a figure of 6% was reported. This conclusion, however, should be taken in context as hospital doctors tend to deal with a higher proportion of unnatural deaths. Hence the number of potential cases to be referred to the coroner is greater in the hospital environment. The main inaccuracies by general practitioners reported in this study were due to poor terminology n=55 and sequence errors n=38. The former was mainly due to the use of the term "cerebrovascular accident". In the cases referred to the coroner in this group one mentioned trauma as the underlying cause of death, another did not exclude trauma as pressure sores were given as the underlying cause of death, and the remaining four did not exclude industrial lung disease. Hospital doctors on the other hand performed less well than their colleagues in the community; again most of their errors were due to poor terminology.

In this study we have illustrated a similar number of inaccuracies which have been documented in other studies,[3,11] but it must be noted that a higher percentage was identified (33.6%). Slater[3] noted inaccuracies in 29% cases and Leadbeatter[11] 25.5%. Similar problems have been described in the USA by Kircher and Anderson.[12] This higher inaccuracy rate has been found despite undergraduate medical education in Northern Ireland. This implies that the issuing of an accurate death certificate is a more complex matter than medical education alone.[13]

We suggest a number of reasons why these inaccuracies still occur:

(1) The subject of death certification is taught relatively early in the student's course (i.e. year 3). By the time these students reach final year (i.e. year 5) a lot of information is poorly remembered.[14] A refresher course to newly qualified doctors is now taught prior to pre-registration year and hopefully this will have some effect.

(2) It is possible that students and medical practitioners do not understand the purpose of death certification. In Start's study one of the mock examples revealed that 24% of hospital doctors would have issued a death certificate despite a clear history of violence or trauma and a possible murder/manslaughter case.[1]

(3) The writing of a death certificate is not seen as an important task by medical practitioners, and the consequences of inaccurate death certification are not appreciated.

(4) Death certification is often delegated to the most junior medical graduate available at the time. In many instances this leads to incorrect assignation of the cause of death; a misuse of concepts of modes of death and underlying disease processes, and general misuse of category II of the death certificate.

CONCLUSION

In spite of instruction in writing of death certificates provided in this region to medical students and newly qualified doctors, this study revealed more inaccuracies than other such studies in death certification. This is also the first time general practitioners and hospital doctors' ability to issue an accurate death certificate has been compared. We found the use of poor terminology predominated in both groups. The importance of accurate death certification is obviously not grasped by students, hospital doctors and general practitioners, and the subject is more complex than appreciated. We fear that often it is not seen as an important task by clinical staff and that doctors' ability to categorise coroners' and non coroners' cases is poor.[2] In spite of every medical practitioner having a legal duty to report certain categories of cases to the coroner, they still fail to do so on a significant number of occasions.

We propose additional instruction to final year students and pre-registration house officers, preferably at the commencement of the apprentice year. It will be interesting to observe if the newly instituted instruction to pre-registration house officers, commenced in the Belfast teaching hospitals in 1995, has any effect on medical practitioners' ability to perform this vital task and bring about a change in attitude to the writing of death certificates.

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A standardised breakfast tolerance test in pregnancy: comparison with the 75 g oral glucose tolerance test in unselected mothers and in those with impaired glucose tolerance

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SUMMARY

There is still disagreement concerning the optimal procedure for the diagnosis of milder degrees of hyperglycaemia in pregnancy. We have compared the results of a 75 g oral glucose tolerance test (OGTT) and a standardised breakfast test performed one week apart in 102 non-diabetic women with a singleton pregnancy. There was poor correlation between the two tests (r=0.15) at two hours, and neither test was predictive of adverse maternal or fetal outcome. One hundred and four patients with impaired glucose tolerance, diagnosed at 30 weeks' gestation by 75 g OGTT, subsequently had a breakfast and lunch meal profile. There was no significant correlation between the two-hour OGTT value and either the two hour post-breakfast value (r=0.35) or the maximum profile value (r=0.33). Using the WHO diagnostic criterion of >8 mmol/l for the OGTT and a maximum glucose concentration >6.8 mmol/l for the meal profile, there was no relationship between an abnormal result in either test and pregnancy outcome. In our obstetric environment, the 75 g OGTT, a standardised breakfast test, and a structured meal profile, all failed to provide a useful indication of pregnancy outcome in mothers not already known to have diabetes.

INTRODUCTION

We have previously reported that, in our obstetric population, fetal outcome is not adversely affected by maternal impaired glucose tolerance as defined by the current WHO criteria.[1,2] The most important pathological aspect of carbohydrate intolerance in pregnancy is likely to be hyperglycaemia associated with normal eating habits, and the oral glucose tolerance test (OGTT) does not necessarily reflect this. We have investigated the relationship between the response to the 75 g OGTT and a standardised breakfast test in a group of unselected pregnant women, and related the glucose responses to maternal morbidity and fetal outcome. We have also studied a selected group of mothers who had impaired glucose tolerance by the WHO criteria.[3]

PATIENTS AND METHODS

1) Unselected pregnancies

One hundred and fifteen women attending an antenatal clinic were studied. The patients were contacted by telephone at about 28' weeks gestation and asked to participate.

The only exclusion criteria were multiple pregnancy, pre-existing diabetes, and treatment with steroids or antihypertensive agents. Each patient underwent a 75 g OGTT and a 300 Calorie standardised breakfast test at 30 - 32 weeks' gestation. The tests were performed one week

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apart, after an overnight fast. The order of the tests was alternated by number of entry into the study. The 75 g glucose was in the form of dextrose monohydrate and had the same calorific value as the standardised breakfast. The latter contained 45 g carbohydrate, 10 g protein and 9 g fat, as a portion of breakfast cereal with milk, toast and butter, and a cup of tea.

2) Impaired glucose tolerance pregnancies

Nine hundred and thirty six patients had a 75 g OGTT performed at about 30 weeks' gestation because of positive clinical screening criteria according to the protocol in use at our hospital at that time.[4] The criteria were glycosuria in a second fasting sample, family history of diabetes in a first degree relative, maternal weight >90 kg, history of congenital malformation or unexplained stillbirth, or a previous baby weighing 4.5 kg or more. One hundred and seventeen of these 936 women were found to have impaired glucose tolerance using the WHO two-hour cut off of 8.0 mmol/l. One hundred and four of these patients subsequently had a breakfast/lunch profile with venous samples for plasma glucose measurement before and two hours after each meal: both breakfast and lunch contained 300 Calories and had identical nutrient content.

RESULTS

1) Unselected pregnancies

Thirteen of the 115 patients recruited into the study were unable to complete both tests; in a few cases this was due to vomiting of the glucose load, but several patients did not keep the second appointment. The mean age of the remaining 102 women was 27.7 years (range 18-40 years). Parity varied from 0-3. The mean booking weight was 64.6 kg (range 43.6-107.4 kg), and the mean body mass index at booking was 24.8. The majority of patients attended for the booking visit between six and 16 weeks' gestation.

Forty eight of the women had the OGTT performed before the breakfast test, and 54 had the breakfast test first: there was a greater number of withdrawals among the patients who had the OGTT first, which may indicate that this test was less acceptable to the patients. There was no significant difference in age, parity, weight or body mass index with respect to the order in which the tests were performed.

For the OGTT, the mean (± SEM) venous plasma glucose at 0, 1 hour and 2 hours was 4.4 mmol/l (± 0.04), 7.4 mmol/l (± 0.17) and 6.1 mmol/l (± 0.12), and for the breakfast test 4.4 mmol/l

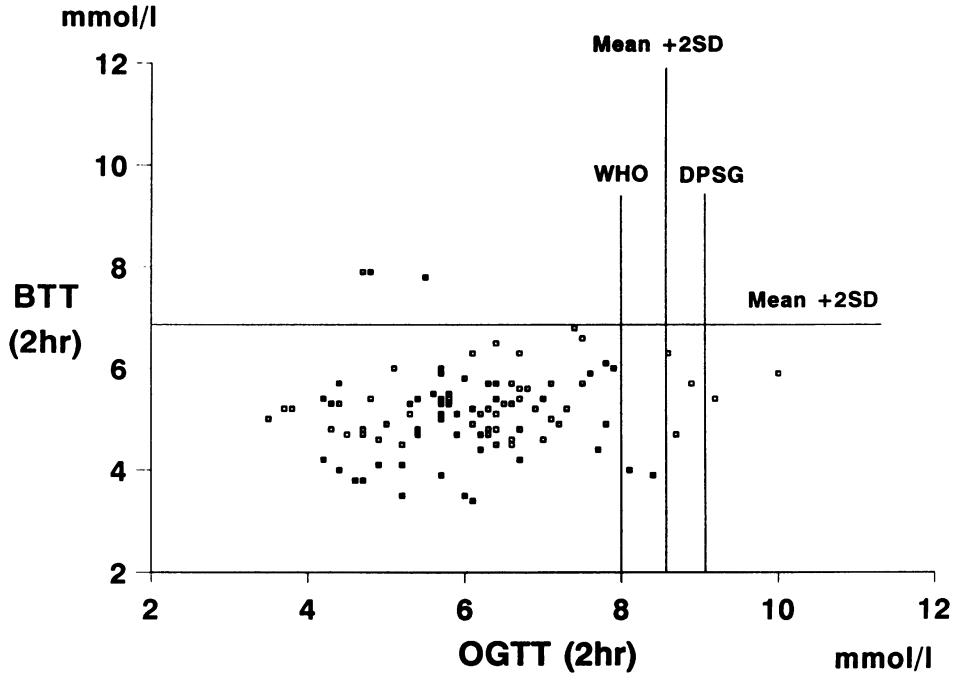

Fig 1. Comparison of the glucose concentrations at 2 hours in the 75 g oral glucose tolerance test (OGTT) and the standardised breakfast tolerance test (BTT): r=0.15.

WHO: World Health Organisation definition of impaired glucose tolerance in pregnancy (>8.0 mmol/l).

DPSG: Diabetes Pregnancy Study Group definition of impaired glucose tolerance in pregnancy (>9.0 mmol/l).

The definition of diabetes is a 2 hour plasma glucose concentration >11 mmol/l.

(± 0.05), 6.2 mmol/l (± 0.12) and 5.2 mmol/l (± 0.08). In general the one-hour glucose concentration was higher than the two-hour level, and the glucose load caused a greater rise in plasma glucose than the isocaloric standardised breakfast. There was poor correlation between corresponding OGTT and breakfast test values within patients; r=0.53 for the fasting values, r=0.36 at 1 hour and r=0.15 at 2 hours.

Figure 1 relates the 2 hour OGTT and breakfast test values. Using the WHO cut-off level of 8 mmol/l for the 75 g OGTT, seven women had impaired glucose tolerance. If the modified cut-off level of 9 mmol/l suggested by the Diabetic Pregnancy Study Group[5] is used, this number is reduced to two. The mean + 2SD value for 2 hour plasma glucose in the OGTT in this study was 8.6 mmol/l. No patient was found to have diabetes (2 hour value >11.0 mmol/l). No patient had a 2 hour glucose concentration above 8 mmol l^{-1} in the breakfast test; the mean + 2SD level for the 2 hour plasma glucose was 6.8 mmol/l and there were three patients with a value above this.

Only eighteen of the women (17%) had a clinical indicator to have an OGTT using the previous standard hospital criteria. The most common criteria were a family history of diabetes and maternal weight greater than 90 kg, but the presence of such indicators was not predictive of either impaired glucose tolerance or abnormal breakfast tolerance.

The results of both tests were analysed against pregnancy complications and fetal outcome. Five women had a urinary tract infection, seven had pregnancy-induced hypertension and two had polyhydramnios, but none of these mothers had either impaired glucose tolerance or abnormal breakfast tolerance by any of the previously defined criteria. There were no significant differences between those with normal and impaired glucose tolerance or normal and abnormal breakfast tolerance with regard to gestation at delivery, onset of labour or mode of delivery.

Fetal outcome in relation to the 2-hour OGTT and breakfast test results is shown in Figure 2. Neither test was of value in predicting adverse fetal outcome. The one stillbirth and two major fetal malformations (Fallot's tetralogy and tracheo-oesophageal fistula) occurred to mothers with normal glucose tolerance and breakfast tolerance.

All of the mothers of the 11 infants who required admission to the special care baby unit had a normal breakfast test and 10 had a normal OGTT.

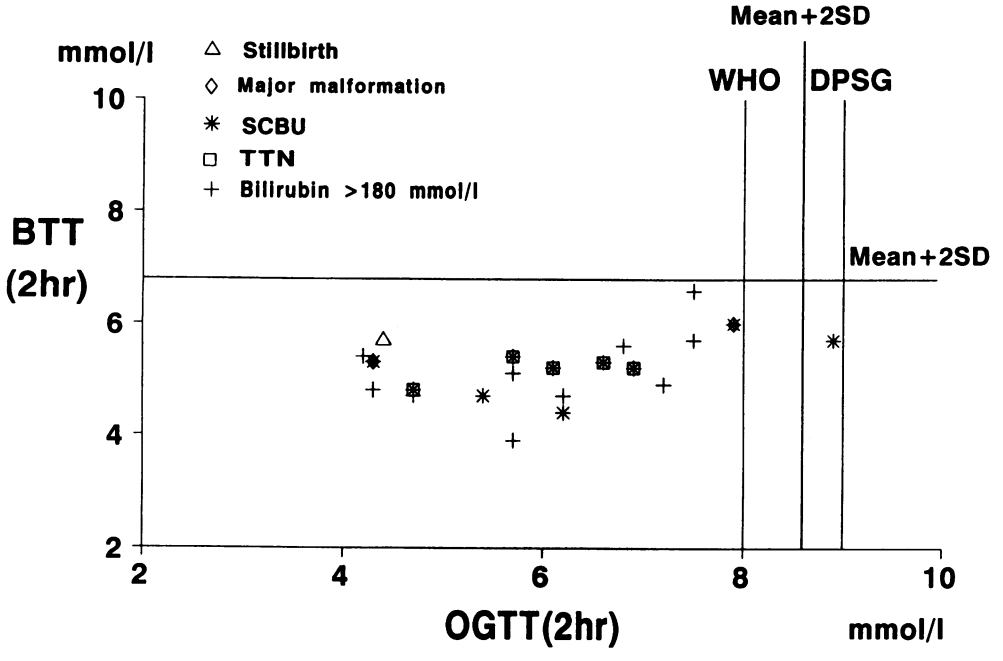

Fig 2. Fetal outcome in relation to the 2 hour glucose concentrations during the 75 g oral glucose tolerance test (OGTT) and breakfast tolerance test (BTT). Outcomes are stillbirth, major congenital malformation, admission to special care baby unit (SCBU), transient tachypnoea of the newborn (TTN), and serum bilirubin >180 mmol/l. The WHO and DPSG criteria are as defined in Figure 1.

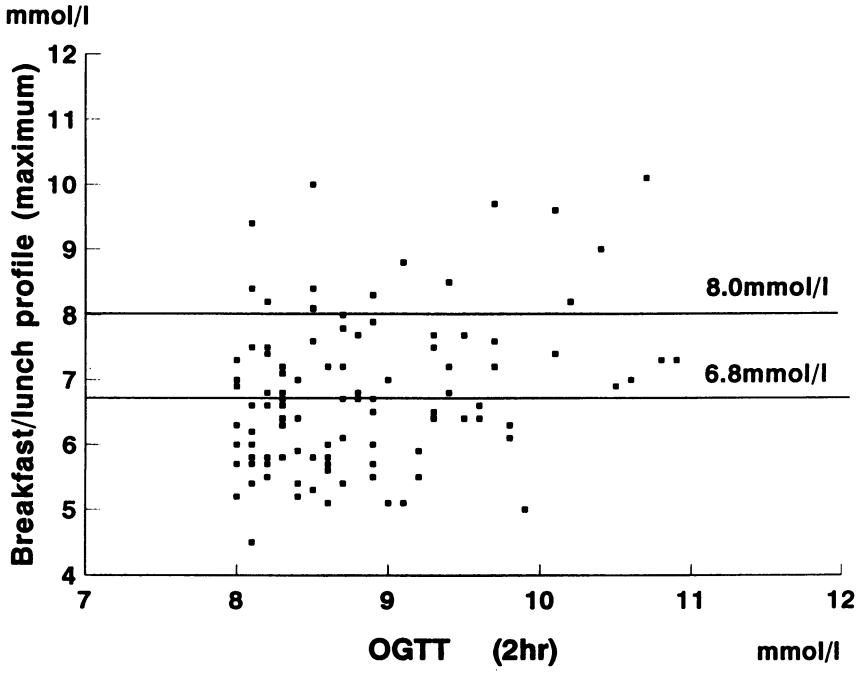

Fig 3. Comparison of the 2 hour plasma glucose concentration for the 75 g oral glucose tolerance test (OGTT) with the highest breakfast/lunch profile glucose: r=0.33. The lines at 8.0 mmol/l and 6.8 mmol/l represent the established abnormal and mean +2SD values for the breakfast tolerance test.

All five infants who had transient tachypnoea of the newborn, all 10 who had hyperbilirubinaemia, and all three who had a birthweight >4.5 kg had mothers in whom both tests were normal.

2) Impaired glucose tolerance pregnancies

The 2-hour post breakfast glucose was the highest of the four breakfast/lunch profile values in 69 (66%) of the women. As with the unselected pregnancies, there was no significant correlation between the two-hour OGTT glucose concentration and the two-hour post-breakfast value (r=0.35). There was also no significant correlation between the two hour OGTT glucose and the maximum concentration recorded during the breakfast/lunch profile (r=0.33). Comparing the two-hour OGTT glucose with the highest meal profile glucose (Figure 3), only 15 of the 104 mothers with impaired glucose tolerance had a meal profile glucose greater than 8.0 mmol/l, but 44 had a value greater than 6.8 mmol/l. These cut-off levels of 8.0 mmol/l and 6.8 mmol/l were respectively the established abnormal value and the mean +2SD glucose concentration for the breakfast tolerance test. There were no perinatal deaths in this group, and the only baby with a congenital malformation (hydronephrosis due to ureteric reflux) was born to a mother with a normal profile. Mean birthweights in those with maximum profile values above and below 8.0 mmol/l were not significantly different, 3634 g and 3706 g respectively.

DISCUSSION

There continues to be concern about the value of the OGTT in diagnosing hyperglycaemia in pregnancy. There is much logic in the concept that hyperglycaemia in response to the normal food intake of the mother is the only relevant clinical criterion. An OGTT which gives a large unphysiological load of glucose is a stress test, and the diagnosis of impaired or abnormal glucose tolerance is thus based on conditions not experienced in day to day life. Other medical disorders in pregnancy, such as hypertension, are diagnosed by observations made in the unstressed state. The study by Nelson-Piercy and Gale[6] in the North East Thames region of London showed very great variation in the screening protocols and interpretation used in a number of maternity units in the UK. If there is to be any logical development and ultimate agreement in this field, a structured approach to the diagnosis of hyperglycaemia in pregnancy will have to be followed.[7]

Whole day profiles of blood glucose in normal pregnancy and selected mothers known to have

gestational diabetes have been undertaken and do show consistent differences.[8] The post-prandial hyperglycaemia in gestational diabetes is reflected in a mild but consistently higher basal glucose level throughout the night.

