Volume 67 No. 2 NOV. 1998
ISSN 0041-6193

[continued on back cover

THE ULSTER MEDICAL JOURNAL

Published by
THE
ULSTER MEDICAL SOCIETY

The Ulster Medical Journal, Volume 67, No. 2
November 1998

Contents continued from front cover

The Ulster Medical Journal, Volume 67, No. 2, November 1998.

The Ulster Medical Journal

The Journal of the Ulster Medical Society. First published in 1932.
Successor to the Transactions of the Ulster Medical Society (1884-1929), and the Transactions of the Belfast Clinical and Pathological Society (1854-1862)

The Ulster Medical Society was founded in 1862
by the amalgamation of the Belfast Medical Society (founded 1806)
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THE ULSTER MEDICAL JOURNAL

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The Ulster Medical Journal

VOLUME 67

PUBLISHED BY

THE ULSTER MEDICAL SOCIETY

1998

CONTENTS

The Ulster Medical Journal, Volume 67, No. 2, pp. 147, November 1998.

Acknowledgements

We are grateful to the following for their continuing generous support:

Royal Victoria Hospital Medical Staff Committee – £750

Northern Ireland Council for Postgraduate Medical and Dental Education – £400

Mater Infirmorum Medical Staff Committee – £200

Erratum

UMJ 67 (S1) June 1998 p 85

Brian J Rowlands Introduction of the Purce Lecture

Surgeon Purce's Christian names were George Raphael Buick and not as they appeared.

The editor is grateful to Dr G B Purce for bringing this to his attention.

THE ULSTER MEDICAL SOCIETY

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The Ulster Medical Journal, Volume 67, No. 2, November 1998.

Editorial

Reflection, revelation, judgement and hope

Four events in recent months have been of significance that they have affected all of us either directly or indirectly. These events like the four horsemen of the Apocalypse bring with them reflection, revelation, judgement and hope.

The first of these events is "the Bristol case", a drama of huge proportions which reverberated far and wide and has held the attention of doctors, patients and politicians. If the medical profession is to regain the trust of patients then we must prove that we are serious about self-regulation and we need to embrace wholeheartedly the concept of clinical governance. The Apocalyptic rider on the black horse was holding a pair of scales in his hand. In the aftermath of Bristol we doctors must be prepared to have our work weighed against agreed clinical standards. The GMC has an important role to play, as do the Royal Colleges. Within Northern Ireland we can also look to the Council for Postgraduate Medical Education and to the Medical Faculty at Queen's for leadership and direction. However, we all must play our part in keeping a careful watch on maintaining standards of clinical practice.

The second important event was the 50th Anniversary of the NHS. Whilst the birthday celebrations were rather muted we were nonetheless afforded the opportunity to reflect on the success of this very treasured national institution. Many articles have been written over recent months reminding us of the foundation of the health service. The emotions of 1948 are captured for posterity in the words of Aneurin Bevan: "We are doing the most civilised thing in the world – putting the welfare of the sick in front of every consideration". There is no doubt that as a society we still believe that the NHS is "the most civilised thing". The medical profession in recent years has been a very loud advocate of the service, often lambasting successive governments over any perceived threats to the health service. Many young doctors born since 1948 find it almost incredible that just months before the NHS was due to be launched eighty six percent of doctors voted to have nothing to do with it. The lesson for us all is that we need to be ever watchful that a gap does not appear between medical politics and the greater good. The 50th Anniversary has given us an opportunity to reflect on the hardship and deprivation prior to the welfare reforms and to re-affirm our allegiance to a comprehensive national health service.

The third event was ushered in by the rider of the pale horse of the Apocalypse. Its rider was named Death and he carried the bomb to Omagh. That dreadful tragedy has brought to us all a grief which is still too raw and too unspeakable. However, through the tears and the bloodshed of that day we saw doctors, nurses, ambulance-men and a whole host of others working tirelessly and expertly: each man and woman working together to save, to mend, to comfort and console. As these images were flashed across continents we were immensely proud of their bravery and commitment and proud to know them as our colleagues and friends.

The fourth event was the Good Friday Agreement, leading to the Referendum and the Assembly elections. Whilst this will change the whole political face of Northern Ireland it will have particular consequences for the health and social services. The responsibility for health and social services will in the future rest with men and women who live amongst us, use our health services and depend on us for their electoral mandate. The new local minister for Health will need all our help and advice in one of the most challenging remits in the new administration. It would be tempting for the Assembly to concentrate their efforts on resolving the debate over our acute hospitals; however, if we are to build a sustainable future for our province public health needs to be placed firmly on the agenda. The enjoyment of the highest attainable standard of health is a fundamental human right. It will only be achieved if there is an integrated approach to combating the causes of ill health in our society. The Assembly will have to pursue policies which are aligned across all departments and sectors not

only because this is a political imperative, but because health is everyone's business.

Four events; – each one distinctive but like the horsemen of the Apocalypse bringing cause for reflection, judgement, revelation and finally hope. In the light of these events how can anything be the same again?

Dr HENRIETTA CAMPBELL
Chief Medical Officer.

The Ulster Medical Journal Index

With four issues 1998 has been a bumper year for the Journal. It has been an interesting year for other serious reasons. Dr Campbell mentions some in her editorial. The 200th anniversary of the United Irishmen has prompted a reappraisal of a period when a radical and enlightened movement struck a chord with those who were concerned with the conditions of their fellow countrymen. Those who heard Randal Hayes' lecture on Dr William Drennan will be aware of the role of one doctor in that process. (Those who missed it will be able to read his paper in our next volume) Whatever ones viewpoint, all would admit that a knowledge of history is a good thing. This applies equally to our medical history and culture. The Ulster Medical Journal has published a fair number of historical articles over the years. But scientific and clinical papers rapidly become historical documents themselves. We may be surprised, amused or shocked at what was published in the past, yet can always learn from it.

The Index which has been produced as a supplement to this issue of the journal provides a clear window into our first sixty four years. I would challenge any doctor not to find much of interest in its pages. And if your particular medical hobby horse is poorly represented there is an obvious remedy.

The Index is a fine piece of work and we owe a considerable debt to its three dedicated authors.

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MARK GIBSON

The Ulster Medical Journal, Volume 67, No. 2, pp. 79-90, November 1998.

Ulster says 'NO'; explosion, resistance and tolerance

Nitric oxide and the actions of organic nitrates

G D Johnston

Those who have started to read this review expecting a discussion of the political situation in Northern Ireland will either be relieved or disappointed. The title refers to the discovery and actions of nitric oxide and the role played by investigators in Northern Ireland, its relationship to the explosive nitroglycerine and the concepts of nitrate resistance and tolerance in cardiovascular medicine.

In 1867 Thomas Brunton, a newly qualified house surgeon at the Edinburgh Royal Infirmary pioneered the clinical use of the sphygmomanometer by employing it to monitor the increase in blood pressure associated with episodes of angina pectoris. Brunton speculated that amyl nitrite, a drug which he had observed to lower blood pressure in animals, might be used to relieve angina pectoris. He obtained a sample of amyl nitrite and poured it on to a cloth for his patient to inhale. Within a minute the pain disappeared and the patient remained free of pain for several hours.[1] Along with other nitrates and nitrites Brunton investigated the compound nitroglycerine which had become widely available following Alfred Nobel's discovery of its property as an explosive. Later the following year, William Murrell, a registrar at the Westminster Hospital decided to resolve the conflicting reports in the literature as to whether nitroglycerine caused severe headache or not. The French chemist, Ascagne Sobrero, who had first synthesised the compound, reported in 1847 that he experienced an intense headache after tasting a small drop placed on his finger. Others had similar experiences including Arthur Field, a Brighton dentist who claimed in the Medical Times and Gazette that if placed on the tongue it could alleviate toothache and neuralgia. He contended that it would be a highly effective remedy for these conditions if it were not for the severe accompanying headache. In contrast, others reported no effects whatsoever after swallowing large amounts of nitroglycerine. Murrell suspected that the differences were largely due to variation in the susceptibility of different individuals, and decided to conduct an experiment in healthy volunteers. In the course of one of his outpatient clinics he licked the moist cork of the bottle containing nitroglycerine solution and within a few seconds began to experience a throbbing headache and a pounding in the chest. After five minutes he had recovered sufficiently to resume his clinic but the headache persisted for most of the afternoon. With further experimentation, Murrell determined three important pharmacological properties of nitroglycerine; the effect lasted longer than amyl nitrite, the headache was usually related to overdosage and larger doses were required if the drug was swallowed than if it was allowed to dissolve slowly in the mouth. Murrell treated his first patients with nitroglycerine in 1878 and the following year published his report in the Lancet.[2] As a result, nitroglycerine was introduced into clinical practice for the treatment of angina pectoris. British doctors took steps to avoid any unnecessary alarm that might result if patients discovered that they were receiving the same explosive that was in dynamite and renamed the compound glyceryl trinitrate. No such niceties were adopted by their American colleagues, and in the United States the drug is still known as nitroglycerin. The high lipid solubility of glyceryl trinitrate facilitates good absorption across the buccal mucosa and the poorer response seen after oral absorption relates to first pass metabolism

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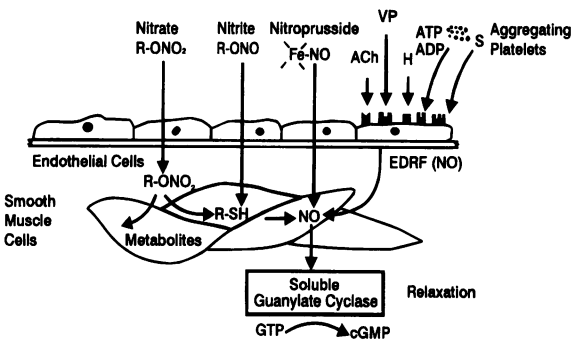
by the liver. The headache is due to the well-described vasodilator effects of nitrates on the extra-cranial blood vessels.

Despite widespread use of organic nitrates for over a century, the method by which they dilated veins and arteries was unknown. A new chapter in cardiovascular physiology and pharmacology opened in the early nineteen eighties with the discovery of a hitherto unknown vasodilator substance produced by the vascular endothelium EDRF (endothelium derived relaxing factor).[3] This compound is one of the most active endogenous vasodilators and is involved in the modulation of blood vessel tone. It took almost eight years of intense research to establish that this vasodilator compound was one of the smallest molecules known, NO (nitric oxide).[4] Organic nitrates enter vascular smooth muscle cells where they are reduced by sulphydryl groups to liberate nitric oxide. This in turn activates the enzyme soluble guanylate cyclase which converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) resulting in reduced intracellular calcium concentrations and smooth muscle relaxation (Figure 1). Sodium nitroprusside is an inorganic nitrate which forms nitric oxide directly without the need for biotransformation. It is a useful tool for assessing vascular smooth muscle responsiveness to nitric oxide, and distinguishing between impaired dilator responses which are due to an abnormality in the vascular smooth muscle, and those due to an endothelial defect. Recent observations have suggested that resistance to the action of nitrates occurs in a significant percentage of the population probably due to deficiency of intracellular sulphydryl donors, and this is more commonly seen in diabetes mellitus[5,6] and heart failure.[7,8] Continuous administration of organic nitrates can also lead to vascular tolerance through a similar mechanism. Repeated doses probably result in fewer S-nitrosothiols, leading to reduced activation of guanylate cyclase and a lower concentration of cyclic GMP with a resulting decrease in vascular relaxation.[9]

Fig 1. Proposed action of nitrodilators and nitric oxide in smooth muscle cells

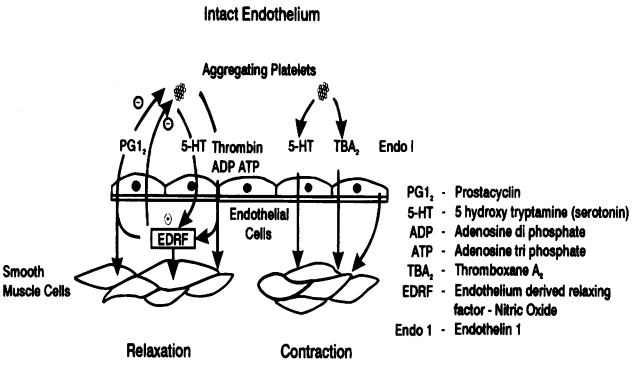


ACH - Acetylcholine
VP - Vasoactive peptides
H - Histamine
ATP - Adenosine triphosphate
ADP - Adenosine diphosphate
S - Serotonin

THE PHYSIOLOGY AND PHARMACOLOGY OF NITRIC OXIDE

Endothelial cells secrete nitric oxide which relaxes vascular smooth muscle.[10] Under physiological conditions NO is constantly released and ensures patency of the blood vessel. In the endothelial cells, NO is synthesised from the amino acid L-arginine by NO-synthase.[11] This enzyme is continuously active ensuring the constant release of NO. Disturbances in endothelial cell function decrease the production of NO and thus reduce vasodilation.[5,12] In addition to NO, endothelial cells also release prostaglandins with vasodilator activity such as prostacyclin. This endoperoxide induces vasodilation and inhibits platelet aggregation.[12] Damaged or excessively activated endothelial cells can also secrete vasconstricting factors of which the recently discovered endothelin-I is the best known.[13] Although thromboxane, a powerful vasoconstrictor, is produced by activated platelets, it is also released by damaged endothelial cells[14] (Figure 2).