A number of workers have studied the use of more physiological challenges. Hollingsworth used an isocaloric breakfast meal (400 Calorie) and also a 2000 Calorie 24 hour diet programme.[9] This defined that pregnant women with gestational diabetes mellitus (criteria of O'Sullivan et al[10]) had a delay in the release of insulin, but there was considerable heterogeneity, particularly in relation to obesity. The Aberdeen group have simplified the concept with a standardised prepacked formula meal given as a breakfast test containing 58 g carbohydrate and 453 Calories. They found the meal test to be readily accepted by pregnant women, and the plasma glucose response to be highly reproducible within subjects.[11] In unselected pregnancies they showed that the glycaemic response to this standardised breakfast test differed from that to a 75 g OGTT and related better to fetal birthweight percentile.[12] In the clinical field, Peterson and Jovanovic-Peterson have studied the glycaemic response by self-monitored blood glucose one hour after a series of meals in pregnancy, and found that the glucose response to a mixed meal in mothers with gestational diabetes is highly correlated with percentage carbohydrate in the meal, but varies greatly between individuals and between breakfast, lunch and dinner.[13]

In the present study we have identified normal values for a standard breakfast test which is closely related to the normal food for this Belfast population. The most relevant measurement in screening for hyperglycaemia appears to be a 2 hour post breakfast value >6.8 mmol/l (mean + 2 SD). There was a poor correlation between the results of the OGTT and the breakfast test when performed in the same pregnant women, one week apart in the third trimester. The question of whether one test is more appropriate than the other can only be answered by reference to measures of outcome in a large series of patients. In this small study, neither test was predictive of maternal morbidity or poor fetal outcome.

To investigate this further, we studied breakfast and lunch profiles in selected mothers who were identified to have impaired glucose tolerance by the WHO criteria. Less than half of these would have been classified as having an abnormal meal profile using the normal range established from the breakfast test. There was again no relationship between impaired glucose tolerance or abnormal meal profile, and maternal morbidity or fetal outcome. It has long been recognised that the glucose rise after the first meal of the day is the greatest and the results of the profiles confirmed that there is no value in continuing the test into the pre and post lunch period.

Our data are relevant to Northern European caucasian populations. The much greater prevalence of hyperglycaemia in pregnancy in other ethnic groups and in other parts of the world makes it desirable that these relationships between blood glucose responses to oral glucose and normal foodstuffs be investigated in more detail, so that the most appropriate diagnostic tests can be identified to detect hyperglycaemia and prevent the associated fetal morbidity.

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A 3 year audit of fine needle aspirates from a symptomatic breast clinic

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SUMMARY

A total of 2431 fine needle aspirates of symptomatic breast lumps was performed on 2096 patients over the last three years at the weekly head, neck and breast clinic at the Belfast City Hospital Trust. Diagnostic accuracy was achieved within the recommended standards although the "insufficient" rate was high at 31.8%. False negative and positive rates were low and the positive predictive value for malignancy was 99%. Excision biopsy for benign breast disease had decreased by almost a third during this period. Fine needle aspiration cytology is a highly accurate and cost- effective technique for the investigation of symptomatic breast lumps and results in significant savings.

INTRODUCTION

Fine needle aspiration cytology (FNAC) is now a well established investigative technique for the pre-operative diagnosis of breast lumps. It has gained wide acceptance due to its simplicity, high accuracy, tolerability and cost effectiveness. Complications following the procedure are rare. There has been a weekly FNAC service for the head, neck and breast clinic at the Belfast City Hospital since 1990. This audit covers the last three years. The aim is to assess our diagnostic accuracy and to determine if we have achieved the standards set by the National Health Service Breast Screening Programme (NHSBSP), which also apply to symptomatic cases.[1]

PATIENTS AND METHODS

Since August 1990, Histo/Cytopathology Consultants and trainees have been involved in the taking and interpretation of fine needle aspirates of symptomatic breast lumps. New patients and review cases are first seen by a consultant surgeon and his team at the weekly head, neck and breast clinic. Patients are first assessed clinically and referred to the aspiration team if appropriate. Aspirates are performed freehand with a 23-gauge needle and 20ml syringe mounted on a Cameco handle. The aspirates are air-dried and stained with Speedy-Diff (Clin-tech). The slides are assessed firstly for adequacy of material, and in some cases an immediate provisional diagnosis is given to the surgeon. Written reports on specimens are issued the next day and are grouped into five categories:

1. Insufficient or inadequate – if less than five groups of epithelium are obtained.
2. Benign – including cysts, inflammatory conditions and benign tumours.
3. Atypia - probably benign.
4. Suspicious of malignancy.
5. Unequivocally malignant.

RESULTS

Over the last three years 2096 patients were seen yielding 2431 aspirates, including bilateral and multiple lumps in some patients. Table I shows the diagnostic categories, biopsy rates and the ratio of malignant to benign surgical excisions for each year. The statistical analysis of the overall

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results is shown in Table II with suggested minimum values from the NHSBSP in parentheses. 341 patients underwent excision biopsy or definitive surgery. Correlation of the histological diagnosis and cytological results is shown in Table III. Forty-one patients with advanced carcinoma were not operated upon and were managed conservatively.

TABLE I

Year	*1993-4* *1*	*1994-5* *2*	*1995-6* *3*
No. of patients aspirated	653	777	666
Total No. of aspirates	753	922	756
Category 1	235 (31.2%)	315 (34.2%)	224 (29.6%)
2	454 (60.3%)	530 (57.5%)	466 (58.9%)
3	17 (2.2%)	30 (30.2%)	15 (1.9%)
4	11 (1.4%)	15 (1.6%)	13 (1.7%)
5	36 (4.8%)	32 (3.5%)	38 (5%)
Biopsy – Malignant (M)	31	33	44
– Benign (B)	92	78	63
– Total	123	111	107
Excision Rate	16.2%	12%	14.15%
M:B Ratio	1:2.9	1:2.4	1:1.3

TABLE II

Overall results of the three year audit with suggested minimum values in parentheses

Total number of patients seen	—	2096	
Total number of aspirates performed	—	2431	
Insufficient rate	—	31.8%	(<25%)
Absolute sensitivity	—	70.5%	(>60%)
Complete sensitivity	—	90.8%	(>80%)
Full specificity	—	63.7%	(>60%)
PPV (C5 diagnosis)	—	99.1%	(>95%)
False negative rate (excluding C1)	—	3.95%	(<5%)
False positive rate	—	0.7% (0%) *	(<1%)

* Malignant cytology not proven on biopsy

TABLE III

Category	No. of Aspirates (%)	No. Biopsied (%)	Biopsy Result		Histological Diagnosis
			Benign (%)	Malignant (%)	
1	774 (31.8)	77 (9.9)	69 (89)	8 (11)	4 ILC, 3 IDC, 1 TLC
2	1450 (60)	123 (8.5)	117 (95)	6 (5)	2 IDC, X 1 – TLC, MPHY, ICC, DCIS
3	62 (2.5)	47 (76)	42 (89)	5 (11)	3 IDC (R) 2 ILC (R)
4	39 (1.6)	29 (74)	4 (14)	25 (86)	2 FCD 1FA 1 ADH
5	106 (4.4)	65 (61)	1 (0.7)	64 (98)	1 FA

IDC – Infiltrating ductal carcinoma
ILC – Infiltrating lobular carcinoma
TLC – Tubulo-lobular carcinoma
MPHY – Malignant phyllodes tumour
ICC – Intracystic carcinoma
DCIS – Ductal carcinoma in situ
R – Recurrence
FCD – Fibrocystic disease
ADH – Atypical ductal hyperplasia
FA – Fibroadenoma

FALSE NEGATIVES AND POSITIVES

There was a total of 14 false negative cases including insufficient aspirates. These were due to sampling and interpretation error in equal proportions. Importantly, 13 of the 14 cases had either suspicious mammographic findings or were clinically worrying although one was thought to be benign both radiologically and clinically. In category 3, atypical changes in five cases were thought possibly to be related to post-surgical irradiation but these proved to be recurrent tumours in subsequent biopsies.

Four cases were regarded as suspicious of malignancy (category 4). However biopsy revealed one case of atypical ductal hyperplasia while the remainder were of florid fibrocystic breast disease. One case was diagnosed as unequivocally malignant on cytology (category 5) but lumpectomy and axillary sampling showed no tumour. Review of the aspirate confirmed malignant cells and the patient was referred for adjuvant radiotherapy.

DISCUSSION

Fine needle aspiration cytology has largely superseded the use of "Trucut" needle biopsy and frozen section examination in the investigation of symptomatic breast lumps. With the use of FNAC in our centre the number of biopsies of breast disease proven to be benign has fallen gradually from a ratio of almost three benign excisions to one malignant to near parity. Some women with symptomatic lumps however still opt for surgical intervention despite a benign cytology report. Conversely, elderly women with advanced cancers could be spared unnecessary biopsy following confirmation of the diagnosis by FNAC.

The audit shows our "insufficient" rate of 31.8% is higher than the recommended value. However, audit findings from various centres[2, 3] report an insufficient rate ranging from 20% to 46.8%. It is dependent on patient selection and the number and experience of aspirators. Ill-defined clinically benign lumps are usually acellular and are not suitable for FNAC. In some centres,[4] cases of low cellularity which remain inadequate on re-aspiration are not reported as inadequate. Many studies[5-7] have shown that best results are obtained in centres with a small selected group of well motivated aspirators be they pathologists or surgeons although controversy remains as to which of the two should best take the aspirate. In our opinion, where time and resources permit, the pathologist is better suited to perform the aspiration. Important information can be gleaned while needling a tumour such as its consistency, presence of grittiness and tendency to bleed which may help to correlate the cytological and clinical findings. With experience, an aspirator will

develop a "feel" for obtaining a representative sample.

Eleven percent of our insufficient cases proved to be malignant on biopsy follow-up. This compares relatively well with other reports[3] but an incidence of carcinoma in insufficient samples of as high as 32% has been reported.[8] The low specificity in our series is partly due to the high insufficient rate and partly to the low biopsy rate of benign cases. In certain centres the biopsy rate for benign cases was as high as 37%.[4]

False negative cases were due either to sampling or interpretation error. Sampling error was usually encountered with small deep seated tumours or in encysted carcinomas while the under diagnosis of low grade tumours such as infiltrating lobular, tubular, tubulolobular and Grade I infiltrating duct carcinomas is a well recognised pitfall especially in sparsely cellular aspirates.[9] Four of 29 cases (13.7%) were regarded as suspicious of malignancy; they were subsequently proven benign on histology. Matthews *et al*[10] reported 18.4% of the category 4 cases were as wrongly diagnosed. Certain benign lesions, particularly atypical hyperplasia, some florid fibrocystic disease and even fibroadenomas may have disconcerting cytological features. The positive predictive value for carcinoma however remains very high and to reduce both the false-negative and false-positive rates to a minimum a combined (triple) approach with clinical examination and radiological assessment is imperative. A "one-stop" breast clinic with facilities for immediate FNAC reporting offers the most efficient management of patients with symptomatic breast lumps and results in significant savings.

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Doctors' knowledge of post traumatic neurosis

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SUMMARY

Most studies which looked at the civil disturbances in Northern Ireland for the 25 years until the ceasefire declarations in late 1994 concluded that the impact on the psychological health of the population was insubstantial. In the study reported below doctors as a group were quite accurate in identifying the features of post traumatic stress disorder (P.T.S.D.) on a questionnaire but there is evidence to suggest that post traumatic neurosis has been under recognized in the clinical situation and, therefore, undertreated. Improving the accuracy with which doctors recognise psychiatric illness in general, and increased awareness of P.T.S.D. in particular, may well lead to increasing ability to diagnose the condition and thereby provide the individual with the opportunity for treatment.

INTRODUCTION

Northern Ireland was beset by civil disturbances for the 25 years until the ceasefire declarations in late 1994. During that time well over 3,000 people were killed and many times that number seriously injured. A number of studies have been carried out during the period of the civil disturbances to examine the effects that they have had on the mental health of the population. Lyons, who examined the number of referrals, hospitalization rates and suicide rates when the civil disorder first broke out in 1969, found no increase in more serious, i.e. psychotic types of psychiatric illness.[1,2] He felt that there was, however, some effect on the population, and called this an increase in "normal anxiety". There would appear to be some evidence especially in urban areas where civil violence occurs, of increases in tranquillizer consumption with the risks of dependence.[3,4] A community based study found that there was some negative relationship between the violence and an individual's psychological well-being.[5]

In a review Curran concluded that the violence has not resulted in any obvious increase in psychiatric morbidity.[6] He suggested a number of reasons as to why this might be: non reporting of illness, migration of the ill, denial of or habituation to the disturbances, a latency period, catharsis, improvement of those already ill and improved community cohesion. Overall Curran felt that there was a balance of effects with, on the one hand, a certain number of people experiencing psychological distress and, on the other, some gaining protection against psychiatric morbidity. Curran's own group, in a series of papers, reported on over 700 litigants.[7,8] They found that over 25% suffered from an anxiety state, 15% from a depressive neurosis and, using Diagnostic Statistical Manual (DSM-III-R) criteria, 23% from P.T.S.D. Just over 11% of the group were referred to psychiatric out-patients and a further 4.5% required in-patient psychiatric treatment. Comparison of the percentage of individuals diagnosed as ill with the number referred for specialist treatment would suggest that either the general practitioners felt confident enough to treat their patients themselves or that the illnesses were not sufficiently recognized, the latter a point suggested by Curran's own group.[7]

It is quite possible that, as postulated by Curran, much post traumatic psychiatric morbidity has not been reported and that there has, indeed, been a significant increase in psychological disturbance secondary to the Northern Ireland troubles. Many victims, in a state of post traumatic helplessness, may feel that nothing can be done. In addition, clinical experience has suggested that doctors on occasions have not referred individuals because they feel that their post traumatic reactions are

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understandable and not pathological and/or that treatment is either not indicated or ineffective. This paper examines the understanding doctors have of post traumatic neurosis.

METHOD

All general practitioners and Occupational Health Physicians within Northern Ireland were sent a questionnaire which included items with regard to demography and experience in post registration psychiatry, and checklists relating to knowledge of post traumatic neurosis. Additional comments were also welcomed. These results were analysed using The Statistical Package for the Social Sciences (SPSS).

RESULTS

Of 1005 questionnaires sent, 552 were returned (54.9%); 528 of 968 general practitioners replied (54.5%) as did 24 of 37 Occupational Health Physicians (64.8%). Not all respondents completed every section of the questionnaire although most sections were completed by over 99%. With regard to the efficacy of the different treatments and the features of P.T.S.D., there was a higher rate of non-completion, perhaps reflecting the absence of a "don't know" option, left out in order to increase the likelihood that a positive decision would be made. The rate of non-completion was highest for the proposed treatments (critical incident debriefing 14.1%, lithium 13.9%) and next highest for the different symptoms (elated mood 8%, diminished interest 3.3%). There were no significant differences between the two groups of doctors in terms of content of replies and the results presented are for those doctors, general practitioners and Occupational Health Physicians, who responded to each particular section of the questionnaire.

FREQUENCIES

Almost 25% of responses came from doctors working in Belfast, the major urban conurbation in Northern Ireland. Seventy five per cent were male. Eighty per cent were aged 31 to 50. Sixty per cent had no experience of psychiatry, 25% had six months' experience and the remainder had more extensive psychiatric experience. Sixty per cent had never attended a lecture on post traumatic neurosis. Ninety nine per cent felt the majority of psychological reactions to traumatic events were understandable. Ninety five per cent felt that such individuals required treatment usually/sometimes. Eighty eight per cent felt there were effective treatments for such individuals. The perceived effectiveness of different treatments as presented in the questionnaire is detailed in Table I.

Seventeen per cent of respondents said they were very aware of P.T.S.D., 60% quite aware and 23% only vaguely aware of the condition. In DSM-III-R, P.T.S.D. is diagnosed according to four criteria being fulfilled: a person is exposed to a threatening traumatic event which induces a severe emotional response (Criterion A); the event is persistently re-experienced e.g. nightmares, distressing intrusive memories (Criterion B); persistent avoidance of associated stimuli and numbing of general responsiveness e.g. loss of interest, feeling of detachment from others (Criterion C); hyperarousal e.g. sleep disturbance,

TABLE I

Doctors' perceived efficacy of treatments (percentages)

	very useful	*quite useful*	*not very useful*	*not at all useful*
Supportive psychotherapy	53.9	43.3	2.4	0.4
Critical incident debriefing	37.3	50.6	8.9	3.3
Cognitive-behavioural treatment	27.5	54.9	14.7	2.9
Anti-depressants	9.2	61.6	27.6	1.6
Phenothiazines	0.9	16.5	60.6	22.1
Lithium	0.0	3.1	30.0	66.9
E.C.T.	0.0	1.7	23.8	74.5

irritability, poor concentration (Criterion D). Respondents tended to recognize the features of P.T.S.D. as defined in DSM-III-R in the questionnaire, scoring highest for features associated with criterion D (sleep disturbance 99.8%), next highest for criterion B features (intrusive memories 99.2%) and then for criterion C features (emotional constriction 81%). Regarding other symptoms, 84% felt appetite disturbance was a feature of P.T.S.D., 38% disorientation, 37% delusions, 12% elated mood and 10% morbid jealousy. Fourteen per cent of respondents made further comments. The two most common types of comment were those about an individual doctor's own experience of the frequency, cause and treatment of P.T.S.D. and those that were critical with respect to the interface with the legal profession.

SIGNIFICANCE TESTING

The possible associations between the different variables were analysed by chi-squared testing. Female respondents (X 8.47: $p < .005$) and younger respondents (X 37.41: $p < .00001$) were more likely to have post-graduate experience in psychiatry. Females (X 5.96: $p < .05$) and younger respondents, particularly those under 40 years of age (X 14.66: $p < .005$), were more likely to believe that effective treatments were available. Females were significantly (X 5.14-7.91: $p < .05$) more likely to believe psychotherapy, cognitive therapy, critical incident debriefing and anti-depressants were effective and significantly (X 4.64: $p < .05$) less likely to believe phenothiazines to be effective. Females (X 7.12: $p < .01$) and those with experience in psychiatry (X 4.13: $p < .01$) were more likely to be interested in further education. Those who attended lectures on post traumatic neurosis were much more likely to be aware of P.T.S.D. (X 29.28: $p < .00001$). Examining other variables, e.g. younger respondents and recognition of features of P.T.S.D., did not reveal any significant differences. There were some isolated statistically significant results e.g. females were more likely (X 4.79: $p < .05$) to recognize anger as a feature of P.T.S.D. but these were not felt to contribute to the results overall.

FACTOR ANALYSIS

Factor analysis was carried out to examine the relationship, if any, between the different possible features of P.T.S.D. and other variables such as the respondents' acknowledged level of awareness of the condition or his/her experience of psychiatry among others. Using rotating factors, three underlying constructs were identified with regard to the possible features of P.T.S.D. (Table II). The items in factor 1 are features associated with criteria B and D of P.T.S.D. while the items in factor 3 are symptoms associated with criterion C. The items in factor 2 are not features of P.T.S.D. Level of awareness was indicated by multiple regression as being the best predictor of factor 1 (Beta = .248820). Level of awareness was also indicated by multiple regression as being the best predictor of factor 2 (Beta = – .185393) i.e. those who believed themselves to be aware of P.T.S.D. would have been less likely to incorrectly identify the items in factor 2 as being features of P.T.S.D. Experience in psychiatry, as against no experience, was indicated as being the best predictor of factor 3 (Beta = .226744). Multiple regression further indicated that the best predictor of a high awareness of P.T.S.D. was previous attendance at lectures on the subject (Beta = .301165).

DISCUSSION

A response rate of 55% for a postal survey can be considered a satisfactory response. Information received from the Central Services Agency, the overseer of general practitioners within the region, would indicate that the non responders do not differ in terms of sex or age. As an individual would be perhaps more inclined to complete a questionnaire if knowledgeable about the relevant subject, it is quite possible that the non responders have a lower level of knowledge with regard to post traumatic neurosis.

TABLE II

Factor Analysis

Factor 1	*Factor 2*	*Factor 3*
Intrusive recollections	Delusions	Diminished interest
Distressing dreams	Morbid jealousy	Emotional constriction
Sleep disturbance	Appetite disturbance	
Irritability	Elated mood	
Exaggerated startle	Disorientation	

The doctors who returned the questionnaire scored highly in recognizing the features of P.T.S.D. A sizeable number of respondents incorrectly felt that some of the other features were important manifestations of P.T.S.D. That 84% felt appetite disturbance was part of the condition is probably a reflection of respondents' awareness that appetite disturbance, like sleep disturbance, is a very common feature in many psychiatric illnesses. It is perhaps more surprising that over one third of respondents felt disorientation and delusions of persecution or reference were features of the condition. Again this might reflect a general awareness that such features occur in psychiatric illness. If this is the case then it may be that the high recognition level for the features of P.T.S.D. was to some extent a reflection of the fact that these were simply recognized as features of psychiatric illness in general rather than post traumatic neurosis in particular. However, the factor analysis demonstrated that those respondents who believed themselves to be more aware of P.T.S.D., or who were more experienced in psychiatry, were also more skilled at identifying the relevant symptoms.

The vast majority of respondents felt that, while most reactions to traumatic events were understandable, most of these individuals, nonetheless, required treatment. Responders in general, and female responders in particular, were also quite optimistic about the efficacy of certain treatments, and the manner in which they ranked the treatments by usefulness would probably be shared by most workers in the field,[9] with one important exception: Critical Incident Debriefing is a technique developed as a prophylactic intervention and is not particularly useful in the treatment of an established post traumatic neurosis. It is heartening to see so few respondents felt phenothiazines, lithium or ECT to be of much use. Was the particularly optimistic outlook female doctors had a reflection of the greater likelihood that they had post graduate experience in psychiatry and the greater interest in the field as suggested by their declared interest in further education? It is possible that some of the associations found in the statistical analysis were chance findings due to multiple testing.

Factor analysis revealed that awareness of P.T.S.D. was the main variable associated with an ability to distinguish between those features of P.T.S.D. which form criteria B and D of the syndrome and the other features of psychiatric illness. Almost one quarter of the respondents said they were only vaguely aware of the condition. This is not surprising given the fact that 60% had never attended a lecture on post traumatic neurosis and multiple regression indicated that attendance at lectures is the best predictor of awareness of P.T.S.D. What is perhaps surprising is how relatively few of the respondents have attended such lectures, given the recent interest worldwide in post traumatic neuroses, the civil disturbances in Northern Ireland and the amount of research done on the psychological sequelae to these disturbances.

Individual reactions to traumatic incidents can vary considerably. Some victims of trauma seem to cope very well without any psychological decompensation. Some individuals develop acute stress reactions which can cause considerable subjective distress but usually settle within days. Others experience adjustment reactions which can be similar in form to the acute stress reactions or, alternatively, predominantly composed of symptoms of anxiety or depression; these reactions can last for several weeks or a few months. A further group of trauma victims go on to develop phobic states, generalized anxiety states, depressive disorders or, more rarely, hysterical illnesses. A number of individuals subjected to trauma develop the condition known as P.T.S.D., of which the diagnostic criteria are listed earlier in this paper. The frequency of P.T.S.D. depends upon the nature of the trauma but it is usually not the most common post traumatic psychological reaction.

There is considerable literature worldwide which would suggest that the various types of post traumatic psychiatric morbidity are often not detected. Various reasons for this poor rate of detection have been postulated including the presence of avoidant symptoms,[10, 11, 12] symptoms being viewed as understandable[13] or attributed to other conditions,[14] the time of presentation and the manner in which the individual presents e.g. with somatic complaints,[15] and inability by doctors to diagnose post traumatic conditions.[16] Twenty of the first 64 attenders at the Stress Disorders Clinic, Lagan Valley Hospital, Lisburn had first been seen for the purposes of producing a medico-legal report (Daly, O. The Development of a Stress Disorders Clinic. Paper presented at the third ECOTS, Bergen, Norway, 1993). This figure corresponds closely with the experiences at the stress disorders clinic in Edinburgh where one

third of attenders were seen initially for medico-legal purposes (C. Freeman, personal communication). This view, that one of the best ways, into specialist services for individuals with post traumatic neurosis is via the medico-legal system, is supported by others (J. Gunn, personal communication). This would suggest that individuals seen by psychiatrists for non-treatment purposes were considered sufficiently unwell to be offered specialist treatment, an opinion that did not appear to be shared by the general practitioner. It is interesting to note in the present study, that of the two most common types of comment made by respondents, one was of a critical nature with respect to the interface with the legal profession. A doctor and a solicitor can clearly be involved with the same individual who has experienced psychological difficulties following trauma for very different reasons. While clear cut diagnoses are much favoured by the legal profession, clinical psychiatry is frequently much less exact and tensions can perhaps arise when medical practitioners resist pressures brought to bear upon them to try to fit the symptoms an individual has into a diagnostic rubric when this is inappropriate.[17]

While the doctors in the current study performed quite well in identifying features of P.T.S.D. on a questionnaire, identification of those same features in a short consultation during a busy surgery is perhaps a different matter. Other authors have previously shown the wide variation in the abilities of general practitioners and other health professionals to diagnose mental illness.[18, 19] Goldberg has described how a fairly brief programme of instruction can help doctors to recognize psychiatric illness with increased accuracy.[20] The present study has shown that attendance at lectures on post traumatic neuroses may lead to a higher level of awareness of P.T.S.D. among doctors, this awareness possibly being an important factor in helping to differentiate between signs and symptoms which are features of P.T.S.D. and those which are not. It is, of course, also possible that these links are not causal and that individuals with a good knowledge of P.T.S.D. attend lectures on the subject because of their prior interest.

In conclusion, while a survey of doctors has demonstrated that they are as a group quite accurate in identifying the features of P.T.S.D. on a questionnaire, there is evidence to suggest that, as has happened worldwide, post traumatic neuroses have been under-recognized clinically and, therefore, under-treated in Northern Ireland with many individuals experiencing the considerable distress these conditions can cause, perhaps avoidably. Training doctors to recognize psychiatric illness with increased accuracy may also help in the detection of post traumatic neuroses. In addition, it may well be that attendance at post graduate lectures on post traumatic neuroses or, indeed, other forms of education in this field will lead to better awareness of the conditions, better recognition of the features and, therefore, better opportunities to diagnose the conditions and, thereby, provide the individuals with the necessary treatment.

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Copies of the questionnaire can be obtained from the author on request.

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Anaesthesia for appendicectomy in childhood: a survey of practice in Northern Ireland

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SUMMARY

A postal questionnaire was sent to all members of the Northern Ireland Society of Anaesthetists to determine current practice in anaesthesia for children with acute appendicitis. Respondents were asked to describe their usual practice in such cases. They were also asked about the occurrence of complications due to the use of suxamethonium, and for their views on the use of rocuronium in such cases. Few major differences in anaesthetic technique were demonstrated. 74% of consultants and 84% of trainees always perform a rapid sequence induction for appendicectomy. However 15% of consultants do not feel that this is necessary. Only 6% of consultants and 6% of trainees would normally use rocuronium, with the majority still preferring suxamethonium. Only 28% of consultants and 20% of trainees see rocuronium as a possible alternative to suxamethonium in these cases, although others expressed increasing concern over the use of suxamethonium in children. There was wide variation in the type of intra-operative and post-operative analgesia prescribed, with less than one third of consultants and trainees using combinations of opioids, local anaesthetics and non-steroidal anti-inflammatory drugs.

INTRODUCTION

In 1993, following an increase in reports of cardiac arrest in children who had been given suxamethonium, the Food and Drug Administration (F.D.A.) in the United States advised the manufacturers of suxamethonium to alter their product information sheets to state that the drug was contraindicated for routine use in children and adolescents. This led to much heated debate in the anaesthetic literature both in North America and in Europe. The F.D.A's guideline has since been revoked, but in the U. S. the drug still carries a caution against its routine use in children.

In one month in Coleraine hospital one case of malignant hyperthermia and one of masseter muscle spasm were reported in children who had been given suxamethonium prior to appendicectomy. As a newer muscle relaxant, rocuronium bromide, is available which may allow rapid and safe control of the airway without the use of suxamethonium, I decided to survey the practice of my colleagues in cases of acute appendicitis, with particular interest in their use of suxamethonium.

METHODS

In July 1995 an anonymous questionnaire was sent to 188 members of the Northern Ireland Society of Anaesthetists (119 consultants and career grades, 69 anaesthetists in training). Respondents were asked to indicate their grade and number of years' experience, and to describe their usual anaesthetic management of a child with acute appendicitis. Included were questions on pre-operative fasting, pre-medication, induction and maintenance agents, airway management, intra-operative and post-operative analgesia.

Respondents were also asked whether they had witnessed any adverse effects due to the use of suxamethonium, and whether they felt that rocuronium is a suitable alternative in appendicectomies.

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RESULTS

Replies were received from 82 consultants and 35 trainees giving an overall response rate of 62%.

Fifty-four consultants (66%) and 17 trainees (49%) insist on a period of fasting prior to surgery, with times quoted varying from 2 to 8 hours. Apart from analgesia and EMLA cream, pre-medication is rarely prescribed.

Thiopentone is the most commonly used induction agent, favoured by 50 consultants (61%) and 27 trainees (77%). Propofol is the only other commonly used agent. Maintenance of anaesthesia is almost exclusively by volatile agent, with halothane and isoflurane used almost equally. Nine consultants (11%) and two trainees (6%) use enflurane, while one trainee uses a propofol infusion. All respondents intubate children for appendicectomy. Sixty-one consultants (74%) and 30 trainees (86%) always perform some type of rapid induction and intubation, although this is not universal. Some anaesthetists may or may not perform rapid sequence induction, depending on the state of each individual patient, while others never do.

Sixty-four consultants (78%) and 31 trainees (87%) normally use suxamethonium for intubation. Five consultants (6%) and two trainees (6%) use rocuronium, with the remainder using other non-depolarizing relaxants.

Intra-operatively, almost half of consultants who replied give opioid analgesia only. In contrast, trainees tend to use combinations of analgesic drugs more often. Post-operatively however, the differences in the two groups are much less marked, with only a minority of trainees continuing to prescribe non-steroidal anti-inflammatory drugs (NSAIDs) in the post-operative period.

Regarding adverse effects related to the use of suxamethonium in their practice generally, 47 consultants (57%) reported witnessing problems. Prolonged duration of action of the drug ("Scoline apnoea") was the most common (46 cases reported) with malignant hyperthermia next (11 cases). Two consultants reported cardiac arrests. Fewer trainees (11, 31%) have so far seen problems with suxamethonium administration, with the same two events being most commonly reported.

Only 23 consultants (28%) and 7 trainees (20%) feel that rocuronium is a suitable alternative to suxamethonium for children with acute appendicitis. Of the majority that do not, the commonest reason given was lack of experience with the drug, stated by 43 consultants (52%) and nine trainees (26%). Speed of onset and duration of action, especially if faced with a failed intubation, were also common reasons given. When asked for any other comments, eight consultants and five trainees expressed increased concern over the use of suxamethonium, while five consultants commented strongly in favour of its continued use.

DISCUSSION

Appendicectomy is one of the commonest operations in developed countries, particularly in patients 10-19 years of age.[1] Most anaesthetists will be involved in many such cases during their careers. Traditionally it has been taught that because of the risk of aspiration of gastric contents, rapid sequence induction using suxamethonium is the technique of choice in such cases. This is adhered to by 86% of trainee respondents, but by rather fewer consultants (74%). Children with acute appendicitis have usually been fasting for many hours before surgery, and may have been vomiting. Because of this it may be that the remaining 26% of consultants feel that aspiration of gastric contents is unlikely, and therefore that rapid sequence induction is not always necessary.

The adverse effects associated with suxamethonium are well known, and include asystole, brady-arrhythmias, hyperkalaemia, masseter spasm, malignant hyperthermia and prolonged muscle relaxation. Because of these, some authors have suggested that the routine use of the drug in children be re-evaluated.[2] Of particular concern to anaesthetists are the problems which arise if suxamethonium is given to children with undiagnosed or sub-clinical myopathies.[3] In the past the rare but serious problems with suxamethonium have been outweighed by the need for rapid airway control. The availability of rocuronium bromide may now, however, provide an alternative to the use of suxamethonium.

Rocuronium bromide is a new non-depolarizing muscle relaxant which has been generally available since 1994. It is distinguished from other similar drugs chiefly by its rapid onset of action. Some of the pharmacological properties

TABLE

Pharmacological properties and adverse effects of suxamethonium and rocuronium

	Suxamethonium	*Rocuronium*
Dose	0.5-2mg/kg	0.6mg/kg
Onset of action	30-45 secs.	60 secs.
Duration	3-5 min.	30-40 min.
Elimination	Metabolism by plasma Pseudocholinesterase[1]	Biliary and renal, largely unchanged
Trigger for malignant hyperthermia[2]	Yes	No[3]
Effect on heart rate	Bradycardia[4]	Tachycardia[5]
Myalgia	Yes	No
Effect in children	Increased dose required	More rapid onset
Anaphylactic reactions	Yes	Very rare
Serum electrolytes	Raises potassium[6]	No effect
Intra-ocular/intra-cranial pressure	Raised	No effect

[1] caution with atypical pseudocholinesterase.

[2] Malignant hyperthermia.

[3] in animal studies.

[4] especially with second dose.

[5] with doses >0.9mg/kg.

[6] caution with burns, renal failure, paraplegia, traumatic muscle denervation.

and adverse effects of both rocuronium and suxatnethonium are shown the Table.

It has been reported that at a dose of 0.6 mg.kg[1] rocuronium produces acceptable intubating conditions 60 seconds after administration.[4] Clinical duration of blockade (time to 25% recovery of twitch height) at this dose is reported to be 30 minutes.[5] Thus rapid-onset neuromuscular blockade of intermediate duration can be achieved without exposing children to the rare but potentially lethal complications of suxamethonium. The major drawback of rocuronium is its duration of action if the patient is impossible to intubate. The incidence of difficult intubation is unknown, although in the general population a figure of 1.5 % has been reported.[6] A recent paper showed that of all reported difficult intubations, 33% were not anticipated, and 20% proved impossible to intubate.[7] This would give an incidence of failed intubation of 3:1000 in the general population, which is similar to the incidence of some of the adverse effects of suxamethonium. An anticipated difficult intubation would of course be a contraindication to rocuronium, but it could be argued that it would also be a contraindication to suxamethonium. Despite this only 28% of consultants and 20% of trainees feel that the use of rocuronium is acceptable in children with acute appendicitis. Perhaps greater experience with the drug will resolve this apparent discrepancy between published research and clinical practice.

It has been shown that combinations of different types of analgesic drugs are highly effective in relieving post-operative pain.[8] In particular, the value of NSAIDs is well documented, and it would appear that they can be given for up to one

week to otherwise healthy patients with no significant incidence of adverse effects.[9] This view is held by the regional centre for paediatric anaesthesia in Northern Ireland, who strongly advocate the use of analgesic regimens combining opioids, NSAIDs and local anaesthetics wherever possible. Presumably because they have passed through this centre recently, more trainees than consultants use such a regimen intra-operatively (83% vs. 51%). It is surprising, therefore, that post-operatively the balance changes, with only 25% of trainees prescribing NSAIDs in addition to opioids, compared with 32% of consultants. Both these figures are, however, too low to suggest that children are receiving the best possible pain relief after these operations.

Overall it would appear that anaesthetists in Northern Ireland practise a safe if traditional technique for children undergoing appendicectomy. The controversy over the safety of suxamethonium has not swayed most anaesthetists from the opinion that it is still the safest drug to obtain rapid airway control.

Anaesthetists in training tend to use more aggressive analgesic regimens intra-operatively. Post-operatively many anaesthetists could do more to provide better pain relief.

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Change in the use of and attitude to peak flow measurement among general practitioners in Northern Ireland between 1989 and 1994

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SUMMARY

In 1994 we repeated a study first performed in 1989 to assess the change in general practitioners' use of and attitudes to peak flow measurement. Of 232 general practitioners surveyed, 199 (86%) and 192 (83%) responded in 1989 and 1994 respectively. The percentage who reported having patients using domiciliary peak flow monitoring rose from 58.3 (95% confidence limits 51.4 to 65.2)% to 97.9 (95.9 to 99.9)%. The percentage who reported 'usually' using peak flow measurements for the diagnosis and management of asthma rose from 81.9 (76.5 to 87.3)% to 93.2 (89.6 to 96.8)% and from 83.3 (78.1 to 88.5)% to 95.8 (92.9 to 98.7)% respectively. An unchanged proportion took peak flow meters on house calls. General practitioners have become more aware of the potential of peak flow measurements but are still unlikely to have a meter available to assess patients seen at home. They are therefore likely to be ill-equipped to manage acute exacerbations of asthma in this setting.

INTRODUCTION

Peak flow meters became available by National Health Service prescription in 1990. This was accompanied by considerable discussion of peak flow monitoring in the medical press. The British Thoracic Society included a firm recommendation for their use in its guidelines on the management of asthma as well as emphasising the importance of peak flow measurements for the assessment of acute asthma exacerbations.[1]

In 1989, a survey of a one in four sample of general practitioners in Northern Ireland showed that almost all had access to a peak flow meter and many were using them for the diagnosis and management of asthma.[2] Almost 60% of the sample had at least one patient using domiciliary peak flow monitoring although few practitioners took peak flow meters on house calls.[2] This survey has been repeated to determine whether these general practitioners' attitudes to and use of peak flow meters have changed between 1989 and 1994.

METHODS

The 1989 study was based on a one in four random sample of all general practitioners on the General Medical Services (GMS) list for Northern Ireland at the end of March 1989. The same general practitioners were surveyed in 1994 but those who were no longer on the list were replaced by a randomly chosen doctor practising from the same address. They were sent the questionnaire with two postal reminders to non-responders at four weekly intervals in late 1993 and early 1994. The questionnaire was initially tested amongst general practitioners in a large Belfast health centre.