Fig 2. Effects of platelet aggregation on the endothelium and vascular smooth muscle



Three nitric oxide syntheses have been described; an endothelial isoform (eNOS), a neuronal isoform (nNOS) in nitrergic nerves and a macrophage or inducible isoform (iNOS). The genes encoding the three isoforms of NO synthase have been located on human chromosome 7 (eNOS), 12 (nNOS) and 17 (iNOS).[15,16,17] The two predominant isoforms of NOS are eNOS and nNOS. The inducible form of the enzyme is iNOS found in endothelial, smooth muscle and several

other cells. It is involved in host defence mechanisms and immunological reactions. The constitutive form of NO synthase is expressed in endothelial cells and is involved in the regulation of vascular tone, structure and haemostasis. A wide range of factors have been found to stimulate the constitutive form of NO synthase including mechanical factors (shear stress and pulsatile pressure), platelet products (bradykinin, serotonin and histamine) and neurohormonal mediators (angiotensin II, acetylcholine and noradrenaline). Arteries produce more nitric oxide than veins, although veins respond better to organic nitrodilators. The biological half life is approximately thirty seconds and it is rapidly inactivated by haemoglobin, methylene blue and the superoxide anion. The development of competitive inhibitors of NO synthase, the L-arginine analogues N^G monomethyl-L-arginine (L-NMMA) and N^G nitro-L-arginine methyl ester (L-NAME) has provided an invaluable tool for investigation of the role of NO in biological processes. In addition to movement of nitric oxide from the endothelium to vascular smooth muscle, nitric oxide is also released into the lumen of blood vessels. Here it acts synergistically with prostacyclin to inhibit platelet aggregation, smooth muscle growth and cell proliferation.[18]

There is increasing evidence that nitric oxide has important physiological effects throughout the body and production is not confined to the vascular endothelium. Nitric oxide is present in lung epithelium and other pulmonary cells and has been suggested as the mediator of nerve dependent bronchodilatation.[19] Reduced nitric oxide release may also be the mechanism underlying pulmonary vasoconstriction which occurs secondary to hypoxia[20] and inhaled nitric oxide has been shown to reduce pulmonary vasoconstriction and the elevated pulmonary pressure occurring in chronic hypoxia. There is recent evidence that nitric oxide also has an important role in the central nervous system in protecting neurones from degeneration and mediating neuronal activity and nutritive blood flow. In high concentrations however, there is experimental evidence to suggest that nitric oxide may cause neuronal damage.[21, 22] Other functions of nitric oxide include control of gastrointestinal sphincter tone and motility,[23] the release of insulin in diabetic patients,[24] penile erection,[25] regulation of lymphocyte function[26] and producing vasodilation and tissue leakage in the inflammatory response.[27]

ENDOTHELIAL DYSFUNCTION AS A MARKER FOR VASCULAR DISEASE

The discovery of Furchgott and Zawadzki in 1980 of the obligatory role of the endothelium in producing vascular smooth muscle relaxation in response to acetylcholine[3] has provided a valuable method for assessing endothelial function. This method has been widely used to assess endothelial function in vivo in animals and humans. Most in vitro studies of endothelium-dependent relaxation involve mounting an isolated artery in an organ bath. The length of the artery is fixed and changes in isometric tension recorded. The artery is preconstricted with noradrenaline or phenylephrine and the relaxation in response to an endothelium-dependent vasodilator such as acetylcholine or serotonin recorded. In order to confirm that impaired vasodilatation is due to endothelial dysfunction, relaxation in response to an endothelium-independent vasodilator, usually sodium nitroprusside or glyceryl trinitrate is also determined. This helps to exclude non-specific impairment of smooth muscle relaxation. The method has been used to demonstrate impaired endothelial function in animals with diabetes,[28] hypercholesterolaemia,[29] hypertension[30] and vessels with evidence of atherosclerosis.[31] A small number of studies investigating endothelial function in smaller blood vessels have been carried out in diabetic animals examining pial,[32] retinal[33] or mesenteric[34] arterioles. Saenz de Tejada et al 1989 demonstrated that isolated penile corpora cavernosum tissue from diabetic and control subjects taken at the time of penile prosthesis implantation had impaired responses to acetylcholine.[35] The technique of venous occlusion plethysmography has been widely used to assess endothelial function in human subjects. This method involves the measurement of forearm blood flow in response to endothelium-dependent and independent vasodilators infused locally into the brachial artery.[5] It is the method which we in the Department of Therapeutics and Pharmacology have used most frequently to assess endothelial function in a variety of diseased states. Alternatively other vascular beds can be used, particularly those in the coronary circulation.[36]

EFFECT OF DISEASE ON ENDOTHELIAL FUNCTION

The vasodilatory function of endothelial cells has an essential role in maintaining the physiological

Fig 3. Factors associated with endothelial activation and damage

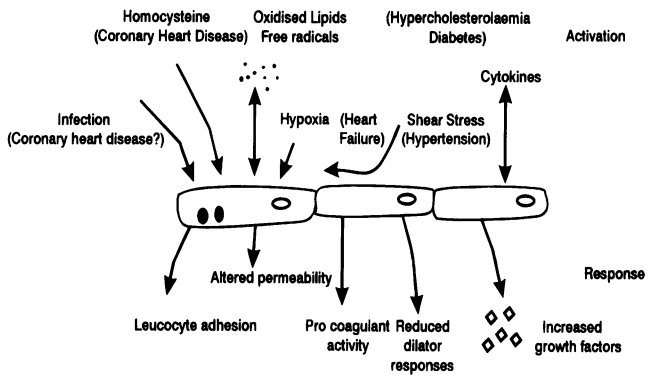
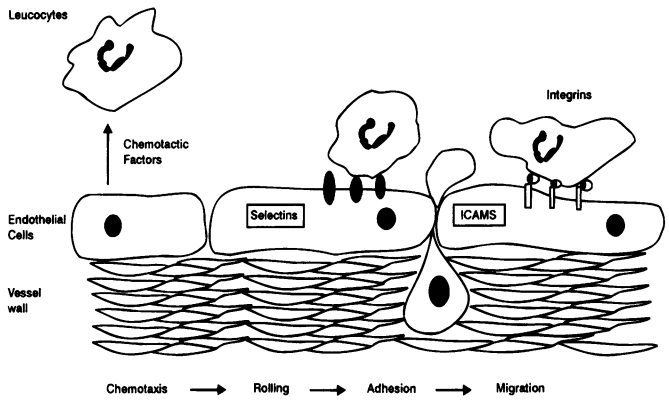


Fig 4. Factors involved in the regulation of endothelial cell adhesion



activity of blood vessels. Disturbances in endothelial cell function decrease the release of nitric oxide and reduce vasodilation (Figure 3). Damaged or excessively activated endothelial cells secrete endothelin-1 and produce a variety of adhesion molecules and chemotactic substances. As a result, leucocytes migrate to the endothelial wall.[37]

Near the wall they slow down and adhere to endothelial cells. This process of cell adhesion has been described over a long period of time and some of the underlying molecular mechanisms have recently been identified.

Endothelial cells induce adhesion by expressing specific surface adhesion molecules which interact with ligands on leucocytes and platelets[38] (Figure 4). Three groups of adhesion molecules have recently been identified: a family of selectins including E selectin and L selectin, a group of integrins such as LFA-1 (leucocyte function-associated antigen) and a supergene family of immunoglobulins such as ICAM-1 (intracellular adhesion molecule) and VCAM (vascular cell adhesion molecule). These adhesion molecules are expressed after stimulation of endothlial cells by specific factors such as tissue necrosis factor (TNF-α). This expression is increased on endothelial cells chronically damaged by risk factors for atherosclerosis such as smoking, hypertension and hypercholesterolaemia. In addition, high blood glucose concentrations and increased LDL cholesterol induce increased expression of ligands such as integrins which are the binding proteins for adhesion molecules.

Binding of blood cells to the endothelium affects the pathogenesis of atherosclerosis in several ways.[39] Increased binding of leucocytes and platelets leads to changes in the laminar blood flow and to the generation of turbulence which in turn increases platelet aggregability and risk of thrombosis. The binding of leucocytes to the endothelium also affects the production and release of reactive oxygen species from these cells.[40] In hyperglycaemic conditions binding of monocytes to glycosylated proteins can also occur.[41]

In diabetes and hyperlipidaemia disturbed permeability of the endothelial layer results in an increased movement of substances from the circulation into the vessel wall.[42] Insulin can migrate across the cell layer and stimulate smooth muscle cell proliferation and the mitogenic and migratory activity of other factors such as PDGF[43] (platelet derived growth factor). In addition, endothelial cell dysfunction can lead to accelerated intravascular blood coagulation by reducing nitric oxide and prostacyclin formation and decreasing fibrinolytic activity[44] (Figure 2).

(1) Diabetes and endothelial function

The relationship between diabetes and its vascular complications is complex but it seems likely that damage to the vascular endothelium plays a major role. Exposure of plasma and cell membrane proteins to hyperglycaemic conditions for prolonged periods results in the attachment of glucose molecules to proteins, a process known as non-enzymic glycosylation. Further slow reactions result in the formation of advanced glycosylation end-products (AGEs)[45] which have been shown to inactivate nitric oxide and impair endothelium-dependent vasodilation.[46] However these vascular responses are also impaired during short term hyperglycaemia suggesting that this is not the principal mechanism.[47] In the presence of hyperglycaemia, the phytol metabolic pathway is stimulated resulting in an increased utilisation of NADPH. Since NADPH is an essential co-factor for nitric oxide synthase reduced availability

within the cell could result in reduced nitric oxide production. Depletion of NADPH could then result in enhanced oxidative stress and increased susceptibility to free radical attack. Aldose reductase inhibitors have proved effective in restoring endothelial function in experimental diabetes[48] although their impact on the vascular complications of diabetes has been disappointing. Increased oxidative stress in diabetes results from several different sources. These include phytol pathway activity, auto-oxidation of glucose and reduced antioxidant concentrations including vitamin E and ascorbic acid.[49] The resulting increase in free radical activity in diabetes can cause cellular damage and inactivation of nitric oxide. Several studies have demonstrated improved endothelial function in response to free radical scavengers in diabetic animals.[50]

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Although the causes of vascular damage in diabetes are in large part due to hyperlgycaemia, other metabolic factors probably contribute. Hyperlipidaemia is associated with endothelial dysfunction and increased morbidity.[51] A large percentage of patients have lipid abnormalities including hypertriglyceridaemia, reduced HDL cholesterol, increased LDL cholesterol and increased amounts of oxidised LDL cholesterol. The role of oxidised LDL cholesterol in causing endothelial damage has recently been described in this department by measuring the cytotoxicity of LDL cholesterol from diabetic patients in culturedllendothelial cells.[52]

Hyperinsulinaemia may also be involved in producing vascular damage in diabetes and increasing the risk of developing atherosclerosis.[53] A major hypothesis is that increased insulin concentrations occurring as a result of insulin resistance cause sodium retention and increased sympathetic activity. Both factors tend to increase blood pressure which is associated with increased cardiovascular morbidity and endothelial dysfunction in the absence of diabetes.[54] Studies linking hyperinsulinaemia with arterial disease and hypertension are inconsistent and increased prevalence of atherosclerosis and hypertension is not a feature of insulinoma, a condition associated with extremely elevated insulin levels.[55]

(2) Hyperlipidaemia and endothelial function

There is now a considerable amount of evidence that low density lipoproteins (LDL) impair the activity of nitric oxide. This is in part due to LDL itself but most evidence suggests that oxidised LDL has a more important and lasting effect.[56] Endothelial cells, macrophages and vascular smooth muscle cells can oxidise LDL cholesterol. If this is not removed by antioxidants such as vitamin E it can be taken up by scavenger receptors on the macrophages where it accumulates to form foam cells and contributes to the development of atheroma. High levels of circulating LDL cholesterol have been shown to reduce endothelium-dependent vasodilator responses to aggregating platelets and prostacyclin release and could predispose to vasoconstriction, platelet adhesion and thrombus formation.[57]

(3) Hypertension and endothelial function

Abnormalities of endothelial function are well described in hypertension. Endothelium-dependent dilation is diminished in experimental hypertension and in patients with essential hypertension. Lowering blood pressure in experimental animals prevents the development of these abnormalities but abnormal responses remain to some degree in adequately controlled hypertensive patients.[58]

(4) Circulatory shock and endothelial function

If a little nitric oxide is good for cardiovascular health, large amounts are often dangerous. In endotoxin shock there is massive release of nitric oxide leading to vasodilation and hypotension. In animal models the blood pressure can be restored by agents such as L-NMMA which prevent nitric oxide production.[59] Release of nitric oxide by endocardial and myocardial cells may also occur accounting in part for the depressed cardiac function which occurs in some patients with endotoxic shock. Increased nitric oxide synthesis probably also has an important role in haemorrhagic shock[60] and we have recently demonstrated increased nitric oxide activity in patients with systemic vasculitis.[61]

(5) Other diseases associated with abnormal nitric oxide production

Impaired nitric oxide activity in the large systemic arteries has been demonstrated in congestive cardiac failure,[62,63] in the coronary circulation, in congestive cardiomyopathy and in vein grafts. Smoking is also associated with the abnormalities

of endothelial and platelet function seen in patients with hypercholesterolaemia.[57] In infantile pyloric stenosis a selective depletion of nitric oxide has been found in the circular pyloric muscle.[64]

Following the identification of a nitric oxide-like factor in brain tissue in 1988 there has been extensive research on the possible role of nitric oxide as a neuronal mediator.[21] A specific nitric oxide synthase enzyme has been purified and cloned and is most abundant in the cerebellum and olfactory bulbs. [21] In Huntington's disease, and in cerebral ischaemia it has been suggested that nitric oxide may protect neurones from oxidative injury.[21] Protection, however, may depend on the concentration of nitric oxide; at low levels it appears to have an enhancing, mediating and protecting role in brain neurones while at high levels nerve damage seems to be more likely.

It has also been recently established that nitric oxide is the principal mediator of penile erection. Nitric oxide synthase is localised in pelvic neurones innervating the corpora cavernosa and in the neuronal plexuses of the adventitial layer of the penile arteries.[25] It seems likely that erectile impotence in diabetic men involves impaired function of the L-arginine-nitric oxide pathway,[65] and anecdotal evidence suggests that the local application of glyceryl trinitrate to the penis of impotent men causes erection with a headache in the sexual partner being the only adverse effect.

Clinical uses of nitric oxide

As discussed previously, drugs which donate nitric oxide to vascular smooth muscle and produce vasodilation have been used in clinical medicine for almost one hundred and fifty years.[1] Glyceryl trinitrate preferentially dilates veins, a principal reason for its clinical value in angina pectoris and congestive cardiac failure. The reason for the venoselectivity could be related to the low basal output of nitric oxide, and consequently the guanylate cyclase in venous smooth muscle is upregulated and responds more readily to exogenous nitric oxide. By the same reasoning, reduced nitric oxide synthesis at sites of endothelial damage or dysfunction in arteries or arterioles should make these vessels more sensitive to the actions of nitrodilators. The antiplatelet effects of nitric oxide provided by organic nitrates may also have some beneficial therapeutic effects. Recent studies have focused on the development of new classes of nitrovasodilators. S-nitrosoglutathione (GINO) has recently been shown to have selective antiplatelet effects.[66]

New uses for nitric oxide are being explored. These include the local application of organic nitrates for the treatment of impotence, systemic administration for acute stroke and delayed labour and inhalation of nitric oxide in a variety of respiratory conditions[67] such as respiratory distress syndrome,[68] acute lung injury, pulmonary hypertension[69] and in diseases associated with ventilation-perfusion inequality.