The data have been analysed using *SAS* and *Arcus Pro-stat*. Responses have been converted into dichotomous variables ('yes' and 'sometimes/no' or 'very useful/useful' and 'of some use/of no use') and confidence limits for all responses have been calculated by the method of Armitage and Berry.[3] Exact confidence limits and P values for

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the change in paired responses have been calculated by the method described by Liddell.[4]

RESULTS

The original survey population was 232 general practitioners. One hundred and ninety nine (86%) were available for re-survey in 1994 and 33 replacements were identified. In 1989, 199 (86%) responded after one postal reminder and in 1994 192 (83%) responded after two postal reminders. Twenty three of the original respondents had left the GMS list by 1994 leaving a maximum of 176 possible pairs of responses of which 148 (84%) were obtained. 82% of respondents were male in 1989 and 79% in 1994. 94% and 90% of respondents were full-time general practitioners in 1989 and 1994 respectively.

General practitioners continue to report that they use peak flow meters more for the management and diagnosis of asthma than for chronic obstructive airways disease, and use them equally for the diagnosis and management of asthma (Table I). Although their reported use of the meters for diagnosis and management of chronic obstructive airways disease has not changed, it has increased for asthma (Table I). From the paired comparison, the likelihood of a respondent changing practice to 'usually' using peak flow meters for the diagnosis of asthma was 3.7 (95% confidence limits 1.2 to 15.5) and 5.7 1.6 to 30.2) for asthma management.

In 1989, 58.3 (95% confidence limits 51.4 to 65.2)% of practitioners reported that they had at least one patient who was using domiciliary peak flow monitoring and by 1994 this had risen to 97.9 (95.9 to 99.9)%, an increase of 39.6 (32.5-46.7)%. Respondents' estimates of the number of asthmatic patients using peak flow monitoring rose from a median (inter-quartile range) of 5 (2 to 10) to 30 (5 to 50) with a seven-fold increase in their estimate of the total number using peak flow meters at home.

Table II shows practitioners' attitudes to the usefulness of peak flow meters when used in the consulting room, and by patients for domiciliary monitoring. Most now feel that peak flow measurements in the consulting room are either 'very useful' or 'useful' for the diagnosis and management of asthma. The paired comparison showed that the likelihood of a respondent changing his/her opinion in 1989 that peak flow meters were of 'some use' or 'no use' for the diagnosis of asthma in the consulting room to their being 'very useful' or 'useful' in 1994 was 3 (95% confidence limits 1.04 to 10.6). The probability of a similar change in their opinion of the usefulness of peak flow meters for the

TABLE I

Percentages (95% confidence limits) of respondents who usually used peak flow meters in diagnosis and management of asthma and chronic obstructive airways disease (COAD) in 1989 and 1994

	ALL RESPONDENTS			
	1989		1994	
	n	% (95% Confidence Limits)	n	% (95% Confidence Limits)
Peak flow meters 'usually' used in the				
A. Diagnosis of:				
Asthma	199	81.9 (76.5–87.3)	190	93.2 (89.6–96.8)
COAD	189	68.1 (62.1–75.4)	187	78.1 (72.1–84.1)
B. Management of:				
Asthma	198	83.3 (78.1–88.5)	189	95.8 (92.9–98.7)
COAD	185	61.1 (54.0–68.2)	185	69.2 (62.5–75.8)

TABLE II

Percentage (95% confidence limits) of respondents who felt that peak flow measurements were 'very useful' or 'useful' in the consulting room and the patient's home for the diagnosis and management of asthma

	ALL RESPONDENTS			
	1989		1994	
	n	% (95% Confidence Limits)	n	% (95% Confidence Limits)
Used in consulting room for:				
Asthma diagnosis	199	86.0 (81.2–90.8)	191	94.7 (91.5–97.9)
Asthma management	198	89.4 (85.1–93.7)	190	96.4 (93.7–99.1)
Used in patients' home for:				
Asthma diagnosis	198	63.6 (56.9–70.3)	191	74.9 (68.2–80.6)
Asthma management	198	78.8 (73.1–84.5)	190	85.8 (80.7–90.9)

management of asthma in the consulting rooms was 4.3 (95% confidence limits 1.2 to 23.1). Similar numbers of practitioners perceive the meters to be useful for the diagnosis and management of asthma in the consulting room but more perceive that domiciliary monitoring is more useful for management than diagnosis. Similarly, more practitioners perceive that peak flow meters are more useful when used in the consulting room than in the patient's home.

We have reported elsewhere[5] that an unchanged minority of practitioners (31.8 (25.2-38.3)% in 1989 and 34.6 (27.8-41.4)%) in 1994 reported that they usually took peak flow meters on home visits.

DISCUSSION

General practitioners have an important role in the diagnosis and management of asthma.[1] They will see most patients at their initial presentation, provide total care for the majority and make decisions on both acute and elective referral to secondary services for an important minority. Each of these aspects should be optimised. In the past however there have been significant delays in the diagnosis of asthma by general practitioners.[6] Similarly, the accuracy of clinicians' subjective assessments of asthma is poor[7,8] and patients who die of asthma are less likely to have had their peak flow measured in their final illness than controls who suffered a severe asthmatic exacerbation.[9,10] General practitioners therefore have to avail themselves of appropriate diagnostic and management aids to optimise asthma care.

Peak flow measurements may reduce diagnostic delay and improve decision-making in asthma by providing an objective assessment of air flow and hence an opportunity to identify the airflow variability which is pathognomonic of asthma and to objectively assess its severity. Although the role of peak flow measurements in the management of asthma has long been discussed there is little objective evidence to support the adoption of widespread peak flow monitoring by patients [11,12,13,14] but monitoring may have a role to play in its diagnosis.[15] Repeating the 1989 survey provided a unique opportunity to assess change in attitudes of general practitioners in Northern Ireland towards peak flow measurements during a period of considerable professional interest in the topic.

More than 90% of general practitioners report that they now use peak flow measurements for both the diagnosis and management of asthma. This, in conjunction with the almost universal possession of nebulizers by practices in Northern Ireland,[5] suggests that asthma care should have improved. This may be reflected in decreased diagnostic delay and increased diagnostic

accuracy, more accurate assessment of asthmatic exacerbations and the delivery of prompt and effective treatment. Although general practitioners' perception of the usefulness of domiciliary peak flow monitoring of asthma has not changed, almost all have some patients who are using the technique. Indeed, there has been a seven-fold increase in their estimate of the number of patients using domiciliary peak flow monitoring. This may reflect patient pressure since respondents' perceptions of its usefulness have not changed.

The majority of acute asthmatic exacerbations will occur outside routine general practice consulting hours.[16] It is therefore important that practitioners have peak flow meters available when working out-of-hours so that they can objectively assess the severity of acute asthma exacerbations. Unfortunately there has been no increase in the number who report taking peak flow meters on home visits, which will include most out-of-hours consultations. Thus many will be unable to objectively assess asthma at this time. Future education of general practitioners should therefore address this issue.

These data need to be interpreted with caution. They may represent a socially acceptable response set with an apparent increase in use of peak flow meters because of increased awareness by general practitioners of "how" they should answer. This is unlikely because there was no reported change in the use of peak flow meters for the care of chronic obstructive airways disease, nor any increase in the proportion of general practitioners who claimed that they take peak flow meters on home visit, which would have been expected with a response bias. We did not define peak flow assisted management and diagnosis for the original survey and, as we wished to measure change, could not do so for the repeat study. The data represents what general practitioners believe that they do and may therefore represent an overestimate of ineffective activity. Nevertheless this data demonstrates an increased awareness of the potential of peak flow measurements among general practitioners in Northern Ireland which, although it cannot be directly attributed to any single intervention, represents important changes. It is interesting that the unproven intervention of routine domiciliary peak flow monitoring has not gained increased acceptance although most practitioners have patients using it. The potential for using domiciliary peak flow records for the diagnosis of asthma needs to be explored and, if found useful, its use could be increased. Finally, more general practitioners should take peak flow meters with them on house calls so that they have the means to objectively assess acute asthma exacerbations when they are encountered.

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Health and Education – the Metabolism of a Teaching Hospital

Welcome to the third year clinical students

Annual Oration at the opening of the 1996-1997 teaching session,

Royal Victoria Hospital, Belfast, 3rd October 1996

David R Hadden

It is my pleasure to welcome you formally as clinical medical students at the Royal Victoria Hospital. All of you already will have been here long enough to realise that the successful metabolism of this hospital depends in large part on the integrative action of the main corridor. As you walk down the corridor you will meet your friends, and recognise all the different members of the hospital staff as they go about their business. At the near end of the corridor is the Good Samaritan window, which was given to the old Belfast Royal Hospital in 1888 by Sir William Whitla (Fig. 1).

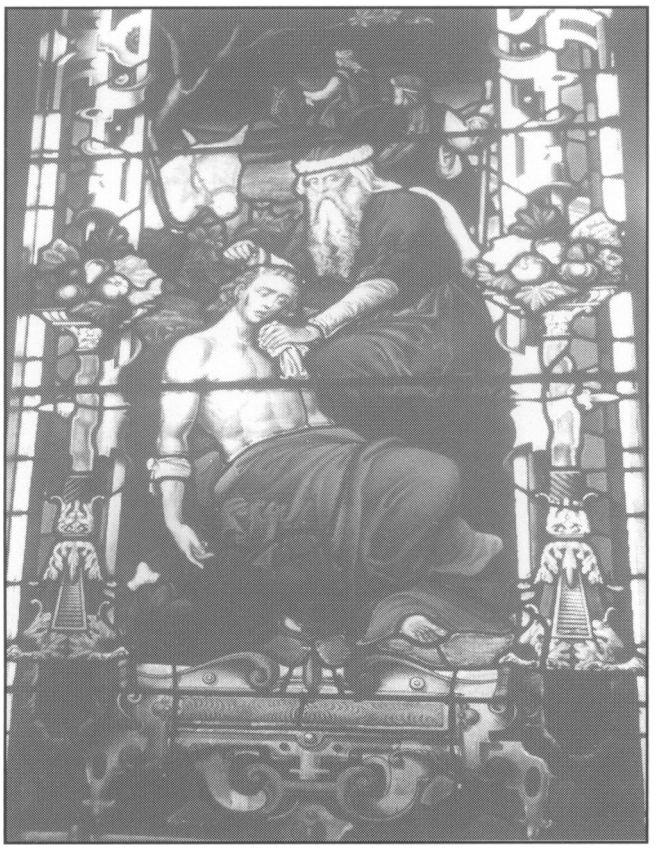

Fig 1. The Good Samaritan (detail).

You will know the story, but if you look on either side of the stained glass window in the centre you will see also the coats of arms of the several university establishments which have been responsible for the academic aspects of medical student training in Belfast since 1849. We will come back to that later. In some ways this window represents the two aspects of a teaching hospital that I want to talk about: the Good Samaritan representing the healer and health; the universities representing education.

My topics include a very brief view of the history of this hospital, and that of course will be dealt with in very much greater detail when the bicentenary takes place next year. I want to look at the politics of health and education. I want to discuss the people who work in the hospital, and the money that makes it tick. And finally I want to discuss your role as students in the hospital and indicate how important you all are in the actual metabolism of this institution.

It starts a long time ago. If you go to the top of Frederick Street in Belfast you will see an elegant building which was built in 1774 as both a poor house and an infirmary. Soon the need for dispensing medicines to the poor became clear, and in 1792 a general dispensary was opened in the basement, which provided a service rather like an outpatient department or a dispensing doctors practice for the sick poor.

Very soon after that a lying-in hospital for maternity cases was opened, but it was not until

Royal Victoria Hospital, Belfast BT12 6BA.

David R Hadden, MD, FRCPEd, FRCP(Lond), Consultant Physician, Sir George E Clark Metabolic Unit, and Honorary Professor of Endocrinology, The Queen's University of Belfast.

1797, because of the ongoing serious recurrent epidemics of fever in the rapidly growing town of Belfast that a general hospital was established. This was simply an obligation recognised by some of the doctors working in the town, that there was a need for a place where people sick of a fever could be isolated. So they rented a small house in a street called Factory Row, and this was the beginning of the present Royal Victoria Hospital. In 1797 it was called 'The Belfast Dispensary and Fever Hospital'.

The Belfast Charitable Society has sometimes been thought to be the first hospital in Belfast and in some ways it was. In the minute books for 1774 it is recorded that they provided seven beds for the sick, but they also had four double beds for sturdy beggars, 22 double beds for the poor, and four single beds for vagrants. It is probable that none of those beds was intended for people who were sick of fever. If you try to find Factory Row today you will not be successful, but by looking at the old maps and recognising that Royal Avenue was later built across some very small streets in the old part of Belfast, it is possible to find Berry Street which was the site of this first Belfast Fever Hospital was. It was somewhere in or around what is now Castle Court.

The hospital was moderately successful. It was certainly needed. There is very little known about it except what is recorded by Dr Andrew Malcolm in his early history, but it is clear that within two years it had to close. It had to close because there was not enough money to keep it going, because the people who came to it were not able to pay, and the citizens of Belfast did not subscribe sufficient money to support it. But whatever happened, within another two years, because of the ongoing epidemics of fever it was necessary to re-open the hospital – this time in three houses beside each other on the other side of Smithfield in West Street, at the back of the Castle Court car park. One of the few facts known about that hospital is that the average patient stayed for 40 days – much longer than they do now – at a cost of nine old pennies (4p) per day.

That Fever Hospital in West Street continued and must have been reasonably successful because by 1815 the citizens of Belfast recognised that they really did need a proper hospital, and subscribed and built a very fine building in Frederick Street just down the road from the Charitable Society. The foundation stone was laid in 1815 and the hospital was opened as The Belfast General Hospital in 1817. Unfortunately, the foundation stone, which was moved to this site when the hospital was ultimately vacated, has been lost. Inscribed upon it was *'Hoc nosocomium aegrotis et arti medicii sacrum . . .'* – 'This hospital to the sick and to the art of medicine is sacred'; at that early time it was recognised that the hospital had a function not only for looking after the sick but also for teaching the art of medicine.

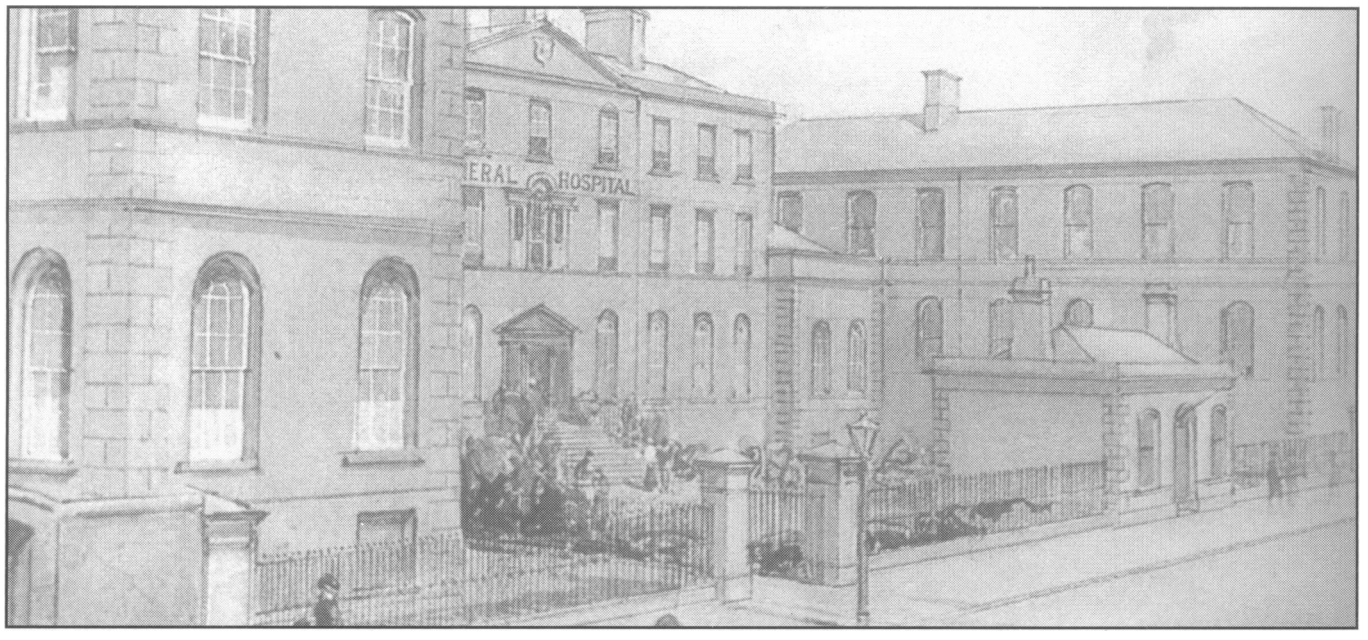

Fig 2. Painting of the Belfast General Hospital, Frederick Street, as it was about 1890. (Frank McKelvey, 1926: from the original in the Ulster Museum Collection, reproduced in 'The Seeds of Time', RS Allison.)

There is a very fine picture of the hospital in its heyday painted by the famous Belfast artist Frank McKelvey, which shows it as an elegant buff-coloured building (Fig. 2). It is unclear whether that was really what it looked like because McKelvey actually painted this picture 25 years after the hospital closed down; the only part of the painting now still visible is the little green door on the left which actually opened into the Friend's Meeting House which was always next door to the hospital. But you can see a fine three bay window above the front door and perhaps that was where the Good Samaritan really started. Frederick Street today is sad, and there is very little to see except for a carpark, but the Charitable Society is still there at the top end of the street.

The medical staff in the Belfast General Hospital were keen to encourage medical students and on 16th January 1820 they passed a resolution "that it was safe and proper to admit pupils to this hospital", the first registered pupil being a certain W Bingham who attended and walked the wards in 1821. Dr Bingham's career has been followed in small part and he subsequently became a family doctor in Donaghadee. There is no formal evidence of any actual teaching at the Belfast General Hospital until a lecture was held on 3rd June 1827 given by the most famous doctor in Belfast at the time, Dr James McDonnell. He was famous because he had been active in a number of intellectual organisations in Belfast, and was intimately involved in the Belfast Academical Institution which we now know as Inst. Dr James McDonnell was aged 65 at the time he gave the first lecture, and this oration today is the direct successor, 169 years later. It is not clear that a formal lecture was actually given every year, and the records suggest that exactly 100 years ago, in 1896, the lecture was not given. Dr James McDonnell is a name we all revere, and when you go today to the Board Room in the King Edward Building you will see his bust on the right-hand side of the door as you go in. That is a bronze copy of the fine marble original which is still in the Ulster Museum on the Stranmillis Road.

Now we turn to the politics of the situation and I refer to two men whom you may not know. One of them is our 'Minister of Health' (Mr Malcolm Moss, Member of Parliament for Cambridgeshire NE and Parliamentary Under-Secretary of State with responsibility for Health and Social Services in Northern Ireland – and also for the Environment), and the other is the 'Minister of Education' (Michael Ancram, Earl of Ancram in the Scottish peerage, Member of Parliament for Devizes, Minister of State in the Northern Ireland Office with responsibility for Education – and also Political Development, Sport, the Arts, and Community Relations). These two are presently responsible for the Government funding of health and education in this province. There is a division between health and education, not entirely confined to Government departments. There is a also a certain division between hospital and university. There is a division in whether you are considered as an apprentice or as a student; both of course are correct. We, in the teaching hospital, like to think of you in many ways as an apprentice, as you are when you attend the practice of the family doctor, although the academic approach to the medical student is rather different.

When Dr James McDonnell and his colleagues started the first medical school in Belfast at the Academical Institution in 1835 they were concerned about all of the proper academic arrangements for the teaching of medical students, which were not necessarily available within the Belfast General Hospital, some distance away in Frederick Street. The plan of the Belfast General Hospital clearly shows that there was a lecture theatre. As you went through the steps and up into the main floor of the building you found the house surgeon's room on the right of the hall and a second room for the house surgeon on the left, which conveniently opened into the housekeeper's room! But if you went down the corridor just beyond that you found a rather fine tiered lecture theatre just beside the rooms for the Belfast Medical Society. There were another two floors above where most of the patients were accommodated.

Lectures and demonstrations were obviously being given, and there is evidence in 1856 that lectures on clinical medicine would be delivered on Mondays and Thursdays, and on clinical surgery on Wednesdays and Saturdays, and that students paid a fee directly for these lectures. The first year four guineas, the second year three guineas, the third year two guineas, and if they were unfortunate enough to have failed their examinations after that the staff were generous enough to allow further attendance free. These payments were made to the medical staff, not to the hospital, and were certainly not payments to the University. That tradition continued for at least 100 years and many of the older members of

Fig 3. A class in the old surgical extern (now the Sir Ian Fraser Lecture Theatre) of the Royal Victoria Hospital, 1959. Professor Harold Rodgers, Professor of Surgery, in the front row.

staff in this audience will remember having their hospital certificates signed by the honorary secretary of the Medical Staff Committee. These certificates then had to be presented to the University to show that one had attended the clinical practice of the teaching hospital (Fig. 3).

Medical students have always been an essential part of the life of a hospital. Although first admitted to the Belfast General Hospital in 1820, it took a long time for them to be accepted in the other hospitals in this city. The Mater Infirmorum Hospital, which was formally opened in 1889, was not formally recognised for the attendance of medical students until 1909, and the Belfast Union Infirmary which had been built in 1857 was not actually recognised for the teaching of medical students until 1924. That was an extraordinarily long delay which was entirely due to the intransigence of the Poor Law Commissioners who ran that hospital. In 1884, Dr William Whitla at just about the same time as he was donating the Good Samaritan window to the Belfast General Hospital, did a survey of the numbers of beds in the different hospitals. The Belfast General Hospital had 180, the Mater Infirmorum, still small, had 14 beds, while the Union Hospital and Infirmary had 1,590 beds, but no medical students.

In 1902, at the time that the new hospital was being built on the Grosvenor Road, the staff recorded in the minute book that "while the Royal Victoria Hospital is an integral part of the Belfast Medical School, there is at present no definite official connection between the Hospital and the College. The staff are of the opinion that in the interests of the School it is desirable that a closer union should be established by the formation of a joint Board". Nearly 100 years after that minute there still is no joint board between the hospital and the University – a small committee which meets irregularly is no substitute.

A very famous teacher in this medical school and hospital was Professor Sir John Biggart. He is widely credited with the unusual arrangements that exist for employment of University staff within the hospitals in Northern Ireland. The concept of a 'joint appointment' was drawn up by the Northern Ireland Hospitals Authority and The Queen's University of Belfast in 1949 when the National Health Service was very new. They suggested that the arrangements being developed in Great Britain "were not regarded as the best possible procedure" – perhaps a sign of people in the North of Ireland wishing to be different for the sake of individualism. It has taken a long time to recognise that the arrangements for academic appointments in hospitals in other parts of the United Kingdom are quite sensible and that there are practical difficulties in our joint appointment system. Many people have looked at this problem and I hope that we will continue to do so. Professor, now Sir Peter Froggatt, just before he

became Vice-Chancellor of the University, got the balance right when he said that "medical education, like truth, is indivisible, that hospital and college must co-operate, that tact and unity of purpose and true partnership will triumph".

Forty years ago, the Belfast Medical Students Association was an active body. In 1959 we ran a very successful national clinical conference for medical students from all parts of Great Britain and Ireland. They came to Belfast in March of that year, the total cost inclusive of travel, regardless of where they came from, being £4.00 each. We raised some funds from the Government, including a dinner at Stormont, and from the hospital and from the pharmaceutical industry. It does seem extraordinary in retrospect that we were successful, and this was largely due to the enthusiastic support of the hospital staff. At least 100 students came from all parts, attracted by the even then rather cheap rate. I hope that you will also run a national clinical conference and the hospital will be very pleased to help (Fig. 4).

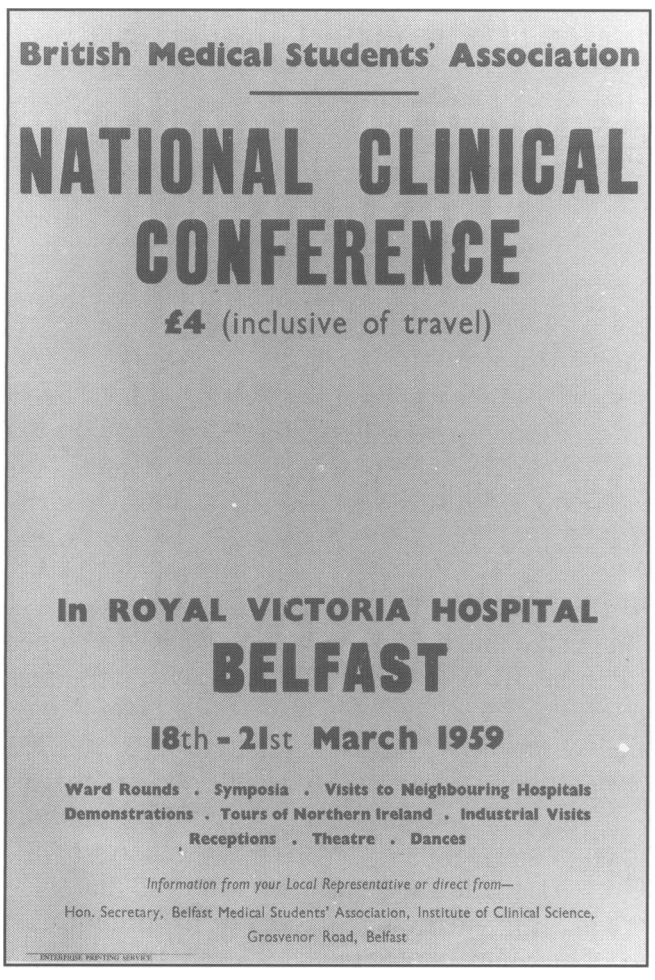

Fig 4. Poster advertising the National Clinical Conference at the Royal Victoria Hospital, 1959.

The next concept is of people in hospitals. The most significant doctor in the early days in this hospital was Andrew Malcolm, who unfortunately died young but had the good sense to have written a history of the hospital on which much of what we know is based. The Malcolm Exhibition, the prize for third year students, is named in his honour.

In 1850 it must have been difficult to get into the hospital as a patient. What was known as the 'board list' system existed, and the waiting list is still called a board list in this hospital. The present Chairman of the Trust Board might like to know what his predecessors' responsibilities were – it was necessary to have a little certificate stating that "We know the bearer and recommend them as a fit object to be admitted to the General Hospital and believe that they will be able to pay towards their support while there". This needed two signatures of subscribers of at least one guinea to the hospital. The certificate was then brought to the Board Room on a Tuesday and the Chairman of the Board had to sign "I have examined the above patient who is afflicted with (whatever disease) and consider it a fit case for admission. Admit the above for (so many) weeks". If the patient was acutely ill there was an over-riding method where the presenting doctor signed the bottom third of the form which said "I certify that this case is urgent, requiring immediate attention and will not admit a delay in order to come before the Committee on Tuesday next".

We have changed a lot since 1850. There are now 4,555 people working on this site. The great majority, 1,736, are nurses. This year we mourn

Fig 5. Miss Florence Elliott, Matron of the Royal Victoria Hospital, with two Assistant Matrons, Miss Earls and Miss Scott in 1966. (Reproduced in 'Yes Matron', reference 8).

the death of Miss Florence Elliott, a very famous Matron of this hospital (Fig. 5). Medical students of my vintage look back with some fear but certainly much affection to the concept of the Matron walking up and down the corridor and keeping us all very much in order. You certainly were on your best behaviour when Matron was going past. When Miss Elliott died recently in the fullness of years it was sad to me that there was no way we could formally recognise the loss of such a greatly respected member of the hospital community. There have been difficulties in hoisting flags on this building for a number of reasons but it would be perfectly in order to hoist a hospital flag. I would suggest to the medical staff and to the nursing staff that we should immediately institute a hospital flag, and what better than the Royal Victoria Hospital nurses' badge on a royal blue background, which could be displayed on a suitable flagpole within the campus of the hospital at times when the staff felt it appropriate (Fig. 6).

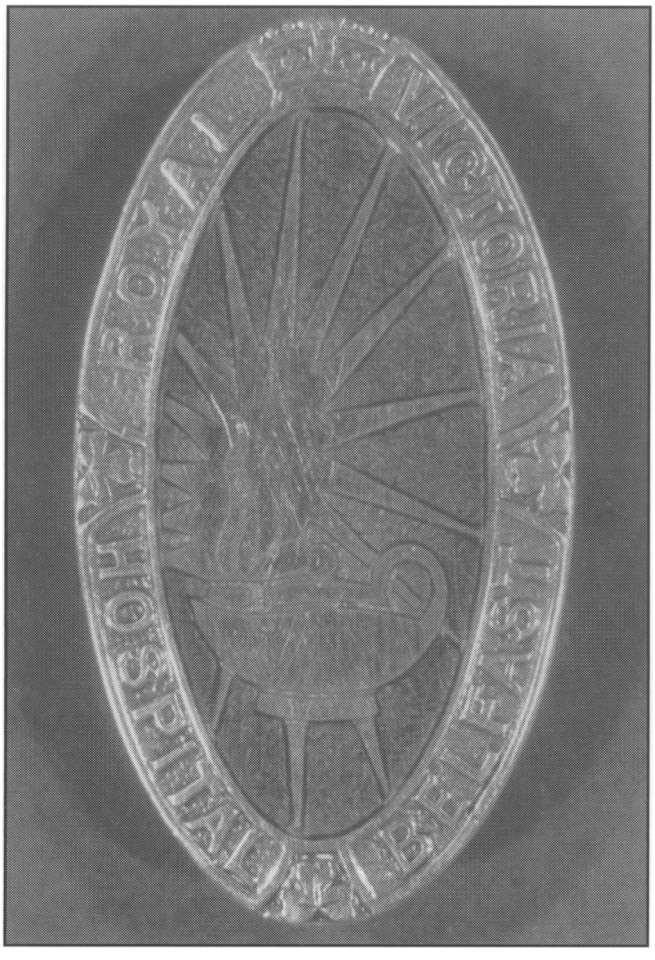

Fig 6. Suggested house flag for the Royal Victoria Hospital, based on the RVH nurses' badge; on a royal blue background.

If you go back to the Good Samaritan window and look underneath you will see a marble inscription which was also brought from the old hospital in Frederick Street. It states *"This memorial was erected by the late Mr Girdwood's numerous friends, who have deeply mourned his removal from their midst, to record their high estimation of him as a citizen and his sterling work as a friend. Also to testify their admiration of his indefatigable energy and his valuable services on behalf of this institution for a period of 18 years"*. I passed that plaque for many years and wondered who Mr Girdwood was, before I discovered that there was a bust of him just as you go into the Board Room in the King Edward Building. When you go for lunch today you will see him on the left-hand side of the door. Mr Girdwood was perhaps the most famous administrator of this hospital. No hospital can function without helpful administrators, and he was so much beloved that they subscribed to his bust which has survived since the move from Frederick Street. Mr Girdwood represents an important aspect of the metabolism of this hospital, the administrator.

The number of doctors who work in the hospital, as best I can count them, is 552. How many of those are actually members of the Medical Staff begins to create a problem. The staff lists of the Royal Victoria Hospital, the Royal Maternity Hospital and the Royal Belfast Hospital for Sick Children indicate that there are 215. The Directorates, which are the organizations run by the administration, consider there are 236, but when counted as whole-time equivalents only 159. Only 95 of these doctors actually work nine-tenths or more of their time in this hospital. There are at least 26 Queen's University joint appointments (counted as people). However, the personnel department of the hospital, who are responsible for the pay cheques, consider there are only 158. It is rather difficult to find who exactly is a member of the medical staff of this hospital, and a new statement of the regulations, which will take notice of new types of appointments such as an Associate Specialist and the Staff Grade, is much needed.

I have a hope for the years to come, when I look out of the window of the Metabolic Unit, down the hill beyond the Microbiology building, and I see in the distance a long way away the Belfast City Hospital – I hope that the distance between the Royal Victoria Hospital and the Belfast City

Fig 7. The Belfast City Hospital seen from the Royal Victoria Hospital.

Hospital gradually will become less (Fig. 7). There are a number of ways in which that can be achieved. One way is by our two medical staffs coming a little closer to each other. Another list, published in the Northern Ireland Medical Directory indicates that there are 214 consultants who consider that they are on the Royal Victoria Hospital staff, and 146 on the Belfast City Hospital staff. Jointly we are a group of 360 doctors, of whom about 10% (38) are actually on the staff of both hospitals. Maybe in the future, when you are old and grey, you will look back on this apparent division between two hospital staffs and wonder why it took them such a long time to come together. Eventually a union of the hospital staffs will be helpful in terms of looking after sick people in Belfast.

Now to the finances of the hospital. People are fond of saying that there is a crisis, but there is no crisis today anything like the crises there have been in the past. In 1799 the first hospital in Factory Row (Berry Street) closed altogether because there was no money to keep it going. In 1850 there was a major financial crisis in the hospital in Frederick Street. There was such a deficit that they had to close half of the beds in the hospital, and the outpatients department, and not only that but they reduced the house surgeon's pay. There was only one house surgeon who was paid £90 a year. The administrator of the day decided to reduce his pay from £90 a year to £10 a year. The administrator who did that was the same late Mr Girdwood who subsequently had the numerous friends, which shows that even a tough administrator can, at the end of the day, leave such a good impression that people subscribe to make a bust of him! There were other crises. In 1902 when they moved to the Grosvenor Road it was only just in time because the old hospital was simply not well enough equipped. In 1948 when the National Health Service was established it was only just in time as the voluntary basis of running the Royal Victoria Hospital was about to collapse.

In 1996 we are now a group of hospitals with 1,040 beds. Some of the staff may wonder whether that is really true, and we have to look very closely to see whether we believe the numbers of beds that are said to be still here. I have been able to compare some statistics from the hospital reports for 1954, 1976 and 1996 – the first date being when I was a third year student, and the second when I was secretary of the medical staff committee (Table). In 1954 there were 570 beds, in 1976 there were 796, and there are still almost the same number in 1996, even though a considerable number of beds have been closed down. Clearly other beds have been opened. The gross expenditure of the Royal Victoria Hospital in 1954 was £600,000, in 1976, £13m, and in 1996 £123m. There has been an enormous increase in costs, by over 200 times. This is not entirely due to inflation; the index of inflation used by the hospital services over the period of time from 1954-1996 works out at approximately four times between each of those three dates. The estimated 'real' cost in 1976 at 1954 values would have been a five times increase, and in 1996 approximately 12 times the 'real' cost in 1954. These figures represent the cost of looking after

TABLE

Royal Victoria Hospital

	1954	1976	1996
Beds	570	796	783
Outpatients (x 1,000)	391	375	344
Gross expenditure (£ million)	£0.6	£13.0 (x 21)	£123.0 (x 205)
Cost/patient/week (£)	£16.0	£342.0 (x 21)	£3,125.0 (x 195)
(at 1954 values)		£81.0 (x 5)	£195.0 (x 12)
Cost of food/patient/week (£)	£1.80	£6.04 (x 3.4)	£17.40 (x 9.6)
(at 1954 values)		£1.55 (x 0.8)	£1.09 (x 0.6)
Gross hospital costs			
Royal Group of Hospitals	£0.6	£13.0	£123.0
Northern Ireland (£ million)	£6.2	£83.0	£596.0
RGH %	10%	17%	20%
Senior medical staff	50	154	236
Bed/consultant ratio	1:10	1:4	1:3

Estimate of price inflation in 1976 and 1996 compared to 1954 obtained from the Health and Community Health Services Pay and Price Inflation Index, and the adjusted GDP deflator index.

a patient per week. Another statistic in the annual reports of the hospital is the cost of food per patient per week: this has gone up from £1.80 to £17.40 over the 40-year period. Applying the same inflation multipliers, there is actually a reduction in the 'real' cost of the food per patient per week of 40%. Food is now relatively cheaper, but it seems extraordinary that the proportionate amount spent by the hospital on food has reduced by so much in real terms. The gross costs of this group of hospitals, which are currently £123m per year, represent almost 20% of the gross hospital costs in the whole of the North of Ireland, which is a greater proportion than 40 years ago. The numbers of senior medical staff have increased greatly from 50 to perhaps 236, which means that the patient/consultant ratio has fallen from 1:10 to 1:3. The reason why the cost of health care in hospital has risen so much is a mixture of all these reasons, although we cannot blame the cost of food.

The hospital was funded in 1954 by direct grant through the Northern Ireland Hospitals Authority. Recently the concept of a market economy has been introduced in which money is paid by the Boards and the fund-holders in general practice in fulfilment of various contracts. In 1996 that was £102m. There is a further grant called STAR, or the Supplement for Teaching and Research, which is to compensate the Trust for the excess costs of undergraduate teaching and research, and that amount was £21m for last year. From the Department of Health there is an allocation of about £37,000 per student to pay for the additional costs in teaching hospitals of clinical teaching and research. The university at the same time receives a grant from the Department of Education of about £10,000 per clinical student which goes towards the university facilities and staff. If we want to do research in the future we may have to get separate funding from the research councils. Each medical student, as you sit in front of us today, is worth £47,000 to the conglomeration of hospital and university on this site: you are a very valuable commodity and that's why we're asking you to lunch afterwards!

But there still is not sufficiently good communication between the university and the hospital to discuss these matters at both high level and at staff level. When I asked at the

Department of Education for their view on these matters, they identified the 'ten key principles' that had been agreed by the Committee of Vice-Chancellors and Principals throughout the UK in 1990. These include the concept of educating our medical students in the spirit of enquiry and research, of efficiency and cost-effectiveness, that both parties – the hospital and the university – should agree locally, and should involve the senior staff of each. We should share information, research implications for teaching and service should be honoured, and both parties should consult on appointments. STAR, or the other similar funds in other parts of the UK, should be jointly agreed. These ten key principles are still important, and we should look at them jointly with our colleagues in the universities.

Fig 8. The blackstone wall of the grounds of the old Belfast Lunatic Asylum.