There have been a number of encouraging reports on the value of inhaled nitric oxide in pulmonary hypertension. The condition is frequently observed in neonatal and in adult respiratory distress syndrome and following cardiopulmonary bypass surgery. However, inhaled nitric oxide remains an experimental form of treatment and there is no useful information on the benefits of nitric oxide in any chronic respiratory disease. Most chronic lung diseases are associated with structural changes so that the effects of inhaled nitric oxide are unlikely to result in major benefit. Inhaled nitric oxide is not without its own problems. Nitric oxide can combine with oxygen resulting in nitric acid formation and increased toxic radicals. Methaemoglobinaemia can occur and at high concentrations it could exert pro-inflammatory effects.

Other drugs may increase the production of endogenous nitric oxide. Angiotensin converting enzyme inhibitors inhibit the breakdown of bradykinin which in turn stimulates the release of nitric oxide from the endothelium in patients with coronary artery disease[70] and congestive heart failure.[71] Recent interest has focused on the possibility of enhancing nitric oxide production by providing excess of its substrate L-arginine. Although arginine is plentiful in the diet and is not the rate limiting factor for nitric oxide synthesis, there are reports that arginine prevents the onset of atheroma in experimental animals and improves endothelial function in patients with hypercholesterolaemia,[72] angina[73] and in patients following cardiac transplantation.[74] In a recent study involving patients with heart failure, chronic L-arginine supplementation was found to improve blood flow.[75]

Clinical methods and indications for the reduction of nitric oxide

In some clinical situations it may be valuable to inhibit the synthesis or activity of nitric oxide. Inhibition of nitric oxide synthesis with substrate analogues such as N^G monomethyl-L-arginine reverses the local vasodilation associated with inflammation and the profound hypotension and cytotoxic effects which occur in endotoxin shock.[59] Selective inhibitors of the inducible isoform of nitric oxide synthase are being developed as possible anti-inflammatory drugs. Such agents would have the theoretical advantage that they would inhibit the pathophysiological production of nitric oxide without impairing endothelial, neuronal or platelet function. Drugs in common clinical use may also reduce nitric oxide synthesis. Corticosteroid drugs inhibit the induction of nitric oxide synthase but are ineffective once the enzyme is expressed. Methotrexate inhibits the synthesis of tetrahydrobiopterin, an essential cofactor for the induction and activity of nitric oxide synthase.[76] The relationship between this and the drug's clinical effect is unknown but the findings raise the possibility of developing more specific anti-inflammatory or immunosuppressive drugs based on alteration of the inducible nitric oxide pathway.

Nitrate tolerance

Although nitric oxide is the active component of drugs collectively known as the nitrovasodilators some are able to release nitric oxide directly while others require metabolic conversion by muscle cells. Sodium nitroprusside spontaneously releases nitric oxide from its complex.[77] Organic nitrates such as glyceryl trinitrate, isosorbide dinitrate and isosorbide mononitrate require the presence of sulphydryl (SH) groups within the cells to release and generate nitric oxide[78] (Figure 1). With continuous administration of organic nitrates tolerance to their effects in angina and heart failure has been described especially if the transdermal route is employed.[79,80]

Tolerance to the vascular effects of organic nitrates has long been recognised in the munitions industry.[81] The headaches, flushing and lightheadedness experienced during early exposure became less intense or disappeared when workers had been exposed for several days. Such tolerance was short lived and when workers were away from the factory for short periods symptoms recurred on re-exposure. In addition, Lang and colleagues 1972 described chest pain in munition workers during periods away from work which were thought to be due to coronary vasoconstriction.[82] Current concepts of nitrate tolerance have focused on impaired intracellular metabolic conversion of nitrate to nitric oxide. When tolerance develops there appears to be a decreased ability of the organic nitrate to undergo metabolic conversion to nitric oxide probably due to a relative unavailability of reduced intracellular thiol groups.[83] Recent evidence suggests that extracellular pathways of organic nitrate metabolism may provide an alternative pathway for conversion to nitric oxide.[84] In the tolerant state, there is reduced nitric oxide generation leading to failure of smooth muscle relaxation.

In vitro experiments have documented decreased generation of cyclic guanosine monophosphate in the presence of nitrate tolerance. There appears to be no abnormality of the enzyme guanylate cyclase however which remains fully responsive to sodium nitroprusside and bypasses the cysteine-dependent metabolic cascade. Several studies have demonstrated that sulphydryl donor administration with N-Acetylcysteine or methionine can reverse or prevent tolerance which occurs during sustained nitrate administration.[85] The value of this type of treatment, in preventing nitrate tolerance is at present of little practical value.

INTERVAL THERAPY FOR NITRATE TOLERANCE

A number of investigations have demonstrated that nitrate dosage regimens, punctuated by prolonged nitrate-free intervals, can maintain the beneficial clinical effects of nitrates in angina pectoris[86, 87] and congestive cardiac failure.[88, 89] Overall, most studies support the view that the use of intermittent nitrate therapy is less likely to result in tolerance than continuous therapy administered by the oral,[90] intravenous,[85] or transdermal[91] routes. While maintaining a dosage-free interval of at least eight hours has been successful in reducing the incidence of nitrate tolerance, the approach has a number of potential disadvantages. The main problem is a worsening of the chest pain during the period when the drug is withdrawn. Fortunately the adverse consequences of intermittent therapy have been minimal in most studies. However in a large placebo-controlled study intermittent transdermal

glyceryl trinitrate therapy produced nocturnal or rest angina during the drug free interval in the active treated group but not in the placebo group.[92] The possibility of glyceryl trinitrate rebound phenomenon must be kept in mind in view of the previous observations experienced by munition workers.[92]

Studies of silent myocardial ischaemia in coronary heart disease have demonstrated a low frequency of ST segment depression in the period from midnight to 7 am in patients with chronic stable exertional angina. This supports the view that the usual nitrate-free period during sleep causes problems in patients with stable angina without rest or nocturnal pain. The use of other antianginal drugs such as beta adrenoceptor antagonists and calcium channel antagonists is clearly an important strategy in providing protection against ischaemia during the nitrate-free interval.

Nitrate Resistance

A variety of cardiovascular conditions are associated with primary nitrate tolerance or resistance. Failure to reduce blood pressure with intravenous doses of glyceryl trinitrate in excess of 200 μg/min is commonly seen in patients with congestive cardiac failure.[93] Possible mechanisms include primary receptor resistance and secondary mechanisms such as catecholamine-induced increases in vaso-constrictor tone, activation of the renin angiotensin system, haemodilution, impaired dilation due to vessel wall oedema and impaired hepatic metabolism of the nitrate.[94] Impaired or absent haemodynamic responses are also occasionally observed in the period following an acute myocardial function.[95] Failure of the blood vessels to dilate suggests primary receptor tolerance which is not overcome by very high doses.[96] In a series of experiments we demonstrated impaired vasodilator responses to glyceryl trinitrate in patients with non-insulin dependent diabetes mellitus when compared with age and sex matched controls.[5, 6] This impaired response was somewhat surprising since diabetes is associated with impaired endothelial function and nitrate-induced vasodilation has been shown to be increased when the endothelium is damaged. I have already discussed that the biotransformation of organic nitrates requires intracellular sulphydryl groups to produce vasoactive intermediates which stimulate guanylate cyclase. Oxidation or depletion of these sulphydryl donors will lead to impaired responsiveness to organic nitrates. In diabetes antioxidant activity is decreased.[97, 98] Increased oxidative stress and enhanced free radical activity occurring in diabetes probably alters the oxidation – reduction equilibrium of intracellular thiols and results in primary oxidation or depletion of the essential sulphydryl donors. This seems the most likely explanation for the impaired responses observed in diabetes.[5, 6] In conclusion, resistance to the action of organic nitrates has been demonstrated in congestive cardiac failure, type II diabetes and following an acute myocardial infarction. Studies performed in our laboratory would also suggest that a significant percentage of normal subjects show impaired vasodilator responses to organic nitrates.[99]

CONCLUSIONS

Although nitrates have been prescribed for patients with angina pectoris for over a century and more recently for congestive cardiac failure, it is only over the last few years that new insights into their mode of action have been identified. The discovery of the endogenous nitro vasodilator nitric oxide, produced in endothelial cells by the enzyme nitric oxide synthase has greatly expanded our knowledge of the action of organic nitrates. Nitric oxide, when released from endothelial cells can interact with vascular smooth muscle and platelets by activating soluble guanylate cyclase and increasing cyclic GMP. In vascular smooth muscle this causes vasorelaxation and reduced platelet adhesion. Exogenous nitrodilators exert their action by producing nitric oxide. Their vasodilator activity is greatest in blood vessels with low basal production of nitric oxide such as veins and vessels in which the endothelium is removed or damaged. A significant percentage of patients with heart failure, diabetes and ischaemic heart disease fail to respond to nitrate therapy however. Long term use of organic nitrates is associated with the development of tolerance or of reduced therapeutic efficacy when administered in doses or formulations which maintain therapeutic plasma levels over a twenty four hour period. The administration of N-acetylcysteine, angiotensin converting enzyme inhibitors or diuretics do not consistently prevent nitrate tolerance. At present intermittent therapy is the only satisfactory method to reduce nitrate tolerance although other antianginal drugs may be required during the nitrate-free intervals.

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The Ulster Medical Journal, Volume 67, No. 2, pp. 91-98, November 1998.

Outcome in Hodgkin's disease: A 20-year cohort of patients

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Accepted 1 July 1998

SUMMARY

We reviewed the long-term survival, treatment-related mortality and morbidity of a continuous cohort of patients with Hodgkin's disease diagnosed and staged at the Haematology unit of the Belfast City Hospital between January 1973 and October 1992. The analysis included a comparison of the survival of those patients who were entered into BNLI (British National Lymphoma Investigation) trials compared to those not entered during this 20 year period. In addition univariate and multivariate analysis of prognostic factors was performed.

The complete remission rate (CR) was 79.6% with a 15 year survival of 55.3%. On multivariate analysis in which deaths due to active Hodgkin's disease only were considered age >50 emerged as the most significant prognostic factor (P<0.0007), the presence of B symptoms also having independent significance (P=0.008). Trial status did not have any independent prognostic significance. Eighty one deaths occurred: active Hodgkin's disease (50), second malignancy (9), treatment-related (10), unrelated (9), unknown (3).

This long-term follow up study provides useful information additional to the data produced by clinical trials which are biased by selection criteria. The occurrence of *Haemophilus Influenzae* meningitis in a patient 17 years following splenectomy highlights the need for appropriate vaccination of patients splenectomised for Hodgkin's disease.

INTRODUCTION

It is now 166 years since Thomas Hodgkin published his original article *"On some morbid appearances of the absorbent glands and spleen"*, in which he described six cases of a condition which he believed to be a specific disease entity. Within the last century Hodgkin's disease has emerged as a curable malignancy due to the efficacy of megavoltage radiotherapy, combination chemotherapy, and more recently marrow ablative chemotherapy followed by stem cell grafting. The survival of patients today has dramatically improved when compared with that of untreated patients, whose five-year survival was reported to be 5.6%.[1] With the advent of kilovoltage radiotherapy in the 1920's this figure rose to 51%,[2] and a further significant survival increment (73.3% at 5 yrs) resulted from the use of megavoltage radiotherapy in the 1950's.[3] Within the last 3 decades the use of combination chemotherapy and combined modality therapy has improved survival with approximately 85% of patients alive at five years.

Such survival data is mainly obtained from the results of clinical trials, which are designed to evaluate different therapeutic regimens in strictly equal patient cohorts, a process which necessitates the use of inclusion/exclusion criteria. This inherent selection process means that clinical trials cannot assess the real survival probability of all patients with a specific disease. For this reason single centre outcome studies are an important means of determining survival outcomes in unselected cohorts of patients. This study was undertaken primarily to ascertain the long-term survival of all patients suffering from

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Hodgkin's disease who were diagnosed and staged at the Belfast City Hospital over a twenty year period. Secondary objectives were to compare the survival of those patients entered into BNLI trials with those patients who for various reasons were not, to assess the delayed effects of treatment to identify the various causes of death and to investigate those factors which adversely affected survival in this continuous cohort of unselected patients.

METHODS

We reviewed the case notes of 209 consecutive patients with previously untreated Hodgkin's disease who were diagnosed/staged in the Haematology unit of the Belfast City Hospital from January 1973 to October 1992. One hundred and twelve of these patients had been entered into various BNLI trials, following acceptance of the histological diagnosis by the BNLI panel.

Pathology review

Limited resources prohibited histological review of all the 89 non-trial patient's diagnostic biopsies, but a local panel of pathologists was formed to review the original histology of any of the non-trial patients in situations known to be associated with diagnostic difficulty (i.e. original diagnosis had been made on extranodal tissue, original histology had not been classified using the Rye classification, a second biopsy had questioned the original diagnosis, a second malignancy had been diagnosed simultaneously (within 6 months).) These criteria identified 18 cases for review and with the additional aid of immunocytochemistry a diagnosis of non Hodgkin's lymphoma was favoured in four cases, myeloproliferative disorder in two, and non-diagnostic in two, leaving a total of 201 cases for analysis.

Patients

The characteristics of the patient population (N=201) which includes two sets of siblings are shown in Table I. The median age was 32 (range 9 to 81), with the usual male preponderance being noted.

Staging method

Patients had been staged in accordance with BNLI protocols. Routine staging investigations included: FBC with DWCC, baseline ESR, serum copper, lactate dehydrogenase, liver function tests, bone marrow examination and chest xray with or without tomography. Prior to 1981 lymphangiography with or without abdominal ultrasound was used to detect infradiaphragmatic disease, and following these investigations patients with apparently localized disease and absence of B symptoms (fever, night sweats and/or unexplained loss of 10% of body weight) who would have been suitable candidates for local radiotherapy routinely underwent staging laparotomy with splenectomy, wedge liver biopsy, and biopsy of suspect abdominal glands. Since then the increasing use of CT scanning of the thorax, abdomen and pelvis effectively made lymphangiography and laparotomy redundant[4] as it became clear that staging laparotomy had no impact on survival owing to the effectiveness of salvage chemotherapy for patients relapsing after initial radiotherapy.