As you go across the road after this lecture and have your cup of coffee, look at the wall that you cross over on the bridge to the Mulhouse building (Fig. 8). That old black wall was the boundary wall of the old Belfast lunatic asylum, and used to surround the whole site. It was a fine building, but was eventually pulled down in 1926 and all of the patients transferred to the new buildings in Purdysburn. An old map at that time shows both the Royal Victoria Hospital, then relatively new, and the old asylum just behind it, more or less where the maternity hospital is now. There were a number of trees growing in the grounds, some of them in a row. The new Royal Victoria Hospital was a considerable architectural innovation because of its central heating and air conditioning system, and it is considered to be the first air conditioned building in the world. The air came into the wards not through windows but through ducts in the walls and was extracted and brought out through further ducts at the very end of each ward. Underneath the main corridor there was a long, long ventilation duct, along which cleaned and moistened air was blown by an enormous fan. This part of the hospital has been designated as a site of architectural importance and listed as a building which must be preserved.

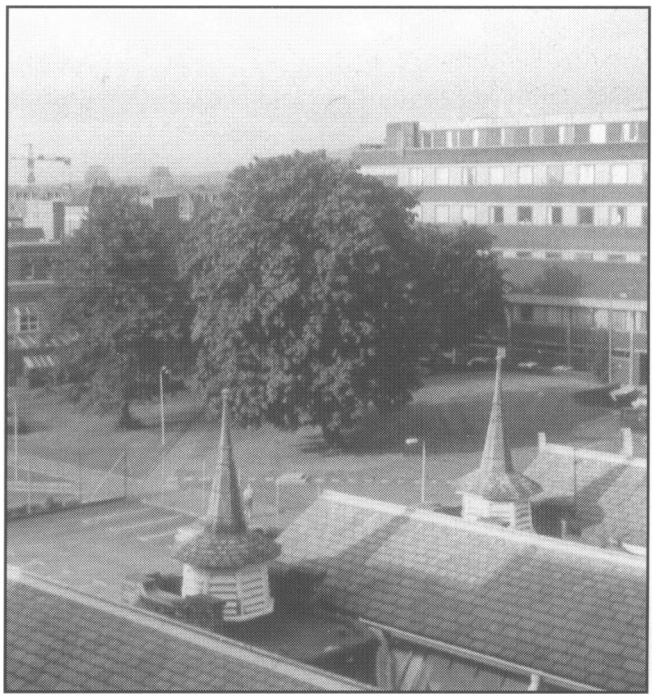

Fig 9. The central lawns of the Royal Victoria Hospital in 1996, showing the chestnut tree and the ventilation 'pagodas' at the ends of each ward.

If you had looked out of my office window in the Metabolic Unit in 1957 you would have seen that same row of trees, and if you look out now 40 years later, although there are not so many trees, one of them has grown considerably. The famous RVH chestnut tree attracts small boys from all over Belfast who come to throw sticks to get the 'conkers' (Fig. 9). If you want to know the age of a tree, you stand and put your arms around it at a height of 5 feet. The girth of a tree at a height of 5 feet, in inches, is approximately equal to the age of the tree in years. On this basis the chestnut tree is now 127 years old, which means that it was there long before the RVH was there and was planted sometime about 1870, in the grounds of the lunatic asylum.

If you look out of the window in the Metabolic Unit in another five years' time (if it's still there) you will see a new building. It is a tribute to the architects Ferguson & McIlveen of Belfast and their colleagues Percy Thomas of London that they have incorporated in the new building a new corridor which, hopefully, will preserve the metabolism of the hospital so that we will continue to be able to work together in close harmony, both in looking after patients and in teaching students. This corridor will also require a suitable stained glass window at one end, and I suggest that the medical staff committee should consider presenting one.

There are other new buildings which have gone up on this site, particularly the recently renovated laboratories (the old Kelvin and previously Grosvenor High School), and the work going on at present at the Royal Belfast Hospital for Sick Children which will be finished in two years. But when we look back to remember the old wards of the Royal, what we will really remember will be those curious pagodas that sit at the end of each ward, which are the exhausts for the air conditioning system. Perhaps some of them will be preserved for posterity.

One certain way to concern all of us in what is happening in the metabolism of this hospital today is to talk about car parking. A picture of the car park at the Royal Victoria Hospital in 1950 shows that not only the very fine fleet of Daimler ambulances but also all of the senior medical staff motor cars shared the small area just outside what is now the kitchen of the hospital, but had been built as the original casualty department (Fig. 10). If you came into the casualty department before 1940 there was a very fine waiting hall which has now been subdivided. At the end of that hall was the Good Samaritan window. It was finally moved to the end of the main corridor about 1944. You can only see it well in the morning when the sun is shining through it. I hope you will not consider it inappropriate to study the window carefully. The Good Samaritan didn't have to ask whether he had a contract to attend to the man who fell among thieves, or whether he was funded by the Department of Health or the Department of Education: like a good Belfast medical student he was well prepared and he got on with the art of medicine. I wish each of you every success in all of your future healing and educational endeavours.

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No orator can afford to be without the essential histories of Belfast medicine. I have learnt what I know from the following books and articles, in many instances by personal contact with the authors.

Fig 10. The staff car park outside the casualty department in 1950.

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Case Report

Mixed sex-cord stromal tumour of the testis

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Sex-cord stromal tumours account for only about 6% of testicular neoplasms.[1] Leydig cell tumour is the commonest sub-type but other tissues that can be represented in varying amounts and degrees of differentiation include Sertoli, granulosa and theca-lutein elements. Testicular granulosa-cell tumour of the adult type is particularly uncommon. This report details a mixed sex-cord stromal tumour of the testis in which the adult granulosa cell component predominates.

CASE REPORT A 54 year-old male presented with a four week history of a painful, right sided testicular swelling. He was otherwise well and symptom free. Physical examination revealed a small swelling in the lower pole of the right testis which was hard in consistency. There were no other findings. The clinical impression was that of a testicular tumour. An ultrasound scan of the scrotum was performed. This revealed a 2-cm diameter, low echogenic mass in the lower pole of the right testis. Several small cystic areas were noted within the mass. Tumour markers were all within the normal range (alpha-fetoprotein <4 kU/1, HCG <2 U/L, CEA 5 ug/1). Orchidectomy was performed. CT scanning of his chest, abdomen and pelvis showed no evidence of metastatic disease. Post operatively the patient remained well and symptom-free. At his most recent review, 28 months after initial presentation the patient was well and had no symptoms. Tumour markers have remained within the normal range and a CT scan of the chest, abdomen and pelvis has again shown no evidence of metastatic disease.

PATHOLOGICAL FINDINGS

The 5 x 4.5 x 3 cm testis, its coverings and the 11 cm of spermatic cord had a total weight of 80 grams. The lower pole of the testis contained a 2 x 1.7 x 1.6 cm circumscribed, pale, rubbery tumour with central areas of cystic change and haemorrhage, abutting on to the adjacent tunica (Fig 1A). Histology showed a mixed sex-cord stromal tumour of the testis with a circumscribed, lobulated margin compressing the inner aspect of the tunica and adjacent testicular parenchyma

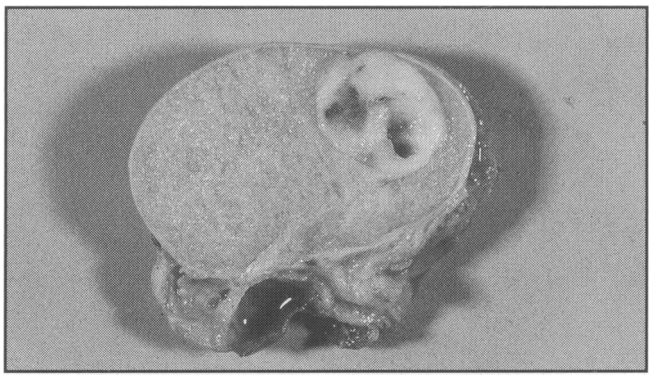

Fig 1(a). A well circumscribed lower pole testicular tumour, pale in colour with focal areas of cystic degeneration and haemorrhage.

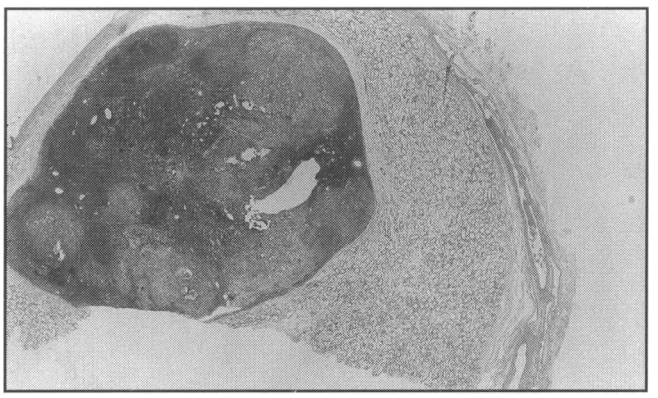

Fig 1 (b). The tumour is compressing the adjacent tunica and testicular parenchyma.

(Fig 1B). The differentiation was predominantly that of an adult type granulosa cell tumour with minor (< 5%) Sertoli cell tubular elements. In keeping with a granulosa cell lesion the periphery of the tumour had a poorly differentiated fascicular and storiform spindle cell pattern (Fig 2A) but centrally a well to moderately differentiated insular and trabecular arrangement with focal myxoid and microcystic change and stromal

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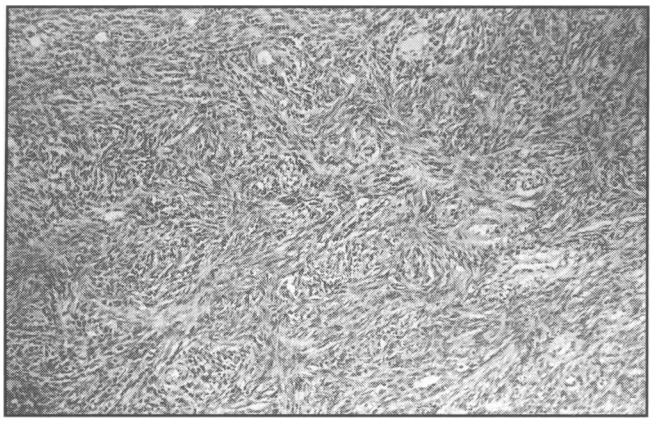

Fig 2(a). The periphery of the tumour showed a fascicular and storiform spindle cell arrangement.

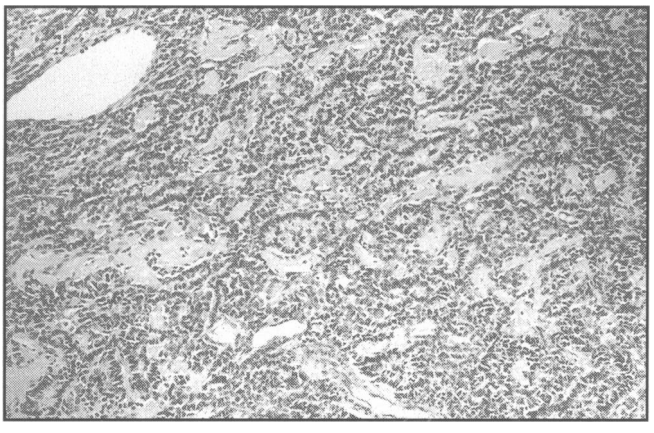

Fig 2 (b). Centrally the tumour showed a trabecular and insular arrangement of cells in a hyaline stroma.

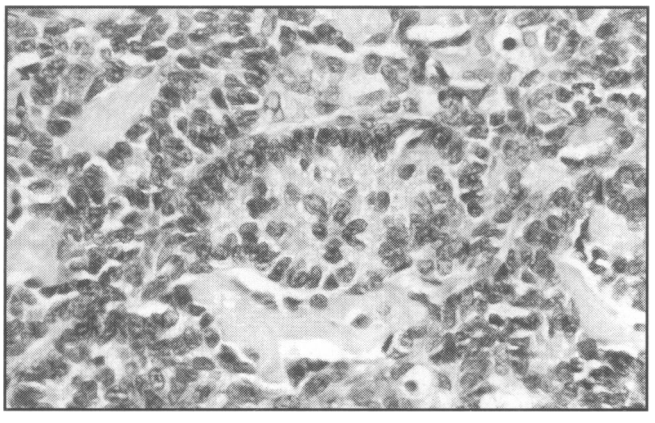

Fig 2(c). The tumour cells have irregular ovoid nuclei with longitudinal grooves.

hyalinisation (Fig 2B). The cells had an ovoid, vesicular nucleus in which longitudinal nuclear grooves were present and clear to light eosinophilic cytoplasm (Fig 2C). There was no significant necrosis, nuclear atypia or mitoses. Call-Exner bodies were not present. Immunoperoxidase on the paraffin sections showed strong positivity with vimentin antibody but negative results for CAM 5.2 and AE1/AE3 cytokeratins, placental alkaline phosphatase (PLAP) , MIC-2 oncogene product and oestrogen and progesterone receptors. Electron microscopy showed groups of cells within a loose collagenous matrix – there was a high nuclear cytoplasmic ratio and a degree of nuclear irregularity, the features being consistent with those of the granulosa-theca cell type. The adjacent testicular tubules were compressed but there was no evidence of germ cell neoplasia. There was no invasion of the tunica, rete, epididymis, spermatic cord or vessels.

DISCUSSION

Sex-cord stromal tumours of the testis are uncommon with a spectrum of differentiation including Sertoli-Leydig and the cagranulosa cell elements. There is debate as to whether they arise from the primitive stroma of the gonad or the mesothelium of the genital ridge.[1] Most testicular granulosa cell tumours occur in childhood or adolescence and are of the juvenile type. In 1952 Laskowski[2] described an adult type testicular granulosa cell tumour which is still regarded as a rare neoplasm.[3-5] They are well circumscribed tumours with a range of solid, microcystic, microfollicular, gyriform, insular, trabecular and spindle cell patterns in which Call-Exner bodies may be identified.[4,5] The nuclei are irregular with characteristic longitudinal grooves seen on both light and electron microscopy.[4] The cells are positive for vimentin intermediate filaments and negative for EMA and cytokeratins.[4,5] However, use of cryostat frozen sections has shown positivity for cytokeratins 8 and 18 but confirmed an absence of staining with antibodies to EMA, common leucocyte antigen and desmoplakin.[6] The mean age of presentation is 47 years and the patient may have noted testicular enlargement over several years.[5] Some lesions are endocrinologically active presenting with gynaecomastia[3,7] Interestingly a proportion of the cells can be positive for oestrogen and progesterone receptors although again there is a discrepancy in results between frozen and paraffin sections.[6] Düe *et al*[6] have postulated the detection of steroid hormone receptors as a possible basis for tumour development and therapeutic management by oestrogenic manipulation.

Most adult granulosa cell tumours appear to have been benign and this is corroborated by the low mitotic activity and small growth fraction on Ki-67 staining.[6] However, as with ovarian granulosa

cell tumours, biological behaviour cannot be accurately predicted from the histology although features worthy of comment are young age at presentation, extra-testicular hormonal effects, tumour size, pleomorphism, mitotic activity and local invasiveness. Matoska *et al*[7] reported a 26 year old male presenting with bilateral gynaecomastia, and metastases to retroperitoneal lymph nodes. The primary tumour showed 3-10 mitotic figures per ten high power fields and focal infiltration of the rete and lower part of the spermatic cord. Jimenez-Quintero *et al*[5] in their series of seven cases had one patient who presented with retroperitoneal lymph node secondaries and who developed inguinal lymph node secondaries one year later. Histology showed focal infiltration of the tunica in the primary tumour. Another patient developed retroperitoneal lymph node and liver secondaries 121 months after diagnosis and subsequently died 13 months later. Mitotic figures in their series ranged from 1-26 per 50 high power fields. They concluded that testicular adult granulosa cell tumour is a rare and slow-growing neoplasm with the potential to form distant metastases. Recurrence and metastases may occur late in the clinical course, emphasising the need for long-term follow-up in these patients. This emphasises Talerman's[3] view that testicular adult granulosa cell tumour is potentially of low-grade malignancy.

The minor Sertoli cell element in this case takes it from pure granulosa cell tumour into the mixed sex-cord stromal tumour category. However there are insufficient numbers of the latter reported in the literature to determine whether they follow any particular behaviour pattern and individual lesions are perhaps best assessed according to their predominant component of differentiation.

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Case Report

Hypercholesterolaemia in a Vegan

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A vegan is a person who abstains from all food of animal origin.

It is generally accepted that a vegetarian diet and especially a vegan diet is associated with a low serum cholesterol.[1,2,3] When vegans are surveyed they have a significantly lower intake of total energy and especially energy from fat[4] and their mean serum total cholesterol is also lower than expected values for the normal population.[5] We present a patient who was a strict vegan but had a high serum cholesterol. No identifiable evidence was found for either familial or secondary hypercholesterolaemia.

Case Report

A 58 year old man was admitted for coronary artery bypass grafting for severe triple-vessel disease. He had been a vegan for fourteen years, and since 1980 had rigidly adhered to a diet of black tea and coffee, dry bread and vegetables. He gave a history of increasingly severe angina over two years reaching New York Heart Association Grade 4 in the immediate pre-operative period. There had been several admissions to hospital with unstable angina.

With regard to risk factors, there was no history of hypertension or diabetes mellitus, and he had stopped smoking twenty years previously. There was however a strong family history of ischaemic heart disease, but no definitive evidence of familial hypercholesterolaemia. The serum cholesterol of all the patient's siblings was measured, and ranged between 5.7-6.9 mmol/l.

Thyroid function tests prior to admission were normal as were full blood picture, renal profile, total protein and albumin in the ward.

His medications were isosorbide mononitrate LA 50mg mane, atenolol 25mg mane, glyceryl trinitrate 3mg tid, diltiazem 120mg bd, chlorpheniramine 8mg nocte, bismuthate 240mg bd, omeprazole 20mg bd and cyanocobalamin intramuscularly every month.

A random serum cholesterol on admission was 8.39mmol/l.

On examination the patient was thin, his height was 173cm and his weight was 64.7kg. No corneal arcus or xanthoma was detectable; his blood pressure was 110/60mmHg. The remaining full clinical examination revealed no abnormality and his ECG was normal.

Cardic catheterization in December 1993 had shown severe triple-vessel disease with good left ventricular function.

Pre-operatively his fasting lipids were measured. They were:

Cholesterol	7.9 mmol/l
HDL Cholesterol	1.03mmol/l
LDL Cholesterol	5.21mmol/l
Triglyceride	3.14mmol/l

Successful coronary artery bypass grafting was performed in November 1994 and he made an uneventful post-operative recovery.

DISCUSSION

The vast majority of publications on vegetarian diets relate them to lowering serum cholesterol. Hostmark et al.[1] quoted a fall from 6.6lmmol/l to 4.83mmol/l in total serum cholesterol on a three-week vegetarian diet. Vuoristo et al.[2] and Krajcovicova-Kudlackova et al.[3] found vegetarians as a group had lower serum total cholesterol and LDL cholesterol.

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A study of vegans of the Seventh-Day Adventist faith showed their mean cholesterol level at 3.4mmol/l.[4] Their triglyceride and (low density lipoprotein) cholesterol were also lower when compared to the normal population. The Adventist Health Study[5] examined their diet in more detail. It was found that frequent nut consumption [more than four times a week] protected against both fatal and non-fatal myocardial infarcts.

Marniemi et al.[6] recently studied the effects of a vegetarian diet over one year. They found that serum cholesterol decreased rapidly at first but at six and twelve month intervals was no longer significantly different from pre-study cholesterol.

The above patient's diet would be high in plant sterols. In some cases this may lead to a falsely high serum cholesterol level but the assay used in our case was quite specific and was able to differentiate between sterols and cholesterol. Recent evidence suggests a close relationship between serum sterol level and cholesterol absorptions.[7]

After collecting the fasting lipid levels of all the patient's siblings there was no evidence for either familial hypercholesterolaemia or triglyceridaemia. It is well noted however that individual responses to changes in dietary cholesterol are very variable. Factors such as efficiency of absorption, rates of cholesterol biosynthesis, LDL-receptor activity, secretion of cholesterol into bile and hepatic conversion of cholesterol into bile acids all account for this variability.

The opposite extreme to our patient is an 88 year old man who ate 25 eggs a day and had a normal serum cholesterol.[8]

In our case the high serum cholesterol could be explained either by the vegan diet failing to sustain an effect after fourteen years or a cholesterol metabolic pathway specific to this patient.

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Case Report

Coexistence of Cystic Fibrosis and Phenylketonuria

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Phenylketonuria (PKU) and Cystic Fibrosis (CF) have an incidence in Northern Ireland of 1 : 4000 and 1 : 2000 respectively (1994 figures). Management problems are dietary, disease-related and psychological. Search of the literature has revealed no previous report of a child with both conditions.

We present the case of a child in whom both CF and PKU were identified on routine neonatal screening. The case highlights the value of this procedure.

Case Report A female infant weighing 3370 g was born by normal delivery at 39 weeks gestation to parents who believed that they were distantly related. They had one other child, a female, aged five years who was alive and well. There were no perinatal problems but an abnormal phenylalanine result from routine neonatal Guthrie card screening was confirmed by a plasma phenylalanine concentration of 934 mcmol/l on the fourteenth day (normal range 64-92 mcmol/l). Urinary phenylalanine was elevated at 45 mcmol/l (normal range 4-17 mcmol/l) and urinary phenylalanine excretion was 163 mcmol/mmol creatinine. Protein, ketoacids and phenylketones were absent from the urine. PKU was diagnosed and she was commenced on XP Analog (Scientific Hospital Supplies) together with 60 ml SMA Gold Cap (Wyeth) for 3 days increasing to 210 ml SMA Gold Cap to provide a small but essential amount of phenylalanine.

By 5 weeks of age concern was expressed about a poor weight gain of 90 g from birth. Neonatal screening had confirmed high immunoreactive trypsin and subsequent sweat tests revealed raised sodium concentration of 104 mmol/l. At 7 weeks she was admitted to hospital for assessment and management of CF. There were no respiratory symptoms but stools were loose and foul-smelling. Serum vitamin A was low at 0.61 mcmol/l (normal range 1.1-3.5 mcmol/l), and serum vitamin E at 5.23 mcmol/l (normal range 16-35 mcmol/l). Nutrizym GR(3) (Merck), flucloxacillin, and vitamin supplements including vitamin E were prescribed and physiotherapy commenced three times daily. There was an increase in height and weight velocity (Figure 1) and phenylalanine tolerance fell (Figure 2) following the commencement of pancreatic enzyme replacement therapy.

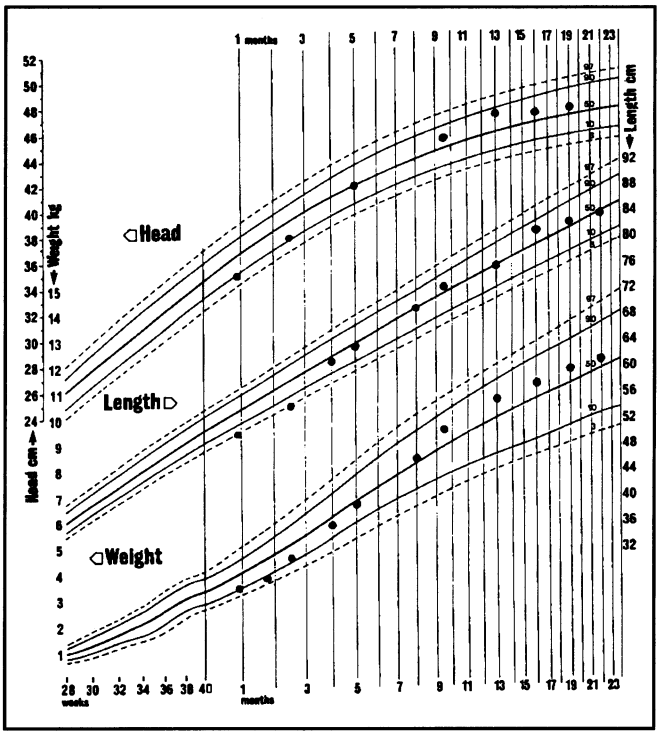

Fig 1. Figure 1 shows height, weight and head circumference data. Enzyme treatment commenced at 7 weeks.

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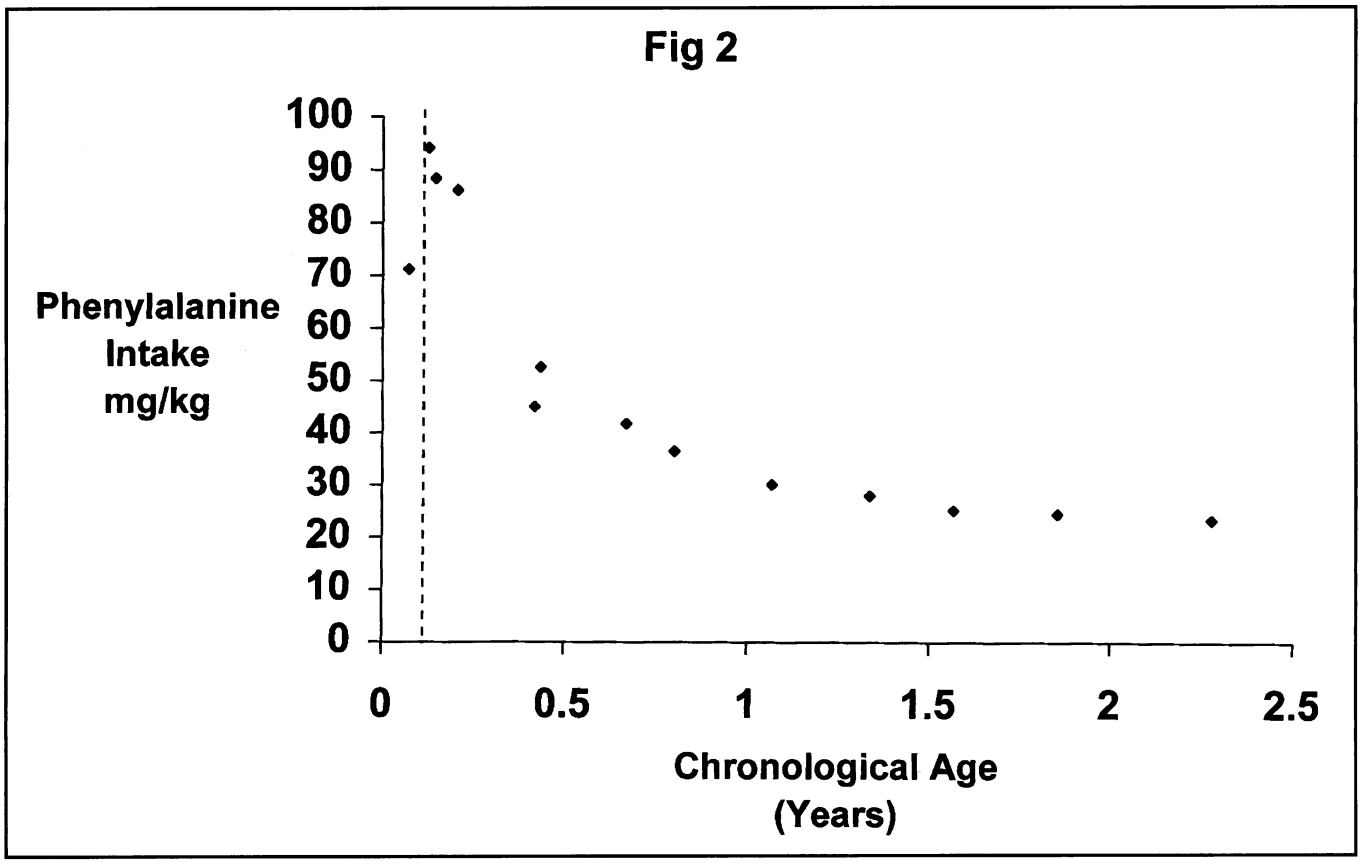

Fig 2. Figure 2 shows the variation in phenylalanine intake (mg/kg/day) with chronogical age. Age of commencing enzyme treatment is indicated by the perpendicular dotted line.

At the age of eight months she was admitted with a lower respiratory tract infection for intensive physiotherapy. Prophylaxis with Augmentin suspension, an aspartame-containing antibiotic (7.015 mg phenylalanine/5 ml), was inadvertently prescribed for six weeks although the dosage was low (7.5 ml daily) and unlikely to have affected phenylalanine control significantly.

Genotype analysis has shown that she is homozygous for delta F 508, and also shows the PKU mutations R408W, Y414C. At the age of twenty-eight months she is making good progress with normal development. Height and weight are both just above the fiftieth centile.

DISCUSSION

The case highlights the value of neonatal screening. The chance of an individual having both CF and PKU in our population is very low at approximately 1:8,000,000 and we have been unable to find any previous report of their coexistence. It is possible that CF-related malabsorption may have led to a lower diagnostic plasma phenylalanine concentration than would have otherwise occurred. Most patients with the common CF genetic defect, the delta F508 mutation, have steatorrhoea[1] and there is also known to be a specific defect in the absorption of neutral amino acids in CF[2]. In our experience, however, two other PKU patients with the PKU mutations R408W, Y414C have had similar plasma phenylalanine concentrations at diagnosis suggesting that malabsorption did not affect the result.

Both conditions require skilled nutritional intervention and monitoring by a dietitian. Their coexistence requires a revision of all advice as given for each occurring separately. The management of PKU necessitates a diet with small controlled amounts of natural protein and a daily intake of a protein substitute mixture to meet requirements for normal growth and development. Recommendations suggest a total amino acid intake of 3g/kg/day in children under 2 years of age and 2g/kg/day in children over 2 years.[3] This translates as 3-4g protein/kg/day and 2-3g protein/kg/day for under 2 years and over 2 years respectively. Energy requirements for

individuals with PKU are comparable to those of the general population. Patients who are homozygous for the CF mutation delta F 508 have a significantly higher resting metabolic rate (121% predicted) than those of other genotypes.[2] The estimation of energy and protein requirements used at our centre are 120-150% of requirements for age and a minimum of 2 g/kg/day respectively.[4]

In practical terms the two diets are compatible. From diagnosis our patient was treated dietetically as a PKU patient. At present she is receiving most of her protein requirements from a protein substitute mixture. Low protein products combined with energy supplements play an important role in maintaining her energy intake for appropriate growth and weight gain. Dietary problems can be foreseen. Monotony and taste fatigue are likely to occur because the PKU diet is lifelong and there is a limited number of products available. CF-related chronic respiratory infections will cause an increase in metabolic rate and in energy requirements.[1]

The psychological effects must be recognised. Olsen[5] has described the guilt, marital stress and grief of parents on hearing the diagnosis of CF. The parents of our patient are in the unique position that their child has not one but two chronic inherited diseases both diagnosed on routine neonatal screening. The combined risk of a further child with one or other condition is 1:2. The child herself may suffer from lack of understanding by teachers and peers.[1] Denial of the severity of the illness may lead to non-compliance.[6]

The prognosis of both conditions may be influenced by the coexistence of the other. Poor control of PKU with subsequent intellectual deterioration may lead to non-compliance. Poor control of CF with reduced growth velocity and frequent infections will lead to poor phenylalanine control and its consequences. The frequent use of antibiotics may lead to the child being inadvertently given the aspartame-containing antibiotic, Augmentin, in higher dosage than occurred in our patient. Psychosocial problems associated with CF are likely to be aggravated by those of PKU.

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Case Report

Rhesus haemolytic disease of the newborn, complicating a quadruplet pregnancy

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Quadruplet pregnancy is extremely rare, although the incidence has risen since the late 1970s due to the increased use of infertility treatment. The occurrence of spontaneous quadruplet pregnancy is estimated to be one in 571,000 births using Hellin's hypothesis.[1]

Rhesus haemolytic disease of the newborn (Rh.HDN) occurring in multiple pregnancy is also a rare event but it has been reported in twins[2,3] and in a triplet pregnancy.[4] In this paper we report a spontaneous quadruplet pregnancy complicated by severe Rh.HDN.

Case Report A 26 year old Caucasian woman received an anti-D immunoglobulin after the delivery of her first child who was born at 41-weeks' gestation by normal vaginal delivery in 1991. There was no history of blood transfusion, abortion or stillbirth between the first and second pregnancy.

She was booked at about five weeks' gestation in a small general hospital and transferred to Royal Maternity Hospital, Belfast, at 24 weeks' gestation when quadruplet pregnancy was confirmed. She remained in hospital for six weeks and four days until delivery. There was no past medical history of note, blood group was O-Rh(D) negative and anti-D antibodies were detected (Table). The husband's blood group was O-Rh(D) positive and his probable genotype was CDe/cDE.

The status of the mother and fetuses was closely monitored and assessed in hospital by Doppler studies, cardiotocography and regular ultrasound scanning. Amniocentesis was performed on three occasions.

The results of amniocentesis and lecithin/sphingomyelin area ratio are shown in the Table. She was given five courses of betamethasone 12 mg intramuscularly twice a week until she went into spontaneous labour at 30 weeks and four days of gestation. An emergency Caesarean section was performed under general anaesthesia. Placental pathology was unremarkable and there were no retroplacental or marginal clots.

QUADRUPLET I

The first baby was a boy, weighing 1124 g with Apgar scores of 7 and 8 at one and five minutes respectively and he had no signs of respiratory distress or hydrops.

Cord haemoglobin was 7.3 g/dl, cord bilirubin was 87 umol/L, blood group (Bl.gp) was O Rh(D) positive and direct Coombs test (DCT) positive. He was initially given a 'top up' blood transfusion of packed red cells and phototherapy for eight days. He required five exchange blood transfusions for hyperbilirubinaemia. He was also given two units of platelets for post-exchange thrombocytopenia.

QUADRUPLET II

The second baby was a boy weighing 1307 g with Apgar scores of 8 and 8 at one and five minutes respectively. There were no signs of hydrops. However in the first hour of life he developed mild respiratory distress which settled with brief

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TABLE

Maternal Antenatal Investigations

Gestation in weeks	*Anti-D antibody titre*		*Amniobilirubin*	*Lecithin/Sphingomyelin Area Ratio*
	Saline	*Albumin*	*Δ O.D at $_{450}$ NM*	
23	1 : 2	1 : 2	———	———
26	1 : 256	>1 : 256	0.115	1.6
27	———	———	0.069	———
29	1 : 64	1 : 1000	0.075	1.3

(Δ O.D = Optical density)

facial oxygen therapy. His cord haemoglobin was 8.3 g/dl, cord bilirubin was 71 umol/L, Bl.gp was O Rh(D) positive and DCT positive. He had six days of phototherapy, a 'top up' of packed red cells and two exchange transfusions.

QUADRUPLET III

The third baby was a girl with Apgar scores of 5 and 7 at one and five minutes respectively, her birth weight was 796 g and she had no signs of hydrops.

Cord haemoglobin was 10.9 g/dl, cord bilirubin was 79 umol/L, Bl.gp was O Rh(D) positive and DCT positive. She also was given a 'top up' of packed red cells, phototherapy for seven days and two exchange transfusions were required.

QUADRUPLET IV

A girl with Apgar scores of 5 and 7 at one and five minutes respectively, her birth weight was 892 g. Her cord haemoglobin was 10.7 g/dl, cord bilirubin was 72 umol/L, Bl.gp was O Rh(D) positive and DCT positive. She had recurrent apnoeic spells at the age of two hours requiring ventilatory support for 24 hours. She also required a 'top up' blood transfusion and phototherapy for seven days; and three exchange transfusions were given.

Milk feeds were commenced on day five for quadruplet I, II and III and on day six for quadruplet IV, and went up uneventfully, allowing quadruplet I and II to be discharged home aged five weeks weighing 1775 g and 1993 g respectively, whereas Quadruplet III and IV were discharged on day 45 of life weighing 1656 g and 1776 g respectively.

DISCUSSION

The number of babies affected with Rh.HDN has decreased since the introduction of anti-D immunoglobulin prophylaxis in 1969.[5] There has been a similar decline in the number of deaths of affected babies.[6] This trend has been mainly attributed to improved obstetric and neonatal care especially in developed countries.

In the quadruplet pregnancy we describe, regular ultrasound studies showed no evidence of hydrops but revealed a pattern of intrauterine growth retardation in quadruplet III and IV. Amniocentesis was performed on quadruplet II who was used as a control by mapping of the membranes guided by ultrasound. The amniobilirubin results presented in the Table showed an overall reduction in the optical density values at $_{450}$NM from midzone-II to lower zone-II plotted on Liley's graph,[7] so that an intrauterine transfusion was not indicated.

Amniocentesis was not a particularly helpful tool in predicting the severity and outcome of Rh.HDN in this case. The father was homozygous for D-antigen at Rh. locus, so all the babies were Rh.D positive. Maternal anti-D antibody titres had increased steadily during this pregnancy making it possible that the mere presence of quadruplets in themselves and the large surface area of combined placentas had caused a more severe rhesus sensitisation than one might expect with a second pregnancy in this patient. There was no ABO blood group incompatibility between the mother and the fetuses.

A previous study showed that ABO incompatibility could account for the difference in severity of Rh.HDN between twins.[2] Other studies however have failed to show this, and have postulated that other factors such as differences in placental perfusion, fetal erythropoiesis and fetal hepatocellular function may be responsible for the disparity in severity of Rh.HDN between individual fetuses in multiple pregnancies.[3,4]

Our case also shows that the standard anti-D prophylaxis dose is not protective in higher multiple pregnancies.

It took sixteen hours to perform all the exchange transfusions and collectively they required 17 days of 'level one', 46 days of 'level two' and 98 days of 'level three' care (see reference 8).

In spite of the decreasing incidence and severity of Rh.HDN, it still imposes a considerable degree of morbidity in some babies, demanding highly skilful antenatal and neonatal care particularly in multiple pregnancy. From a review of the literature, this report is the first of Rh.HDN affecting a spontaneous quadruplet pregnancy.