TABLE I

Patient population (N=201)

Variable	*Catrgory*	*number*	*%*
Sex	male	125	62
	female	76	38
Age	<50	152	75.6
	>50	49	24.4
Trial status	yes	112	55.7
	no	89	44.3
B symptoms	yes	119	59.2
	no	82	40.8
Stage	I	38	19
(Ann Arbor)	II	69	34
	III	58	29
	IV	36	18
Histology	LP	15	7
	NS	130	65
	MC	40	20
	LD	12	6
	U	4	2
Laparotomy	yes	75	37
status	no	126	63
Lymphangiography	yes	61	30.3
	no	140	69.7

LP=Lymphocyte predominant
NS=Nodular sclerosis
MC=Mixed cellularity
LD=Lymphocyte depleted
U=Unclassified

Patient treatment

The patients entered into the BNLI trials were treated according to trial protocols. Localized disease was treated with either local or regional radiotherapy of the mantle (MR) or inverted Y type, and some patients with stage III disease received total nodal irradiation (TNI). More advanced stage disease was treated with combination chemotherapy regimens: mustine, vincristine, procarbazine and prednisone (MOPP); chlorambucil, vincristine, procarbazine and prednisone (LOPP); or doxorubicin, vinblastine, etoposide and prednisone (EVAP).[5,6] In more recent years the intensive regimen consisting of carmustine, etoposide, cytarabine and melphalan (BEAM) followed by autologous stem cell transplantation has been used.[7] Eleven patients in this cohort have undergone autologous transplantation using bone marrow or peripheral blood stem cells.

The remaining patients who were not entered into BNLI trials were treated in a similar fashion – radiotherapy for localized disease without B symptoms, and combination chemotherapy regimens similar to the above.

Twenty four patients following initial staging were treated and followed up at two other centres: The Northern Ireland Centre for Clinical Oncology and Radiotherapy (22 patients), and Craigavon Area Hospital (two patients).

Response to treatment and patient follow-up

The clinical notes were studied to reassess the response to treatment at the completion of therapy. Criteria for complete remission (CR) were disappearance of all clinical, biochemical and radiological evidence of disease, and if CR occurred it was dated from the completion of therapy. Rates of relapse and subsequent attainment of second, third, and fourth remissions were recorded. Complications of the disease or its treatment such as sepsis, infertility, second malignancy, herpes zoster, cardiac and respiratory sequelae were documented.

Follow-up information on all patients was obtained by telephoning the general practitioner, or by means of a written questionnaire. Information on patients no longer living in Northern Ireland was sought from the haematology-oncology centre responsible for patient care. Death certificates and post-mortem reports were studied, and causes of death were categorized as Hodgkin's disease-related, treatment-related, second malignancy, other causes , or unknown. In 200/201 cases overall survival was measured from the date of histological diagnosis to the date of death or to September 1st, 1993 (date of study commencement), with one patient being lost to follow-up after 6 years of observation.

Statistical Analysis

Statistical analysis was carried out using SPSS software. Survival was calculated using the life table method of Kaplan and Meier. In the analysis of prognostic factors deaths due to active Hodgkin's disease only were included. Unrelated and second malignancy deaths were disregarded as were early deaths during induction chemotherapy, most of which were due to chemotherapy-induced sepsis. Comparisons in univariate analysis were performed using the log rank test. Factors which reached significance on univariate analysis were analysed using a stepwise Cox proportional hazards regression. A final model was obtained containing only those factors which maintained independent prognostic significance.

RESULTS

Response to treatment

The CR rate was 79.6% (160/201) and the majority of these patients (111) did not relapse. Of the 49 patients (31%) who relapsed approximately half went on to achieve second CR(25/49). Second relapse occurred in nine of these 25 patients (36%), five of whom successfully achieved third CR, and one patient achieved fourth CR. Patients who achieved CR were significantly younger than non-remitters ($P<0.001$).

The majority of first relapses (45/49) occurred within five years of the completion of therapy, with only one relapse beyond 10 years and remainder between 5-10 years.

Survival

The overall survival for the 201 patients is shown (Fig. 1) which includes deaths from all causes. The 10 and 15 year survival rates were 61.3% (confidence interval 54 to 68.6) and 55.3% (confidence interval 47.2 to 63.4). The median period of follow-up was 7.4 years for all patients, and 11.6 years for those patients still alive. Survival for patients who achieved CR was significantly better than non remitters ($P<0.0001$).

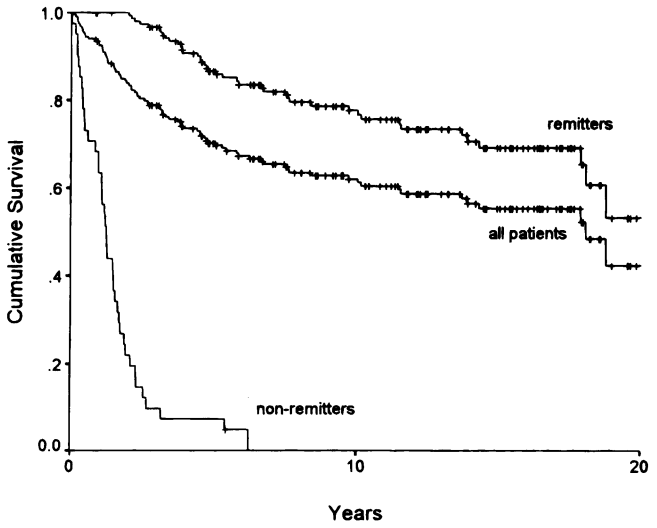

Fig 1. Survival of all patients (N=201), with a comparison of the survival of patients achieving remission (remitters N=160) with that of non-remitters (N=41), P<0.0001.

Figure 2 shows that the survival of trial patients from Belfast is very similar to that of trial patients from other UK centres (G Vaughan Hudson, personal communication).

Causes of death

Eighty one deaths occurred, the majority of which (n=50) were due to active Hodgkin's disease. Ten deaths were treatment-related, including two splenectomy-related deaths: one early death due to subphrenic abscess and haemorrhage from multiple acute gastric ulcers; and one death due to *Haemophilus influenzae* meningitis occurring 17 years following splenectomy in a stage IA patient. Infection was a major contributing factor in the remaining treatment-related deaths with several deaths from gram-negative sepsis, and one death from *herpes simplex* encephalitis. Nine patients died from unrelated causes: trauma 3, myocardial infarction 3 (2 in CR, 1 prior to treatment), pulmonary embolism 1, stroke 1, bronchopneumonia in CR 1. In three cases the cause of death could not be accurately determined.

Second malignancy developing between 0.3-18 yrs (median 4 years) resulted in the death of nine patients (respiratory 4, gastro-intestinal 3, lymphoblastic lymphoma 1, undetermined 1).

Other complications of the disease or its treatment

VIRAL INFECTIONS

Herpes zoster infection occurred in 41 patients (21%) during the period of hospital follow-up, and three of these patients had disseminated zoster. As previously mentioned a fatal case of *herpes simplex* encephalitis occurred.

FERTILITY STATUS

Infertility post chemotherapy/radiotherapy was only documented in eight patients, four male (3 of whom had received MOPP or LOPP, and one who had received TNI + LOPP), and four female (one having received LOPP and EVAP, one TNI, and the remaining 2 patients BEAM chemotherapy. In contrast 8 female patients who received combination chemotherapy have subsequently become pregnant.

Analysis of prognostic factors influencing survival

UNIVARIATE

The results of univariate analysis are shown in Table II. Age >50 (P<0.0001), elevation of the baseline ESR >50 mm/hr (P=0.0001), and elevation of the baseline serum copper (P=0.0009) emerged as the most significant factors influencing survival. There was a trend towards improved survival for patients entered into trials but this did not reach statistical significance (P=0.08). In this analysis the following factors were found not to be significant: sex, absolute lymphocyte count <1.5 x10^9/L, elevation of the serum LDH, mediastinal involvement, histological subtype, and treatment period 1973-1981 vs 1982- 1992.

Multivariate

Two factors alone age >50 and the presence of B symptoms maintained independent prognostic significance (Table II). Elevation of the baseline serum copper approached significance (P=0.056).

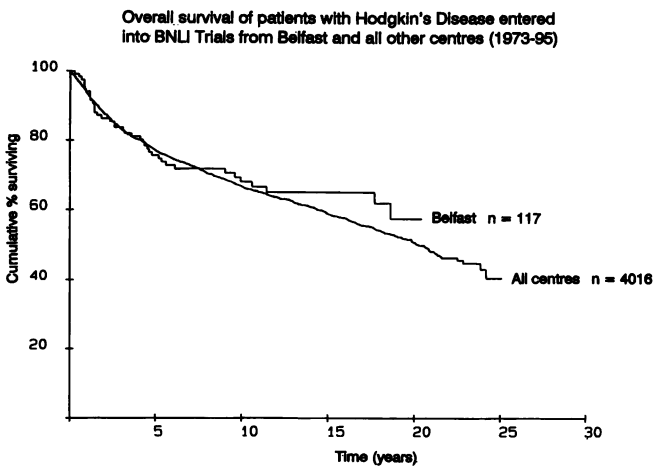

Fig 2. Survival of Belfast trial patients compared to trial patients from other BNLI centres.

TABLE II

Analysis of prognostic factors influencing survival

			Univariate	*Multivariate*		
Factor	*category*	*numbers*	*Significance (P)*	*Significance (P)*	*relative risk*	*95% CI*
Age	<=50	152				
	>50	49	<0.0001	0.007	2.73	(1.31-5.7)
B symptoms	no	82				
	yes	119	<0.0001	0.008	3.79	(1.4-10.2)
Copper	<=26.7	71				
	>26.7	81	0.0009	0.056	2.33	(0.97-5.58)
ESR	<=50	102				
	>50	74	0.0001			
Trial status	yes	112				
	no	89	0.08			
Albumin	>=35	98				
	<35	47	0.0147			
Alkaline phosphatase	<=280	74				
	>280	71	0.02			
Bone marrow involvement	no	163				
	yes	19	0.003			
Stage 4	no	165				
	yes	36	0.0007			
Hb<10	no	165				
	yes	23	0.0042			
Platelets	150-400	118				
	>400	59	0.096			

Analysis includes only deaths due to active Hodgkin's disease (N=50)

Comparison of the trial patients with the non-trial patients

Trial patients were a significantly younger cohort (P=0.028). Univariate analysis showed a trend towards longer survival in the trial patients but this did not reach statistical significance.

DISCUSSION

Long term follow-up studies in curable malignancies are essential to enable clinicians to assess treatment-related morbidity and mortality and subsequently modify treatment protocols in order to minimize unwanted sequelae, without jeopardizing the prospect of cure. The survival data from studies such as this provide a full assessment of the efficacy of treatment and the morbid consequences of it, and are a source of valuable information which can be subjected to meta-analysis. Our survival rates are very similar to the results of the relatively few centres that have investigated long term survival in a consecutive group of patients,[8-10] to the figures produced by the international data base on Hodgkin's disease[11] and to the BNLI data for other trial centres (Vaughan Hudson G, personal communication). An improved outcome for patients managed in comprehensive cancer centres rather than in general hospitals has been recorded.[12] Our data suggests that the benefit of trial participation is not restricted to those patients

randomized into clinical trials but that it reaches the nontrial cohort in the participating centre, a finding noted in the management of patients with myeloma in Finland.[13]

The knowledge of important prognostic factors has significantly modified the staging and treatment of Hodgkin's disease in the past two decades. Advanced age is commonly found to be a highly significant adverse factor on multivariate analysis,[5, 6, 8-11] as is the occurrence of B symptoms.[5,14] In our method of analysis of prognostic factors we have disregarded not only unrelated and second malignancy deaths but also early induction deaths, the majority of which were due to chemotherapy-induced sepsis, believing such deaths to relate to random unpredictable events possibly related to variability of marrow depression secondary to chemotherapy and/or variability in depression of cellular immunity. When this method of analysis is applied, only the factors of advanced age and the presence of B symptoms maintain independent significance, with elevation of the serum copper approaching significance.

Elevation of the serum copper in Hodgkin's disease was first described in 1957,[15] and since then it has been infrequently mentioned in the literature.[16-20] In this study elevation of the serum copper approached significance on multivariate analysis We feel that further evaluation of the prognostic significance of this variable in a larger number of patients would be interesting in order to clarify its status as an independent prognostic factor.

Active Hodgkin's disease caused the majority of deaths 50/81 (64%) in this series, and this correlates closely with data from previously published series,[8] and with data produced from the international data base on Hodgkin's disease[11] in which 14,225 patients were registered. Nine of our patients developed second malignancy (4.5%) which is similar to the findings of other authors,[8, 21-23] and the latter three authors have calculated that up to a 6 fold excess risk of all second cancers exists in patients treated for Hodgkin's disease when compared to general population incidence data. Advanced age at the time of diagnosis has been associated with an increased incidence of second malignancy,[11, 22, 23] and combined modality therapy has also been implicated.[22, 24] The occurrence of acute myeloid leukaemia has been reported between 0.4%–10 % of patients,[8, 24] yet no cases have been seen in this series to date. This may be due to the low use of MOPP therapy in this cohort, as MOPP therapy alone or in combination with radiotherapy has been shown to be a significant predisposing factor.

Two laparotomy-related deaths occurred in this series, one of which was due to *Haemophilus influenzae* meningitis occurring 17 years following splenectomy in a patient in continuing first remission, and this 1.3% incidence of fatal sepsis post splenectomy is similar to that reported by Mazza et al in his series of 570 patients.[9] During the course of this study we were able to identify 47 living asplenic patients whose vaccination status was unknown, we subsequently contacted their general practitioners with a view to having them appropriately vaccinated against *Pneumococcus* and *Haemophilus influenzae* type B in accordance with recently published guidelines.[25]

Infertility was documented in eight patients during the period of hospital follow-up, five of whom had received MOPP, which has been implicated as a major cause of gonadal dysfunction;[26] in contrast live births occurred in eight patients following treatment with combination chemotherapy (MOPP or LOPP). Fertility status proved very difficult to assess accurately as although data on female patients is relatively easily obtained from the hospital or primary care notes, fertility status on male patients is difficult to determine unless semen analysis following therapy has been performed. In addition, pregnancies in the partners of male patients are not usually recorded in the patients' notes, and without DNA testing paternity cannot be confirmed.