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IMMUNOHISTOCHEMISTRY AND MELANOCYTIC INTRAEPITHELIAL NEOPLASIA

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53 cases of melanocytic intraepidermal neoplasia (MIN) were retrieved from the UCHG files 1990-1993, ranging from lentigo maligna, dysplastic naevus to florid in situ malignant melanoma. Sections were bleached in Mallory's bleach (potassium permanganate + oxalic acid) and stained with S-100 and HMB-45, with di-amino-benzene (DAB) as chromogen. Sensitivity was 100% for both stains; and HMB-45 was specific for melanocytes, while S-100 also stained sweat glands and epidermal Langerhans cells, in addition to showing increased background staining. 7/53 (13%) cases showed a subtle microinvasive component, with individual melanocytes or small nests of 2-3 cells infiltrating not more than 0.36 mm into the superficial dermis. Recurrence was zero, however, over a follow-up period of 18 months minimum, suggesting that MIN with microinvasion does not confer a worse prognosis than entirely in situ melanoma.

TYPING OF METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS ISOLATED FROM PATIENTS IN IRISH HOSPITALS BY PULSED-FIELD GEL ELECTROPHORESIS

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Strains of Methicillin Resistant Staphylococcus aureus from three Irish hospitals (St. James' Hospital, Dublin, Regional Hospital, Limerick and University College Hospital, Galway) were compared to determine (i) the similarity of these strains and (ii) their stability over time. Chromosomal DNA was digested with a low frequency cutting restriction enzyme SMA 1. The resultant restriction fragment length polymorphisms (RFLPS) were separated by Pulsed-field Gel Electrophoresis (PFGE). The number of restriction fragments produced were in the range of 7-12 and the sizes of fragments were between 48.5 and 630kb. Dice's Coefficient (DC) was employed to designate strains as identical (D.C. = 1) similar (D.C. between 0.90 and 0.99) and different (D.C. < 0.80). Strains were subcultured for 40 days to determine the stability over time. Baseline PFGE profiles and profiles after 40 sub-cultures were compared. Our results show that MRSA strains from these centres constitute a heterogeneous group and secondly, these strains exhibit stability over time. Comparison of PFGE profiles may prove useful for epidemiological studies of MRSA.

MICROCYSTIC ADNEXAL CARCINOMA OF THE EYELID AN UNUSUAL AGGRESSIVE NEOPLASM

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Microcystic adnexal carcinoma (MAC) is an uncommon locally infiltrating neoplasm of the skin with a 40% risk of recurrence and potential for marked tissue damage. Its relatively innocuous gross and microscopic appearances account for a tendency for misdiagnosis and to underestimate its malignant behaviour.

We present a case of MAC arising in the medial left lower eyelid adjacent to the punctum, in a 30 year old woman. The lesion had been slowly enlarging for 4 years. Biopsy showed a neoplasm composed of small ducts, keratocysts and focal areas of squamous differentiation, which infiltrated muscle and also displayed perineural invasion. She underwent a wedge resection of the left lower eyelid and reconstruction by lateral canthotomy and transposition flap (McGregor flap). The lacrimal apparatus could not be

preserved. MAC is believed to arise from sweat glands but can show dual eccrine and hair follicle differentiation. Some cases have occurred following therapeutic cutaneous irradiation. The nasolabial and periorbital regions are the commonest sites and the majority of patients are 50-60 years of age. The tumour is usually a slowly growing firm yellow/red nodule with ill-defined margins. Because of the marked tendency to recur, wide local excision is the treatment of choice. Metastases have been reported on one occasion.

UMBILICAL CORD OEDEMA: A REAPPRAISAL

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Oedema of the umbilical cord has previously been associated with perinatal complications, in particular with respiratory distress. No recent studies on this topic have been published.

The aim of this prospective study was to assess the value of measuring umbilical cord oedema as a predictor of perinatal problems and secondly, to investigate the best method of measuring cord oedema.

Data was obtained from 52 consecutive placentas which were submitted for evaluation because of complications arising during or immediately after labour. Fifty placentas from normal deliveries were also examined. Cord diameter (the product of two diameter measurements at right angles to one another at the thickest part of the cord) and density were compared within and between the two groups. Density was chosen as a simple method of assessing cord oedema. The diameter product differed significantly between the two groups ($p<0.001$); there was no significant difference in density measurements ($p=0.01$).

Measurement of cord diameter is worthwhile as it distinguishes between the two groups; however, diameter product does not necessarily reflect generalised cord oedema (the two measurements were only moderately correlated in both groups). Localised oedema may be a more significant finding than generalised oedema.

CONGENITAL TERATOMA

J Loane, W F Kealy

Department of Histopathology, Cork University Hospital.

Teratomas, though rare, are the most common congenital tumours. Those arising in the head and neck comprise 2 to 5% of all congenital teratomas. They contain elements of all three germ cell layers, which express variable degrees of differentiation. Malignancy is very rare. The major complications of these tumours relate to their size and their obstruction of the airway and oral cavity. We present a case report of a congenital teratoma of the hard palate which was associated with polyhydramnios, prematurity and perinatal death. It contained well differentiated skin, lung, pancreas and neural tissue and a rudimentary digit, as well as some less well differentiated tissues. There was no evidence of malignancy and no associated congenital malformations. It did, however, cause severe distortion of the nose and maxilla, leading to airways obstruction and death.

DETECTION OF ESCHERICHIA COLI 0157 IN WATER SUPPLIES

F O'Cochlain, M Cormican

Department of Immunology, University College Hospital, Galway.

The entero-haemorrhagic E.coli are strains of E.coli which are associated with severe human infection including haemorrhagic colitis and the haemolytic uraemic syndrome. Their pathogenicity is related to production of a toxin originally recognised by its cytotoxic action against Vero cells. (Vero toxin). Most verotoxin producing strains express the cell wall lipopolysaccharide antigen 0157 and in contrast to most other strains of E.coli most verotoxin-producing-strains fail to ferment sorbitol. The principal source of human infection is contaminated food and in particular meat. Recently it has been suggested that water might also be a source of infection with E.coli 0157. We have examined water samples from group water schemes and private water supplies in Counties Galway, Mayo and Roscommon for the presence of Escherichia coli 0157. Three local water sources (Galway public water supply, Galway canal and the Barna coastal amenity area) were also

monitored over a six week period. Water samples were examined by membrane filtration and culture of the membrane on lauryl sulphate broth containing pads. Colonies morphologically resembling E.coli were subcultured to sorbitol MacConkey agar. Culture of water indirectly in broth and culture of pellets obtained from water by immunomagnetic separation with para-magnetic beads coated in antibody to 0157 were also performed on a proportion of samples. Sorbitol non-fermenting strains were confirmed as E.coli by API 20E and the 0157 antigen detected by latex agglutination. E.coli 0157 was detected on one occasion in samples from 3 separate public water supplies in rural areas. These findings suggest that domestic water supplies may be a source of infection with E.coli 0157 in rural areas.

PROSTATIC CARCINOMA – A COST EFFECTIVE DIAGNOSIS

M Joyce, J Chin Aleong, N Hegarty, J Callaghan, P McCarthy

Department of Histopathology, University College Hospital, Galway.

Approximately 900 new cases of prostatic carcinoma are diagnosed in Ireland every year. Recently prostatic carcinoma has been increasing in incidence, partly due to improved screening methods and partly due to the increasing number of older males in the population.

Prostatic Specific Antigen, a glycoprotein produced by prostatic epithelial cells has been increasingly used to screen for prostatic disease. Patients with an elevated PSA level may undergo prostatic biopsy either as an in-patient or out-patient. In the out-patient setting transrectal ultrasound is used to examine the prostate and guide the biopsy procedure.

100 male patients undergoing prostatic biopsy were reviewed: 50 as out-patients and 50 as in-patients. They were reviewed with regard to age, Prostatic Specific Antigen, the incidence of malignant disease and the cost of the procedure.

No significant differences were found between the two groups with regard to their ages, range of PSA values or incidence of malignant disease. There was, however, a substantial difference with regard to the average cost of the procedures.

We recommend that out-patient transrectal ultrasound guided prostatic biopsy is a cost effective procedure for the detection of prostatic disease.

TESTICULAR TUMOURS: A - 5 YEAR REVIEW

T McHale, J Callaghan

Department of Histopathology, University College Hospital, Galway.

This study consists of a retrospective analysis of all testicular tumour diagnosed in U.C.H.G. between September 1991 and September 1996.

The stimulus for this study was the observation of a greatly increased number of testicular tumours presenting in the first eight months of 1996 compared to previous years.

The study population consisted of 38 cases, which were divided according to age at presentation into two groups. Group A – those presenting at 35 years of age and younger and Group B – those presenting at over 35 years. These groups were then compared as regards tumour type, size at presentation, presence of vascular or lymphatic invasion.

Seminoma was the commonest tumour in both groups, accounting for 55% of tumours in Group A and 61% in Group B. The poor prognostic indicator of vascular invasion and invasion of the tunica vaginalis were present in none of the seminomas in the younger group but in 18 and 9% respectively of the seminomas in the older age group.

The distribution of other tumour types was similar in the two groups apart from two cases of mesothelioma and leiomyosarcoma which occurred only in the older age group. Mean tumour size was notably smaller in Group B. The mean age at presentation was 33 years for the germ-cell tumours and 57 years for the non-germ cell tumours.

LEGIONNAIRES' DISEASE, 2 CASE REPORTS

J Chin Aleong, C E Connolly

Department of Histopathology, University College Hospital, Galway.

Legionnaires' Disease in a pneumonia caused by the intracellular organism Legionella pneumophila. Certain factors, including immuno-suppression predispose to Legionnaires' Disease.

We report two cases of fatal Legionnaires' Disease in immunosupressed patients.

The first case occurred in a 42 year old female with underlying extrinsic allergic alveolitis and asthma. She had been on both steroids and azothioprine. Post mortem examination showed a bilateral confluent lobar pneumonia with an intra-alveolar fibrinous exudate containing neutrophils and macrophages. Intracellular organisms were found on silver stain.

The second case was that a 42 year old male with myelogenous leukaemia following treatment for Hodgkin's Disease. During his final stay in hospital he developed abdominal wall cellulitis, small bowel obstruction and pneumonia. Post mortem examination showed bilateral confluent pneumonia, haemorrhagic pericarditis, small bowel ulceration and abdominal wall fat necrosis. Legionella was identified by silver stains in all of these areas.

In both cases Legionella pneumophila serotype 1 was confirmed by direct immunofluorescence assay.

As Legionella culture requires specific requirements it should be borne in mind as a possible pathogen in cases of atypical and/or fatal pneumonia.

The Ulster Medical Journal, Volume 66, No. 1, pp. 69-72, May 1997.

Book Reviews

Drukker, Parsons and Maher: Replacement of Renal Function by Dialysis 4th Edition. Edited by Jacobs, Kjellstrand, Koch and Winchester. Pub. Kluwer Head, USA 1994. ISBN 0-89838-414-1.

This book, first published in 1978 was one of the earliest to take dialysis as its main topic. The authors, all pioneers of their science, intended it to be the bible of second and third generation nephrologists, combining theory and practice in a single authoritative text. The book was immediately successful, so much so that those second and third generations are now themselves the mentors. This edition is the fourth, with a fresh editorial team and many new contributors. The debt due to Drukker and his colleagues is everywhere apparent however, and it is satisfying to see their names preserved in the title. Outwardly the book closely resembles the third edition, although, probably in view of its expansion to over one thousand five hundred pages, it now contains eight separate sections. There has been a great deal of change in content. This is the expressed purpose of the editors and credit is due to them and their publishers for the result, which many will regard as the leading current reference work on dialysis. The contributors are drawn from the world's leading nephrology centres. Every topic is covered in more detail than ever before, while tens of thousands of references testify to the care taken to ensure that all statements are readily verifiable.

The edition is important because it comes at a time when dialysis is entering a new era, in which it is becoming routine, available without restriction to all and able to deliver a sustainable long-term improvement in health. Much has been achieved since the first edition. Membranes have diversified and become more biocompatible. The technology of dialysis delivery has become more sophisticated, while concepts of adequacy have been greatly improved by better understanding of dialysis dosage. However, as Belding Scribner, one of the greatest pioneers observes in his foreword, a doubt arises as to whether modern nephrologists are truly taking advantage of equipment and techniques which to him seem unbelievably good. Unfortunately, the answer appears to be "no" as evidenced by an important article from Robert Barth on "short, high efficiency, and high flux dialysis". Barth concludes that most dialysis in the United States, using conventional and even high flux, high efficiency membranes, is inadequate, with prescription "frequently founded on erroneously high dialyser clearances supplied by manufacturers". This message from the United States applies even more to Northern Ireland. Head counts of dialysis numbers and wishful thinking about patients' well-being are not enough. Only by measuring accurately, frequently and honestly the dose of dialysis to each patient and comparing it with internationally acceptable criteria of adequacy, can we achieve for our patients the good outcomes outlined in this book.

A feature of the edition is the extra space devoted to the technology of dialysis. This is fully, even rigorously, presented, with excellent, new contributions on access and dialysis delivery. In addition a section is devoted to "organisation and results of chronic dialysis"; and there are good entries on such topics as quantification and prescription of dialysis, and dialysis in special clinical situations.

Changes in practice and modern developments have caused a few chapters to be omitted. Some, such as that on aluminium toxicity can be thankfully discarded. Others are harder to part with. In particular it is sad to lose Drukker's chapter on the history of dialysis, as well as his unique contribution to dialysate regeneration exemplified by the REDY machine. No science can be understood apart from its roots and I hope the editors will reconsider this decision.

The physical quality of this edition is outstanding, but some contributions have a lot of misprints. It is not very easy to find one's way around the book. Each chapter has its subjects, but since these are not found in the main Table of Contents, important information can be missed by the reader, e.g. concerning peritoneal dialysis, which, because of the nature of the presentation, is scattered throughout various sections. The index is some help, but could be fuller. The short articles on "dialysis and the transplant patient" and "assessing the progression of renal disease" (mysteriously entitled "prevention of chronic renal failure" in the Table of Contents) though good so far as they go, are best seen as guides to further study.

This book is essential for all involved in dialysis. For others it has a place as a reference text. For the medical student, shorter works are more suitable.

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J DOUGLAS

At War Within: The Double-Edged Sword of Immunity. William R Clark, pp 276. Oxford University Press. Price £17.99. ISBN 0-19-509286-4.

The author of the book is an internationally recognised authority on cellular immune responses and has published extensively on the mechanism of cell mediated cytotoxicity. This book however, is clearly designed for those with no immunological background and takes us from the origins of vaccination past various milestones in the development of immunology as a science. The introductory section is characterised by a wealth of personal detail regarding the key historical figures, including the intense rivalry between Pasteur and Koch.

The remaining chapters describe the basic components of the immune response, primary immune deficiency diseases, allergy, autoimmunity and not surprisingly a chapter on HIV related disease. The basic concepts are well communicated and the historical perspective is maintained throughout. The primary immune deficiency disorders are increasingly understood as a group of conditions characterised by single

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D EDGAR

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In the last three years the management of hyperlipidaemia has been revolutionised by the publication of large studies demonstrating that cardiovascular morbidity and total mortality can be reduced by decreasing serum cholesterol. At the same time, our understanding of the events in the arterial wall which lead to the development of atherosclerosis has greatly improved, with particular emphasis on the importance of lipoprotein oxidation as a key event in early atherogenesis. With such a large amount of information continually appearing, it can be difficult to assimilate both scientific and clinical advances, and it is therefore potentially useful to have both summarised in a single text.

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I S YOUNG

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Thomas Baskett graduated from Queen's University, Belfast in 1964. He then spent six years training in Northern Ireland towards a career in Obstetrics and Gynaecology before emigrating to Canada where he has been Professor of Obstetrics and Gynaecology at Dalhousie University, Halifax, Nova Scotia since 1980. In the introduction to the book he writes that "like grey hair his interest in medical history has grown insidiously over the years" (at least he has hair).

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This book should prove fascinating for any Obstetrician and Gynaecologist. In our practice we all use the names Ferguson, Sim, Hodge, Kielland, Marshall, Marchetti, Krantz and many others, without knowing anything of who the person was, only something of the procedure or piece of equipment to which their name has been appended. This book provides potted biographies of all of these and of many other people. Many of the biographies are accompanied by photographs.

I would strongly recommend this book as an historical reference text for all Obstetrician and Gynaecologist's shelves. It is a fascinating book into which to dip and browse and to quote Baskett's quotation of Sir Isaac Newton: "If I have seen farther . . . it is by standing on the shoulders of giants".

N McCLURE

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C HAMILTON

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This is a very well illustrated book on all aspects of dermatological surgery. It will mainly be of interest to dermatologists, many of whom now undertake a wide range of skin surgical techniques. General practitioners will find the sections on cryosurgery and curettage useful, as these techniques can deal with the majority of benign skin lesions without recourse to any of the advanced and expensive techniques described in other chapters.

The line drawings are exceptionally clear and often more instructive than the accompanying photographs despite the latter's quality. However, the blood-stained photographs underline the caveat that in practice many of these techniques are less easy than a line drawing would suggest.

The book nicely illustrates the range of techniques other than conventional excisional surgery that can be offered by a modern dermatological 'surgeon'. We should be proud that one of the authors works in this Province.

R FULTON

"Diabetes and Pregnancy – An International Approach to Diagnosis and Management". Edited by Anne Dornhorst and David R Hadden. Published by John Wiley & Sons Limited, London 1996, pp 424. Price £45. ISBN 0-471-96204-X.

This mighty tome covers all aspects of diabetic pregnancy commencing with Hadden's excellent review of diabetes in pregnancy in a historical context, followed by McCance's exhaustive classification of the diagnostic criteria in pregnancy.

Each member of the international panel of contributors approaches different aspects of the problem of diabetic pregnancy in depth, reviewing the literature comprehensively and highlighting areas of contention and areas of special importance. The pathophysiology is dealt with particularly well in terms of the metabolic stress of pregnancy and embryo development and foetal growth. Pre-pregnancy care is dealt with by Steel emphasising counselling which, even in this age of relative enlightenment, in many Diabetic Units is still under-emphasised or neglected. Firth of the Mater Hospital, Dublin, discusses insulin therapy in detail and the different doses and regimens. Eva Kohner outlines the problem of diabetic retinopathy in pregnancy and the Northern Ireland RVH/RMH Axis outlines the practicalities of pregnancy care for high risk diabetic patients. Other contributions from USA, India, Denmark, Australia and Austria make this volume a truly international approach to early recognition and careful management in order to achieve the best possible outcome for diabetic pregnancy.

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J K NELSON

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There is an overwhelming need for books such as this to answer the many queries that patients with lupus so often have. They feel a misunderstood group, perhaps partially because they often have an illness with many symptoms but few signs.

Overall the text is well written. The author has gone to considerable trouble to avoid specific medical terminology and has succeeded in this. The style of the book, however, is fundamentally that of a medical text; it could not be considered to be casual lay reading. I think the place of this book is as a reference text for paramedical and nursing staff working with lupus patients to answer their queries, as a book to keep at ward level for patient reference, and for use by the well-read lupus patient. I think this group of people will find it useful.

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