In this study we did not demonstrate a significant improvement in survival in patients treated from 1982-1992, compared to patients treated in the earlier period prior to 1982, and this has also been the finding of the international data base on Hodgkin's disease,[11] so there is still room for considerable improvement in long-term survival, but how will this be achieved? The major factors identified as contributing to mortality were sepsis, second malignancy, unresponsive disease, and disease relapse. The marked reduction in the use of staging laparotomy should reduce the risk of death in complete remission by lowering the incidence of post-splenectomy sepsis. The use of recombinant human granulocyte-colony

stimulating factor (G-CSF) in selected patients should reduce the risk of sepsis during the neutropenic phase following chemotherapy. Deaths from second malignancies should also decline with the decreasing use of MOPP type chemotherapy. Patients with unresponsive disease constitute around 10% in most series, and this figure must be reduced in order to improve survival. Most centres are currently using intensive regimens such as BEAM followed by autologous stem cell transplant for patients with refractory and relapsed Hodgkin's disease. For patients with resistant relapse the results so far are disappointing, with progression free survival at five years of only 19.2%[27] so perhaps new chemotherapeutic agents will be required to alter CR rates significantly. However a longer period of follow up is necessary to balance fully the benefits of intensification with the long term complications of such treatment.

Results from the IDHD have shown that patients cured from Hodgkin's disease have a relative risk of dying multiplied by 2.09 compared with the general population,[11] and this confirms the need for long term follow-up studies in order to accurately document causes of death and alter treatment protocols to reduce the excess risk of death in patients cured of their disease. This study also provides reliable survival data with follow up on 99.5% of the original cohort, which can be compared to the survival of the patients treated at this centre in the next century, in order to ascertain if apparent improvements in therapy translate into a durable survival advantage.

ACKNOWLEDGEMENTS

We wish to thank all the Haematologists/Oncologists (Belfast City Hospital, Northern Ireland Centre for Clinical Oncology, and Craigavon Area Hospital) whose patients are included in this study. We thank the surgical team at the Belfast City Hospital led by Mr R Curry for their skilful performance of staging laparotomy and biopsies over this 20-year period. Our thanks also to all the general practitioners who assisted with patient follow up, and to Mrs M Beattie (research secretary) for her invaluable help. We are very grateful to Dr R Lynas for his assistance with the pathology review, and Dr C Patterson (Senior Lecturer, Medical Statistics, Queen's University Belfast) for his advice regarding the statistical analysis.

Finally we wish to acknowledge the work of Dr J H Robertson, one of the early BNLI collaborators, whose enthusiastic interest in the treatment of malignant lymphomas has undoubtedly advanced patient treatment at this centre over the past 20 years.

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The Ulster Medical Journal, Volume 67, No. 2, pp. 99-103, November 1998.

General practitioner deprivation payments in Northern Ireland: is the current system equitable?

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Accepted 20 May 1998

SUMMARY

The allocation of General practitioners deprivation payments has been a contentious issue since it was first proposed. This paper examines the method of allocation of such payments in Northern Ireland. A more equitable system would be based on enumeration districts, have a lower Jarman score and a closer relationship between Jarman score and remuneration. Unlike other parts of the UK these changes are now possible in Northern Ireland and should be implemented.

INTRODUCTION

The 1990 Contract for general practitioners makes allowance for a deprivation payment to be made to practices.[1] Under this arrangement practices receive additional funds for patients who live in deprived areas that are thought to generate additional workload. These areas are defined by the Jarman Under Privileged Area score (Jarman score), which is a weighted composite of eight variables derived from the 1991 census.[2] Although the Jarman score is described as a measure of deprivation, it originates from a 1983 survey in which General practitioners identified and weighted the characteristics of those patients they thought might generate additional workload for their practices.

Originally the debate surrounding General practitioners deprivation payments centered on the validity of the Jarman score as an indicator of General practitioners workload.[3,4] More recently attention has shifted to the process of the application of deprivation payments. A recent British Medical Journal editorial indicated that equity remains a problem in GB[5] and it was suggested that this could be ameliorated if the allocation was made at a smaller geographical level and with finer gradients of payment bands, which started at a lower entry point.

At present there are three General practitioners deprivation payments bands identified in Northern Ireland. Patients who live in an electoral ward with a Jarman score of 27.5 or more can attract an additional payment of £6.20 (in 1997). Those in wards with a Jarman score of 37.5 or more attract £8.05 and those in wards with a Jarman score of 47.5 or more attract £10.20 (Table I). Northern Ireland has slightly lower entry points to each of the three payment bands than in other parts of the UK. These were introduced because it was thought that the minor differences in the wording of ethnic minority question in the Northern Ireland census would have resulted in lower Jarman scores. Patients are allocated to electoral wards according to the postcode of their address, which is held at the Central Services Agency patient registry.

TABLE I

GP Deprivation Payments: Present allocation system

Payment Bands	*Electoral Wards (No.)*	*Population 1991 census*	*Jarman Score (N.Ireland)*	*Jarman Score (G.B.)*
High	10	44631	>47.5	>50
Medium	20	74504	>37.5	>40
Low	38	103548	>27.5	>30
None	498	1355153	<27.5	<30

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This paper will address the question as to whether the allocation of GP deprivation payments in Northern Ireland is equitable. To answer this, three subsidiary questions will be addressed: Is electoral ward the most appropriate level for determination of Jarman score and allocating GP deprivation payments? Is the current system, based on three payment bands, too coarse to relate payment to need? Are the inequities in the present system compounded by list and address inflation?

METHODOLOGY

A Jarman score was computed for each of the 566 electoral wards and 3729 enumeration districts in Northern Ireland. (Enumeration district and electoral ward are coterminous, there being on average 6 or 7 enumeration districts within each electoral ward). Each set of electoral wards or enumeration districts was grouped into high, medium or low bands as previously described, with one minor modification for enumeration districts. So as to maintain approximately the same proportion of the population in each band and therefore approximately the same division of deprivation payments allocated to each, slightly different cutoffs had to be used to define the payment bands. These were high (>55.70), middle (>42.92) and low (>32.50). This enabled the visualization of not only the variations in Jarman scores that exist at enumeration district level but also the approximate banding and funding consequences of these variations.

List and address inflation are terms used to indicate the inaccuracies associated with some General Practitioner lists. List inflation occurs when a General practitioners list contains people who have died or left the practice, or perhaps the country. This was calculated by comparing the total patient population registered with the Central Services Agency in 1991 with the population enumerated at the 1991 census. Address inflation occurs when patients change address but there is a delay in updating the information held at the Central Services Agency. This can produce differences between the Census and CSA estimates of population at small geographical areas, as the CSA records patients as living in areas they have moved away from. Usually list and address inflation occur together and the relative effects cannot be separated.

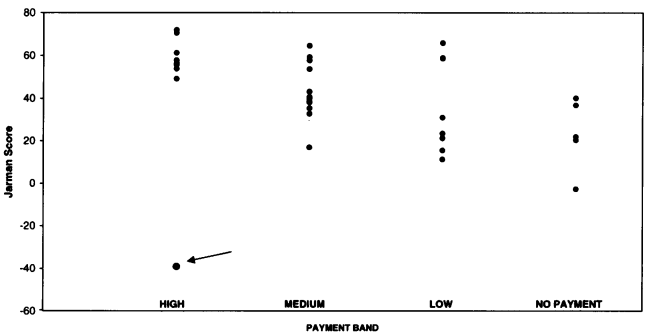
The census and registered population counts were aggregated according to the deprivation band to which they were ascribed and the effect of General practitioners deprivation payments allocations determined.

RESULTS

Geographical unit

Electoral wards are not homogeneous with regard to deprivation. There is nearly as much variation within electoral wards as there is between wards. Fig 1 shows the range of Jarman scores for each enumeration district within the most deprived electoral wards in each of the four payment bands. St. Anne's electoral ward in Belfast is the most deprived in Northern Ireland (according to the Jarman score) and comprises 10 enumeration districts, most of which are also deprived. One enumeration district however (enumeration district 074001), with a Jarman score of –39.33 is very affluent. Thus under the present ward based system GPs will receive an additional £10.75 for every patient within this ward even those in the very affluent enumeration district. It should also be noted that even amongst the majority of deprived enumeration districts within this ward there is still a variation in Jarman scores in excess of 21 points.

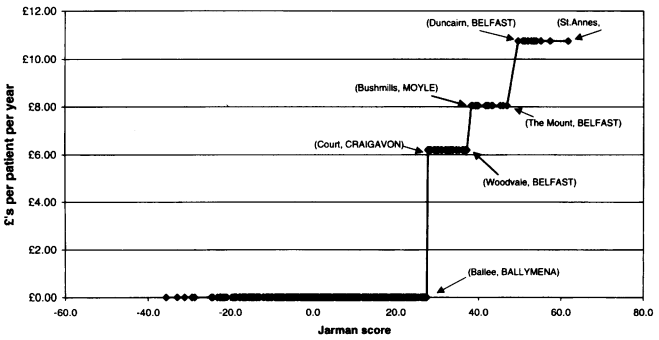
Figure 1 Jarman Scores for the enumeration districts within the most deprived ward in each payment band



Again all these areas and patients will be treated equally despite a significant variation in general practitioner workload. Examination of other wards at the top of the medium and low bands shows a similar picture. The enumeration districts which comprise the Mount ward in Belfast, which attracts 'medium' deprivation payments, span the entire range of deprivation bands with a range of Jarman scores of 47 points. The Woodvale ward in Belfast, which is the highest scoring ward within the present low payment band exhibits a range of Jarman scores of 55. Under the current three band system six enumeration districts within this ward attract too much payment whilst three do not receive sufficient. Ballee ward in Ballymena District council, with an overall Jarman score of

27.49 just fails to be included within the present payment bands. Under an enumeration-based deprivation system two of the five enumeration districts would attract payment at the 'low' banding level.

Figure 2 Structure of present payment bands
Electoral ward Jarman scores and payment per patient per year



Width of Payment Bands

Electoral wards in Northern Ireland have a range of Jarman score from –35.61 to +61.68. The lowest payment band commences at a Jarman score of 27.5 and there are only three bands between this and the highest scoring ward. Figure 2 shows this graphically and highlights those electoral wards at the cusp of the payment bands. A significant range of Jarman scores is evident within each of the three payment bands. The overall average span for the three bands is 10 points, though the greatest range (12.12 points) is between St. Anne's and Duncairn wards in Belfast within the high band. Thus patients within St. Anne's ward with a Jarman score of 61.68 will attract the same per capita payment as those in Duncairn which has a Jarman score which is considerably less, though still in the high payment band. Under the present system, electoral wards with a Jarman score under 27.50 fail to attract any deprivation payments. Therefore patients in Ballee ward in Ballymena (Jarman score 27.49) are treated the same as those in Ballyloughan ward which is also in Ballymena (Jarman score –35.61). This would appear to be inherently unfair.

Table II shows the six wards that fall either side of the three cutoff points on the Jarman scale which define entry to the high, medium and low payment bands. The mean difference in Jarman score that separates those wards which just fail to get into the next highest payment band is 1.3 points. This is a very small difference, but because it separates wards into different payment bands, has a disproportionate impact on the money each ward attracts. This is compounded by the rather large increments in money between bands. For example, there is a difference of £2.55 per patient between the high and middle payment bands. Only 2.71 points separate The Mount and Duncairn electoral wards but every patient in latter attracts £2.55 more than those in the former. If The Mount attracted the same per capita funding as Duncairn it would receive an additional £14,305. However the sharp division between similarly scoring wards is best illustrated by those wards which straddle the division between low and No Payment groups. The difference between the Jarman score of Court electoral ward in Craigavon and Ballee in Ballymena is only 0.23, and yet every patient in Court attracts an additional £6.20, whilst those in Ballee attract none.

TABLE II

Range of Deprivation Scores within Payment Bands

	District Council	*Electoral Ward*	*Jarman Score*	*Payment Band*	*Population*
'High payment' Banding					
Top of High band	Belfast	St. Annes	61.68	H	3983
Bottom of High band	Belfast	Duncairn	49.56	H	4060
		Difference	12.12		
'Medium payment' band					
Top of Medium band	Belfast	The Mount	46.85	M	5298
Bottom of Medium band	Moyle	Bushmills	38.19	M	854
		Difference	8.67		
'Low payment' Banding					
Top of Low band	Belfast	Woodvale	37.13	L	3480
Bottom of Low band	Craigavon	Court	27.72	L	2815
		Difference	9.41		
'No payment' banding					
Top ofNo Payment band	Ballymena	Ballee	27.49	N	2490
Bottom of No Payment band	Ballymena	Ballyloughan	–35.61	N	2819
		Difference	63.09		

TABLE III

List and Adress inflation (in 1991) by Deprivation Payment Group

Deprivation Payment Group	*Population count Enimerated*	*Registered*	*Inflation Numbers*	*Percentage*
HIGH	44631	56697	12066	27.0
MEDIUM	74504	89339	14835	19.9
LOW	103548	123224	19676	19.0
NONE	1355153	1408283	53130	3.9

NOTE:
Enumerated = 1991 Census Counts
Registered = 1991 Central Services Registered Patient Population

List and Address Inflation

The comparison of the two population estimates showed that there were 105,883 more persons registered on General practitioners lists in Northern Ireland in 1991 than enumerated in the census, an overall list inflation of 6.7%. The two main cities of Belfast and Derry show the greatest address inflation. When address inflation is calculated at electoral ward level and aggregated up according to present deprivation band (Table III), a marked gradient is evident. On average, inflation is least for those wards which do not attract any deprivation payments (3.9%) and greatest for wards in the high payment band (27.3%).

DISCUSSION

This paper has clearly demonstrated that the crudity of the current arrangements for allocating General practitioners deprivation payments within Northern Ireland. The geographical level at which the allocation is determined is too coarse. Electoral wards are not homogeneous entities with regard to deprivation (as defined by the Jarman score). There are affluent areas within even the most deprived wards that currently attract deprivation payments and deprived areas within non-deprived electoral wards that do not. Using enumeration districts as the basis for allocating GP deprivation payments would be more equitable as they are more sensitive to local variations in need.

This was supported by a series of letters early last year, in the BMJ,[6] including one from Jarman himself.[7] Majeed [8] agreed that the validity of the current system could be improved if enumeration districts were used rather than an electoral ward as the unit of allocation, but noted the limitations of census data at this level. Jarman suggested that the calculation and applying of deprivation scores at enumeration district level could cause problems in England as only 10% of occupations there had been coded in the 1991 census.[7] This would not be an obstacle in Northern Ireland where 100% of the information captured in the 1991 census was coded and entered.[9]

There are also additional reasons for wishing to use enumeration districts as the basis of allocation. If enumeration districts rather than electoral wards had been used to calculate Jarman scores the changes in deprivation payments to practices, which occur every 10 years with the new census values, would not be as precipitous or unpredictable.[10] It has been reported that one practice had suffered a 15% shift in income after changes in electoral ward boundaries.[11] This would have been obviated if enumeration districts rather than wards had been used. However, this may not be immediately possible in England due to incomplete coding of census forms. It has also been suggested that while an enumeration district based system would be more equitable, caution would be required when interpreting census data at this level. Other authors have indicated that problems might include under- enumeration and the undercounting of homeless patients and have suggested that it may therefore be necessary to retain some local discretion.[12]

The current process recognises three payment bands, with cut-off at about 10 Jarman points apart. It can be shown that this is too crude a relationship between need, defined by Jarman score, and remuneration. The difference in the amount of funding received by areas that straddle the various cut-offs between bands is too severe and disproportionate to the small differences in Jarman score between these wards. Again, the width of the current banding system does not recognise the differences that exist within payment bands. A more equitable system would reduce the difference between those just in and those just outside the payment bands, and would produce a finer grading within the relationship between Jarman score and remuneration. A lower entry point on the Jarman scale and more payment bands would meet these objectives.

If it were assumed that the changes advocated above would produce a more equitable distribution, then such a system, if implemented, would result in a redistribution of General practitioners deprivation payments away from those areas that currently attract the largest allocation towards those that currently attract little or none. Thus those areas which do well under the current system are on average receiving more than their equitable allocation of the General practitioners deprivation payments. The positive correlation between Jarman score and list and address inflation means that the effects of the latter are to significantly compound the inequities in the present General practitioners deprivation payment system.

This paper highlights the inequities in the present *allocation* of General practitioners deprivation payments in Northern Ireland and makes suggestions as to how it could be improved.

Whether the Jarman score is the best method of rewarding General practitioners for the additional work associated with deprivation has not be considered here, though it remains a concern in the medical literature.[13, 14] In one recent study deprivation payments met only half the extra workload cost for patients living in wards qualifying for deprivation payments.[15] Given the debate surrounding the suitability of the Jarman score as a measure of primary care workload, there is clearly a need for definitive research into the association between General practitioners workload and the demographic and social characteristics of practice.

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The Ulster Medical Journal, Volume 67, No. 2, pp. 104-109, November 1998.

A cluster of suspected pneumocystis carinii pneumonia following intensive chemotherapy in a Belfast haematology unit

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Accepted 25 June 1998

SUMMARY

Five cases of pneumocystis carinii pneumonia were diagnosed in adult patients following intensive chemotherapy in the Royal Group of Hospitals haematology unit, Belfast, within a space of six months. The common features and the risk factors contributing to the increased susceptibility of these patients are discussed, as are the likely mechanisms of transmission of infection.

INTRODUCTION

Pneumocystis carinii pneumonia (PCP) is a potentially life-threatening opportunistic infection. It was first recognised in Europe as a distinct clinical entity in children immune-suppressed by malnourishment during the Second World War. There was renewed interest in pneumocystis in the early 1980s when it became recognised as the AIDS defining pulmonary infection. Pneumocystis is a unicellular organism discovered by Chagas in 1909. It was subsequently shown to be a fungus as a result of RNA sequencing.[1] There are recent reports of increasing incidence of this infection following organ transplantation due to high-dose immuno-suppressive agents.

We report a cluster of five suspected cases of pneumocystis carinii pneumonia in the regional haematology unit, Royal Group of Hospitals, Belfast, between August 1995 and February 1996. Case records for these patients were retrieved and studied in detail. Clinical course, treatment and survival outcome were followed up. We also review the literature on this subject and compare it with our own experience.

Patient 1 (index case)

A 28-year-old male with acute monocytic leukaemia presented with lethargy and bone pain. He achieved complete remission following the first course of chemotherapy MAE 3+10+5 (Mitozantrone 12 mg/m^2 daily i.v. on days 1, 3 and 5; cytarabine 100 mg/m^2 12 hourly i.v. on days 1-10 inclusive, and etoposide 100 mg/m^2 daily i.v. on days 1-5 inclusive). He experienced severe nausea during chemotherapy unrelieved by ondansetron, domperidone, cyclizine or metoclopramide. Dexamethasone 4 mg 8-hourly was subsequently used with good effect.

Dexamethasone was also used prophylactically with his second course MAE 3+8+5. He subsequently developed febrile neutropenia. Central and peripheral blood cultures were taken prior to commencing teicoplanin, ciprofloxacin and netilmicin. He was allergic to penicillin. Fluconazole 200 mg i.v. daily was added two days later when his pyrexia failed to settle. Coliform bacilli were isolated from blood culture. Sensitivity testing confirmed that he was receiving the right antibacterial therapy.

However, two weeks later, he remained pyrexic despite bone marrow recovery as indicated by the rise in his leukocyte count. This was followed by a rapid clinical deterioration. He developed a non productive cough, experienced shortness of breath

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at rest and had difficulty in drawing a deep breath. He was cyanosed, tachypnoeic with sinus tachycardia 120 bpm. Chest expansion and air entry were restricted bilaterally. There were fine crepitations in the midzones and bases. Chest radiograph revealed bilateral interstitial hazy shadowing consistent with PCP, compared to a normal chest radiograph four days earlier. Arterial blood gas analysis was contraindicated by the thrombocytopenia. Broncho-alveolar lavage was discussed but deemed inexpedient as the bronchoscopy unit was located in the Belfast City Hospital and a transfer journey by an ambulance would be required. He was hypoxic and dependent on high-flow oxygen. Decision was made to start empirical treatment without delay. Intravenous co-trimoxazole (trimethoprim-sulfamethoxazole) at 1.92 gram q.d.s. and dexamethasone 10 mg daily was started immediately. The use of high-flow oxygen, saline nebuliser and chest physiotherapy failed to induce any sputum for examination. Within 48 hours, there was significant clinical improvement, accompanied by resolution on the chest radiograph. Two days later he was well enough to be discharged on high dose oral co- trimoxazole.

He continued on co-trimoxazole at the prophylactic dose of 480 mg b.d. thrice weekly with no recurrence of PCP at 14 months. Unfortunately, he succumbed to the acute leukaemia 15 months following diagnosis.

Patient 2

A 26-year-old male with acute lymphoblastic leukaemia developed an acute respiratory illness after two months of intensive multidrug cytotoxic regime containing high dose prednisolone (UKALL 12 MRC protocol). Initially, he was pyrexic without respiratory symptoms. Intravenous antibacterial treatment with benzyl penicillin, netilmicin and ciprofloxacin was commenced following blood cultures. When pyrexia failed to settle after 48 hours, he was switched to second line ceftazidime and amikacin. Intravenous fluconazole was subsequently added. However, he soon developed dry cough and shortness of breath. He was cyanosed with bronchial breathing in the right lung, (PO_2 31 mmHg, PCO_2 35 mmHg). Chest radiograph showed diffuse bilateral patchy shadowing suggestive of PCP. He responded to high dose co-trimoxazole and adjuvant corticosteroid within 48 hours. He was doing well at 37 months follow-up.

Patient 3

A 29 year old male with acute lymphoblastic leukaemia developed dry cough, dyspnoea and recurrent pyrexia eight months into chemotherapy as per the UKALL 12 protocol. Chest radiograph revealed perihilar shadowing suggestive of PCP. High dose co-trimoxazole and adjuvant steroid resulted in rapid resolution of symptoms. An allogeneic bone marrow transplantation was performed. The patient was well at 42 months follow-up.

Patient 4

A 38-year-old male with chronic psychosis presented with a large cervical mass shown to be high-grade non-Hodgkins lymphoma. After five courses of 'CHOP' chemotherapy (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 and prednisolone 40 mg/m^2), he became unwell, with pyrexia and cough productive of green sputum. He smoked heavily and refused food, resulting in significant weight loss. His lactate dehydrogenase level (LDH) which had become normal following cytotoxic chemotherapy became raised once again, raising suspicion of a lymphoma recurrence. Chest radiograph was normal. CT scan which was carried out to reassess his lymphoma surprisingly revealed several areas of bilateral ground-glass opacity suggestive of PCP. High dose co-trimoxazole was instituted immediately. His pyrexia settled.

Patient 5

A 36-year-old male with multiple myeloma was treated with four courses of chemotherapy (vincristine, adriamycin and dexamethasone) followed by allogeneic bone marrow transplantation. Methotrexate, cyclosporin and prednisolone were used to prevent graft versus host disease. He received cytomegalovirus specific intravenous immunoglobulin and prophylactic co-trimoxazole. He experienced occasional nausea and vomiting after transplantation but tried his best to comply with his medication.

Ten weeks later he became unwell, with shortness of breath on exertion, pyrexia and cough productive of purulent sputum. On examination he had sinus tachycardia and basal crepitations at both lung bases. Chest radiograph showed bilateral chronic inflammatory changes. Computed tomography revealed peripheral ill-

TABLE I

Lactate dehydrogenase level at different clinical stages illustrating a transient elevation during infection with PCP

LDH level u/l	*At presentation*	*Post-chemotherapy*	*During PCP*	*Post-high dose Co-trimoxazole*
Patient 1 (AML)	2023	250	704	312
Patient 2 (ALL)	1939	758	1601	477
Patient 3 (ALL)	1749	378	1296	502
Patient 4 (NHL)	2702	684	1143	415
Patient 5 (MM)		989	1161	963

(LDH normal range in our laboratory 360-720 u/l)

TABLE II

Haematological parameters at diagnosis of PCP showing recovery of neutrophil count but persistent lymphopenia following myelosuppressive chemotherapy

	Total leucocyte 10^3/ul	*Neutrophil 10^3/ul*	*Lymphocyte 10^3/ul*	*Monocyte 10^3/ul*	*Eosinophil 10^3/ul*
Patient 1 (AML)	4.9	3.38	0.59	0.69	0
Patient 2 (ALL)	2.7	2.51	0.11	0.03	0.05
Patient 3 (ALL)	12.7	9.9	1.65	0.76	0.38
Patient 4 (NHL)	5.7	4.1	0.86	0.63	0.06
Patient 5 (MM)	3.1	2.79	0.09	0.16	0.03

Normal range (10^3/ul): Total leucocyte 4-11; Neutrophil 1.7-6.1; Lymphocyte 1-3.2; Monocyte 0.2-0.6; Eosinophil 0.03-0.46

defined opacities and interstitial changes in the peribronchial region and mid zones. Penicillin resistant *streptococcus pneumoniae* was isolated from blood culture. It was sensitive to cefotaxime and he was treated accordingly. Liposomal amphotericin was added later when his pyrexia failed to settle. Fluorescent antibody testing of the sputum for PC was positive. He was commenced on high-dose co-trimoxazole with dose modification for impaired renal function. He made a good recovery and remained well at 38-months follow-up.

The common features of the above patients are summarised below:

1. All had intensive chemotherapy which had been started at least 6 weeks before developing PCP.
2. All had been on a corticosteroid.
3. All showed a transient elevation in lactate dehydrogenase level (LDH) during pneumocystis infection without evidence of underlying disease recurrence (Table I).

4. All failed to respond to initial broad spectrum anti-bacterial and anti-fungal agents but improved after high dose co-trimoxazole and adjuvant corticosteroid.
5. A recovering leukocyte count after cytotoxic treatment did not curtail the respiratory illness.
6. All had been in the same four-bedded male bay or in the cubicles opposite, which were managed by the same nursing team (the nursing responsibility in the ward is divided into team A and team B). Patients 1, 4 and 5 were hospitalised at around the same time and developed PCP within a space of 2 months. Patients 2 and 3 started induction chemotherapy in the same month. They subsequently developed PCP one month apart. All cases occurred within a 6-month period. All patients had spent many months in and out of haematology ward receiving treatment as dictated by current cytotoxic protocol. In the case of patient 4 with lymphoma, his chronic psychosis and social circumstances necessitated in-patient supervision of treatment, which otherwise would have been administered as an outpatient.

DISCUSSION

The data on the incidence of PCP in haemato-oncology patients is quite scanty. A report in 1995 followed up 214 adult patients with acute lymphoblastic leukaemia (ALL). 5% were diagnosed with PCP at some point during the two years of treatment.[2] Another group of investigators from Helsinki looked for PCP in 29 new adult ALL and 44 acute myeloid leukaemia (AML) from July 1990 to December 1993. PCP prophylaxis was not included in the therapeutic protocol. 24% ALL and none with AML developed PCP.[3] This incidence is similar to childhood ALL in which 21% developed PCP prior to co-trimoxazole prophylaxis.[4]

All patients reported above had been started on intensive cytotoxic regime and corticosteroid at least 6 weeks prior to the onset of their respiratory illness. To the best of our knowledge, PCP has never been reported in untreated patients with leukaemia or lymphoma. This suggests the patients' susceptibility to PCP is more closely related to the type and the intensity of treatment than to their haematological malignancy. Over the years, little has changed in the treatment of non-Hodgkin's lymphoma. CHOP type regime remains the cornerstone, which is less intensive and the duration of leucopenia is short compared to the treatment protocols for acute lymphoid and myeloid leukaemias. However, patient 4 with non-Hodgkin's lymphoma illustrates that malnutrition and heavy smoking may be adding to his susceptibility to pneumocystis infection. He suffers from chronic schizophrenia and his behavioural problems had contributed to his eating disorder and subsequent weight loss.

The chest radiograph in PCP maybe normal and hence unhelpful in the early stages. It typically shows bilateral perihilar interstitial infiltrates, progressing to diffuse confluent alveolar shadowing as patients deteriorate clinically. Our experience with patients 4 and 5 above indicates that CT scanning may be more sensitive than plain x-ray in revealing the interstitial changes in early or subacute PCP.

Serum LDH level is a non specific test useful for monitoring the cell turnover rate and the disease activity in malignant haematological disorders. It has also been noted to be raised in HIV positive patients who develop pneumocystosis. Hence an increase in the LDH level in patients whose underlying disease has attained complete remission should alert the clinician to the possibility of pneumocystis infection.

In general, most patients with bacterial and fungal infections associated with cytotoxic therapy show clinical improvement coinciding with a rise in their leukocyte counts from their lowest level. From our experience, the recovery of haemato-logical parameters, notably the neutrophil count (Table II) following chemotherapy, did not prevent or curtail PCP as would be expected in bacterial infections. Absolute lymphopenia was found in 4 out of the 5 patients at diagnosis of PCP. This supports the view that cell-mediated immunity is most important for protection from PC. Although the lymphocyte subsets were not measured in our patients, solid data from HIV patients had shown that the risk of PCP correlates with CD4 T lymphocyte count of <200/ul (multicentre AIDS Cohort Study). Limited reports in cancer patients suggest a similar relationship.[5,6] However, the predictive value of CD4 count has not been evaluated in non-HIV patients.

Most of the experience in managing PCP also came from HIV patients. Some clinicians strongly advocate that all who present with symptoms and chest x-ray or arterial blood gas findings

suspicious of PCP should have a bronchoscopy to demonstrate the presence of PC in bronchial secretions or tissue. Others have suggested that such patients may be treated empirically, reserving bronchoscopy for those with atypical presentations and those who do not respond or deteriorate on specific therapy.[7] In clinical practice both strategies seem equally effective.[8] Many centres in UK and USA treat PCP empirically.[9]

Exercise-induced arterial desaturation detected by oximetry in patients with normal resting PaO_2 may help to detect PCP. In the lung function tests, the carbon monoxide transfer factor (TLCO), total lung capacity and forced vital capacity may be reduced, whereas peak expiratory flow and forced expiratory volume in 1 second are frequently normal. A reduction in the TLCO is the most sensitive marker of PCP but this lacks specificity as it is also decreased in bacterial infections. We need a sensitive, reliable and non-invasive tool for early diagnosis of PCP, as patients with malignant haematological conditions immune-compromised by intensive chemotherapy can deteriorate very rapidly. Sputum induction is uncomfortable and the yield is poor. Bronchoalveolar lavage is not always possible as these patients may be too tachypnoeic and hypoxic. Transbronchial biopsy may be contraindicated by thrombocytopenia or coagulopathy. Open lung biopsy, though the most sensitive and specific, is also the most hazardous. Many clinicians believe that transbronchial and open lung biopsies have little to add to bronchoscopy and bronchoalveolar lavage. In practice, empirical treatment must be started without delay. Recent studies showed that it is possible to amplify pneumocystis carinii DNA by PCR directly from blood and nasopharyngeal aspirates of PCP patients. [10,11] However, cost and availability are limiting factors. There is no established culture system for pneumocystis carinii that would allow traditional antimicrobial sensitivity testing. This and a serologic test that will distinguish recent from past infections are needed.

PCP is fatal in almost all cases if left untreated. Adjuvant use of steroid has contributed to decreased mortality rate and has reduced the need for assisted ventilation in the most severe cases. The mechanisms for this paradoxical response may be attributed to a reduction in the cellular infiltrates within alveolar spaces, allowing better gas exchange and improving chest expansion.

Patient 5 illustrates a well-recognised complication following bone marrow transplantation, that of functional hyposplenism related to total body irradiation. This predisposed the individual to infection by capsulated bacteria, especially pneumococci. The superinfection with pneumococci had enabled production of sufficient amount of sputum to allow confirmation of PCP by fluorescent antibody testing. Although he had been on prophylactic co-trimoxazole since his bone marrow transplant, his susceptibility to PCP was probably increased as a result of hyposplenism.

It is possible that PCP in immune-compromised patients arises by reactivation of a latent asymptomatic infection acquired in childhood. This hypothesis is supported by the finding of antibodies to PC in most healthy children and adults.[12] Immunosuppression in later life may lead to clinical manifestations. However, over the years a steady flow of reports has described clusters of PCP cases not readily explained by reactivation of latent infections. Recent studies have suggested that the duration of latency is very limited, usually less than one year.[13,14] There may be an alternative explanation.

Although person-to-person transmission of PC is yet to be proven in human, we are concerned about the clustering of cases in the ward within a space of 6 months. PC DNA has been identified from ambient air sampled from rural Oxfordshire in the UK,[15] and from rooms of animals and patients with PCP in United States.[16] Recent studies have demonstrated genetic variation in PCR – amplified pneumocystis carinii DNA from the lungs of patients during recurrent PCP episodes.[17] All these data indicate that PC is caused by airborne organisms and that person-to-person transmission of pneumocystis carinii is possible. At least some cases of PCP are due to acquisition of new infection from an exogenous source rather than relapse of an existing infection. This has significant implications on the management of immune-compromised patients in the haematology ward. Studies are needed to decide whether case to case transmission contributes to infection significantly more than airborne sources in the environment. Consequently, preventative measures and decontamination procedures might be drawn up

to protect patients. Until the epidemiologic features and mode of acquisition of PC are better understood, antimicrobial drugs remain the only available method for PCP prophylaxis. Some haematologists are reluctant to use co-trimoxazole for fear of exacerbating myelosuppression and inducing antimicrobial resistance. Besides, pneumocystis infection in non-HIV haematology patients appears to be sufficiently uncommon to justify prolonged use of co-trimoxazole. We need to define the risk factors in order to target a subgroup of patients for PCP prophylaxis after institution of cytotoxic therapy.

The risk factors we have identified are:

1. Lymphoproliferative malignancies after intensive chemotherapy.
2. Corticosteroid therapy.
3. Bone marrow transplantation.
4. Lymphopenia.
5. Poor nutrition and possibly smoking.

In conclusion, PCP is a preventable complication in patients treated with cytotoxic chemotherapy and corticosteroid. It should be considered in the differential diagnosis of pneumonia. A rise in LDH level in patients who have attained remission from their haematological malignancy should prompt a search for PC, as rapid deterioration may ensue if treatment is delayed. Prophylaxis for PCP is now routinely started in our unit in selected high-risk patients approximately one month following institution of intensive chemotherapy.

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The Ulster Medical Journal, Volume 67, No. 2, pp. 110-114, November 1998.

Locations for renal services – patient satisfaction surveys

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Accepted 7 August 1998

SUMMARY

Renal services have been given priority in recent years in an attempt to align them with levels of provision in other European countries. A survey of patients receiving renal replacement therapy in the Northern Ireland Regional Centre, Belfast, was carried out to ascertain their views on services (survey I). After the establishment of a Northern Health and Social Services Board (NHSSB) sub-regional unit in 1995, the survey was repeated for patients attending the new unit (survey II). In survey I, 53% NHSSB patients responded. Travelling time to and from hospital was a major issue for the majority of patients, with 33% of haemodialysis patients receiving twice weekly treatment unwilling to attend more frequently, even if clinically advised to do so. In survey II, 60% of patients responded. Travel times to the sub-regional unit were significantly shorter and patients felt it provided a similar or better standard of service, compared with the regional centre. All the twice weekly haemodialysis patients would increase to thrice weekly if clinically advised to do so. The study underlines the importance of locating dialysis facilities closer to patients' homes.

INTRODUCTION

The number of patients accepted for renal replacement therapy (RRT) has risen more than three-fold since the early 1980s.[1] This increase has been largely due to the referral and acceptance of older patients for RRT, many of whom have co-morbidity.

Morbidity and mortality in haemodialysis patients are related to the quality and quantity of the dialysis provided.[2] It is widely accepted that the majority of patients should receive dialysis three times per week. This regimen results in better control of uraemic symptoms and fewer peaks and troughs in general wellbeing.[3] The Renal Association and the Royal College of Physicians report on treatment standards for adult patients with renal failure in 1995, recommend three times weekly haemodialysis.[4] The 1995 review of renal services in Northern Ireland by the Department of Health and Social Services recommended that the target of 90% of haemodialysis patients receiving dialysis thrice weekly be achieved as soon as possible.[3] At the time the survey was carried out here, less than 50% of haemodialysis patients were receiving treatment three times weekly.

Long travel times are thought to detract from RRT patients' quality of life and will have a bearing on patients' willingness to increase from twice to thrice weekly dialysis. Little information exists about the distances travelled and the subsequent impact on their satisfaction.[1,15] A study was therefore carried out to determine the influence of travelling duration and timing of treatment on dialysis patients and patients' perceptions of the service provided. The study was repeated after the opening of a sub-regional dialysis unit closer to the study population.

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METHODOLOGY

Survey I

After piloting an initial questionnaire on patients attending the regional centre for RRT, questionnaires were redesigned to be specific for either haemodialysis or CAPD (continuous ambulatory peritoneal dialysis) treated patients, as separate issues had been identified in these two groups.

Questionnaires were distributed to every patient attending the regional centre for RRT during November and December 1993 by the nursing staff, regardless of Board of residence. Patients completed only one questionnaire each. The centre treats patients from all four Boards in Northern Ireland, but for the purposes of this paper only the views from Northern Health & Social Services Board (NHSSB) patients are reported. Patients were asked to return the questionnaires in a pre-paid envelope. Due to the method of distributing the questionnaires no information was available on non-responders. The questionnaire covered issues of choice about types and timing of treatment, verbal and written information received and the travel times involved. Views about the relative importance of some quality issues, e.g. access to a counselling service and contact with the same nursing team were scored on a scale of one to four, where one was "not at all important" and four was "very important".

Survey II

Following the opening of a six-bed haemodialysis unit in the NHSSB area, run by a single consultant nephrologist retaining academic and clinical links with the regional centre, a second patient satisfaction survey was carried out on those attending the new sub-regional unit.

The questionnaires remained unchanged apart from the addition of one section, to allow comparisons between the regional centre and the sub-regional unit, for those patients who had transferred their site of treatment. The haemodialysis patients were given the questionnaires at the end of a dialysis session and were asked to return them in a pre-paid envelope. The CAPD patients were surveyed by post. As a list of all patients attending the unit for RRT was available, information on age of nonresponders could be collated. The data was analysed using the Statistical Package for Social Sciences (SPSS). Differences in proportions, using the Chi-squared statistic for contingency tables, were assessed.

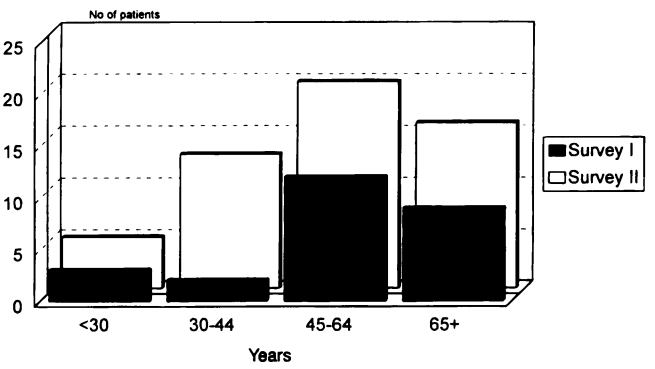
RESULTS

Survey I

Forty-nine NHSSB patients were given questionnaires. Twenty-six responded (53%); 16 of these were receiving haemodialysis and 10 were receiving CAPD. The ages of responders are shown in Figure I. Employment status is shown in Table I.

Figure 1

Age of patients



The travel times from home to the regional centre, for haemodialysis and CAPD patients, are shown in Table II. Fifty-six percent of the haemodialysis patients spent between one to two hours travelling for each dialysis session, and 25% spent two to four hours travelling, up to three times per week.

The mean scores for the quality issues for haemodialysis patients are shown in figure 2 "Leaving for home promptly" was ranked as the most important, closely followed by "commencing treatment promptly". The CAPD group ranked "discussion of progress and management with the consultant at regular intervals" as being the most important.

As a result of travelling, and other factors, one third of haemodialysis patients receiving treatment twice weekly said they would not be prepared to attend more frequently even if clinically advised to do so.

Survey II

During February 1996, 45 questionnaires were given out to NHSSB patients attending the sub-regional unit, 26 of whom were receiving haemodialysis and 19 were receiving CAPD. Responses were received from 14 (54%) haemodialysis, 13 (68%) CAPD.

TABLE I

Employment status of patients

Employment Status	*Survey I - 1993*	*Survey II - 1996*
Employed	4 (15%)	7 (13%)
Full-time	1 (4%)	1 (2%)
Part-time	3 (11%)	6 (11%)
Not emloyed	22 (85%)	47 (87%)
Unemployed	5 (19%)	10 (19%)
Homemaker/housewife	2 (8%)	12 (22%)
Retired	13 (50%)	20 (37%)
Invalidity	0 (0%)	2 (4%)
Not known	2 (8%)	3 (5%)

TABLE II

Travel times

Travel Times	*Regional Centre (Haemodialysis & CAPD)*		*Survey II (Haemodialysis, CAPD & Transplant)*	
	Survey I	*Survey II*	*Regional*	*Sub-Regional*
Less than 30 minutes	3 (11%)	4 (16%)	5 (9%)	22 (41%)
30 - 59 minutes	14 (54%)	9 (36%)	19 (36%)	22 (41%)
60 - 89 minutes	8 (31%)	8 (32%)	20 (38%)	6 (11%)
90 - 119 minutes	1 (4%)	3 (12%)	4 (8%)	3 (5%)
At least 120 minutes	0 (0%)	1 (4%)	5 (9%)	1 (2%)
Total	26 (100%)	25 (100%)	53 (100%)	54 (100%)

Figure 2
Mean scores of quality issues
Haemodialysis patients

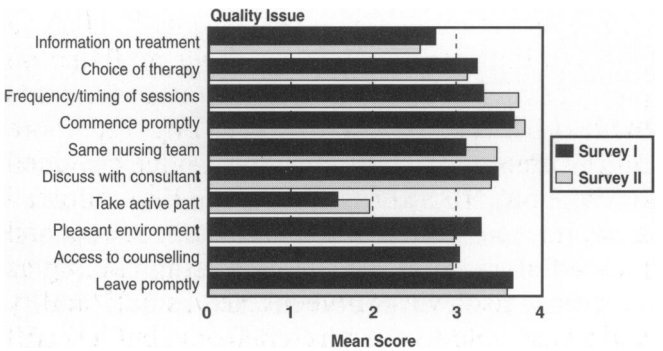
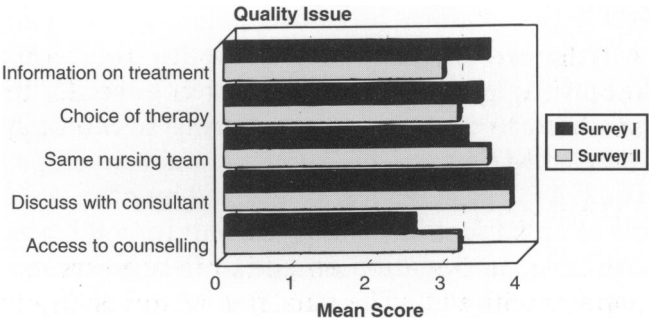


Figure 3
Mean scores of quality issues
CAPD patients



The ages of the responders are shown in figure 1. Employment status is shown in Table I. There was no significant difference in age ($x^2 = 1.87$, p = 0.39, 2 df), or employment status (Fisher exact 2 – tailed p-value = 0.19) between the responders in survey I and II. Nor was there a significant difference in age between the responders and non-responders in survey II ($x^2 = 1.76$, p = 0.41, 2 df).

There was no significant difference between the travel times to the regional centre for patients in survey I and survey II ($x^2 = 0.94$, p = 0.33, 2 df). It was therefore assumed that the two patients groups were broadly comparable with regard to geographical distribution.

The sub-regional unit was described as being more convenient than the regional centre by 24/25 (96%) patients who answered this question. Travel times from home to the sub-regional unit were significantly shorter than to the regional centre ($x^2 = 7.45$, p = 0.024, 2 df).

Ninety-six percent of patients had attended the regional centre before the sub-regional unit opened. Patients who had attended both were asked did they find the service at the sub-regional better, similar or worse compared to that at the regional unit. Twenty-seven percent found the service in the sub-regional unit to be better and 69% found it to be similar to the service in the regional centre.

When asked to nominate one most important quality issue, most haemodialysis patients answered "being able to leave promptly", as in survey I. However, this did not accord with the results from the quality issue questions, which rated "commencing sessions promptly" as the most important (figure 2), although both are concerned with time management. "Discussion of progress and management with the consultant at regular intervals" consistently rated as the most important quality issue by the CAPD patients.

All (three) of the haemodialysis patients currently receiving treatment twice weekly would be prepared to attend more frequently if clinically advised to do so.

DISCUSSION

Concern has been expressed in recent years that patients with end-stage renal failure are less likely to receive RRT in the UK than in other European countries.[1] It has been reported that referral of patients aged 60 years and over declines with distance from the main renal unit for the area, independently of other variables. The effect was most noticeable for patients aged over 75 years.[1] Various explanations have been given for this, including the relatively small number of renal units in the UK in comparison to elsewhere.[1] It has also been suggested that clinicians in remote areas may either be unaware of the potential for treating elderly patients with renal failure, or may feel that the difficulties associated with the travelling to treatment may outweigh the benefits.[1]

The results of the first survey clearly indicated that time spent travelling to and from a treatment session/appointment; waiting for treatment to start or rapid departure after treatment, are very important to haemodialysis patients. However, the inability to commence treatment promptly, or leave for home promptly, is not necessarily a reflection of the management of the renal unit, but may be a problem with the hospital transport facilities, for example ambulances taking circuitous routes to collect several patients on one journey. This problem is reflected in the fact that 33% of haemodialysis patients receiving treatment twice weekly said they would not be prepared to attend more frequently, even if clinically advised to do so. Although in practice when the possible outcomes of restricting dialysis time to less than that clinically recommended are explained to patients they generally agree to attend as frequently as needed.

As CAPD patients have fewer hospital visits one would expect travelling time to have less of a social impact. This was confirmed in finding longer "maximum travelling times" acceptable. This group of patients was more concerned with issues about their actual treatment such as getting more information, involvement in the decision – making and discussing their progress, particularly with the consultant.

The opening of the sub-regional unit made a positive impact on travelling times and also on patient satisfaction. Over half of the respondents made positive comments regarding the more relaxed, convenient and quicker service provided in the smaller sub-regional unit which allowed more time for discussion with the consultant and nursing staff. This is not a surprising finding as the comparison was between a new, small facility and a large, older, overstretched one, but it is still

useful to confirm that patients are satisfied with the new service.

The questionnaire was deliberately simple and short to increase the likelihood of response and avoid misinterpretation. As a result detailed analyses are not possible on all the issues and therefore some further questions have been raised. Also, the numbers were small in both studies as there was a limited patient population available. As there was no facility for identifying non-responders in survey I, reminders could not be sent out. In order to maintain comparability between the two studies, it was decided not to send reminders to the non-responders in survey II.

When targets are set or recommendations made it is important to evaluate whether they have been met. The recommendations from the initial survey were for the setting up of a sub-regional renal service in the NHSSB area, primarily to improve accessibility for patients and meet the clinical needs of an increasing patient population. The results from the second survey show that after the setting up of such a unit, there was a reduction in travel times for patients as well as an overall increase in patient satisfaction. The study therefore serves to underline the importance of locating dialysis facilities closer to where people live.

ACKNOWLEDGEMENTS

The authors would like to thank the consultant and nursing staff, of both the regional centre and the sub-regional unit, for their co-operation and help in carrying out this study.

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The Ulster Medical Journal, Volume 67, No. 2, pp. 115-116, November 1998.

The Throne Hospital: a short history

T R O Beringer

The Throne Hospital was established due to the generosity of the Martin family of Shrigley, Killyleagh, whose wealth was derived from the Shrigley flax spinning mills. Mr Samuel Martin conceived the idea of establishing a Children's Hospital in a rural district close to the City of Belfast. Sadly he died in 1872, but his philanthropic wishes were honoured and carried out by his father John Martin who survived him. Twenty-eight acres of land entitled "The Throne Lands" were purchased and a Children's Hospital with 32 beds erected at a cost of £4,000 to the designs of the architect Mr T Hevey. The site was considered an ideal one situated on the lower escarpment of Cavehill, and commanding an uninterrupted view of Belfast Lough, the County Down coast and the Crumlin Hills. The hospital first opened its doors to patients on October 1, 1874 and was subsequently transferred by Mr John Martin in 1875 to be incorporated within the Belfast Royal Hospital with a stipulation that a convalescent home should be built on the Lands within 2 years of the transfer.

In the first Annual Report of the Throne Children's Hospital for the year ending 31 August 1876,[1] it is recorded that 121 patients were admitted of whom 44 were deemed cured, 41 relieved, 29 incurable, 4 died and 3 discharged for bad conduct. The list of diseases in the cases admitted included hip disease (26), spinal disease (20), paralysis (6), scrophula (9) and rickets (5) with an average stay of 177.14 days. The detailed accounts of this report also include expenditure on:

		£	s	d
Bread 5,568 pounds	cost	38	7	5½
Milk 1,550 gallons	cost	75	0	3
Brandy 1½ gallons	cost	1	16	0
Chloroform		0	3	8
Bandage Calico		4	8	3
Splints, spinal apparatus		28	15	8

Whether the consumption of brandy and discharge for bad conduct were related is not, however, recorded! The annual staff costs listed included the £50 salary of the matron and nurses wages of £42.

The Hospital was then extended by the Board of Management of the Belfast Royal Hospital to incorporate a convalescent home at an additional cost of £7,000 [2] for which the memorial stone was laid on Thursday, October 18 1877. The Morning News [3] the following day described the ceremony at length. *"Yesterday the very interesting ceremony of laying the Memorial Stone of the Convalescent Home, Throne Lands was performed by Sir Richard Wallace, Bart., M.P., in the presence of a large assemblage, which included a numerous proportion of ladies. A train which started from Belfast shortly before 12 o'clock brought the greater number of visitors to Greencastle, whence they enjoyed a very pleasant walk to the Home which is about a mile distance from the station. The morning, though at first murky, cleared up about noon, but remained in a favourable state only for a short time. Just at the hour appointed for the performance of the ceremony – 1 o'clock – a drizzling rain descended, and detracted a little from the enjoyableness of the occasion, the speeches being delivered in the open air, immediately in front of the main entrance, where the stone was laid . . . The building which is in the Gothic style of architecture is elegantly and tastefully designed . . . The dressings are of white sandstone from the Scrabo Quarries, County Down. The building is divided into 2 departments – that situated on the right being devoted to the Children's Home, and that on the left to the Convalescent Home. The former branch is designed for 32 children, and the latter for upwards of 30 patients. A spacious corridor 240 feet in length, extends from one end of the block to the other. This corridor is 10 feet in width with a ceiling of about 18 feet in height. At the end of this corridor is a beautiful stained glass memorial window,* (actually a pair of windows Ed.) *erected by the late John Martin, Esq., to the memory of his son Samuel Martin,*

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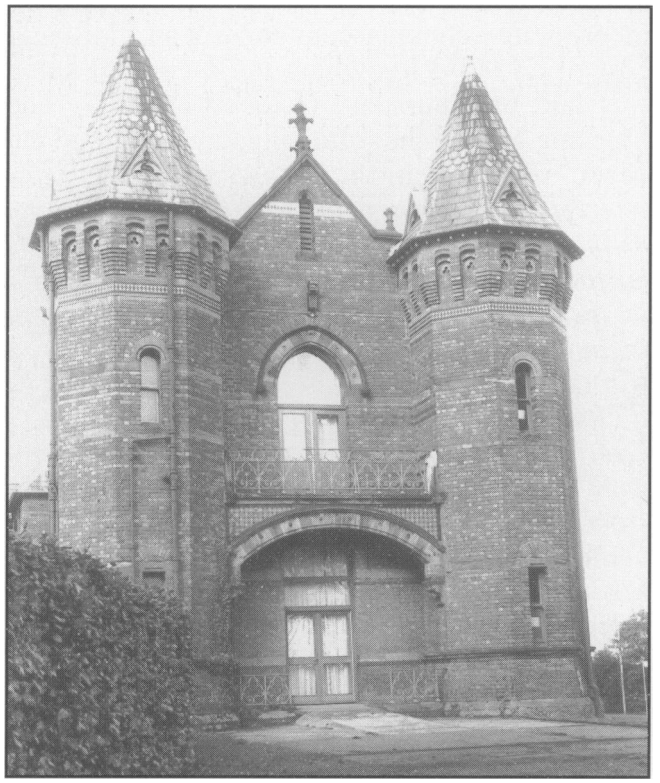
Esq., who died during the progress of the erection of the building. The inscription is taken from the 18th chapter of Luke and 16th verse – "Suffer little children to come unto me, and forbid them not, for of such is the kingdom of God." The contractors for the building were Messrs. H. and J. Martin.



The Throne Hospital 1990

The article then outlined the address of Sir Richard Wallace who stated that the Throne was the first Convalescent Home to be erected in Ireland and that it would enable the Royal Hospital (then based at Frederick Street) to receive more patients, to ensure a complete recovery of the convalescent patients admitted to the Throne Hospital and to send them back full of health, and he hoped gratitude, to their different homes and avocations.

After a prolonged series of speeches the proceedings terminated. The company were entertained at luncheon in one of the rooms of the hospital and a programme of music was performed by the Band of the 91st Regiment including L'Italiana in Algiere (Rossini), Il Trovatore (Verdi) and Come Back to Erin!

Thus with not a little pomp and ceremony the Throne Hospital was opened. The role of the Throne Hospital slowly evolved with the introduction of Plastic Surgery, Maxillo-Facial Surgery and the Dental Technician Laboratory in 1963.

In 1973 it began its last role, as a Hospital for the care of elderly patients. The Throne Hospital provided long term and rehabilitation care primarily for the 20,000 elderly population aged 65 and over residing in North and West Belfast. Patients were admitted under the care of Dr Tom Ryan until his retirement in 1982, Dr Ian Taylor from 1982-1985 and subsequently Dr Timothy Beringer from 1985 until its closure on 4 November 1992. The number of beds slowly declined (to reduce overcrowding in the smaller wards), to a total of 33 upstairs and 26 on the ground floor. The old Theatre Block was adapted to provide facilities for occupational therapy and physiotherapy. The majority of patients were admitted directly from home. In 1984 there were 102 admissions, with 64 discharges and 34 deaths. Over 75% of the patients received long-term continuing care.

On the closure of the Hospital on 4 November 1992 the remaining long-term care patients were transferred to long-term hospital care in the Royal Victoria Hospital geriatric medical unit or to nursing home care. The beautiful pair of stained glass windows were removed from the hospital for safe keeping and are currently in Whitehouse Presbyterian Church. Although the Throne Hospital was listed in 1987 as a building of special architectural and historical interest sadly it has fallen into disrepair. The adjoining lands are now developed with private housing.

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The Ulster Medical Journal, Volume 67, No. 2, pp. 117-120, November 1998.

The Throne Hospital and early Plastic Surgery in Northern Ireland

J Colville

The Throne Hospital was built on a 28 acres site on the northern outskirts of Belfast and was opened in October 1874 as a convalescent hospital for children and adults; by its location it was well removed from the grimy atmosphere of central Belfast. Donations were headed by the Martin family from Killyleagh in memory of their son who had recently died from an infectious disease. Other significant contributions were donated by families whose names were associated with the Belfast Royal Hospital; they are recorded in Dr Sidney Allison's "The Seeds of Time"[1] in which he refers to the incorporation of the new hospital with the newly-created Royal Belfast Hospital, formerly the Frederick Street Hospital. The first annual report refers to 32 beds in two wards, 12 of which were designated the Martin Children's Beds for "spinal cases". In general, it is clear that most of the patients suffered from spinal and hip disease and various glandular swelling and that most of these surgical conditions were tuberculous in origin. Transfers from the Royal Hospital were admitted and were under the care of Dr H C Manley, a local general practitioner. Adult transfers had to await the completion of the hospital which was not finished until 1877. A surplus of 20 acres was leased for housing development, the income from which contributed to the running of the hospital. The Belfast Royal Hospital report for 1884 reflects the convalescent nature of the hospital where each bed was occupied by less than three patients per year. By comparison the Children's Hospital and the Ulster Hospital for Women and Children, each had approximately eight patients per bed per year. An additional unit was opened in 1885 for treatment of advanced pulmonary tuberculosis. This declined in importance when the Forster Green Hospital was established in 1896, but there were still ten beds for this purpose in 1903. It was under the care of the Royal Hospital physicians, successively Dr (later Professor) James Lindsay, Strafford Smith and William Calwell.

The first lady superintendent was Miss Markham. In 1878 she was followed by Mrs E A Shiel and in 1887 Miss M F Bostock was appointed, who later became the first matron of the new Royal Hospital in 1902. Subsequent matrons were Miss Mildred from Grantham in 1902-09, Miss Hilson from the Royal Victoria Hospital 1909-36 and Miss Magee, a former sister in the Throne Hospital from 1936-48. She was followed by Miss Betty Boyce who went to South Tyrone Hospital in 1951. Miss J McCollam took over and continued until 1955 when she was replaced by Miss Agnes Campbell. Miss Campbell continued at the Throne Hospital until a few years before its closure and the last few years of the hospital were supervised by Miss Ann Burnside from the Royal.

In the early years surgical procedures were carried out in the Royal and Children's hospitals before the patients were transferred to the Throne Hospital, but the 1881 Annual Report has the statement "Seven operations were performed during the year, chloroform being administered in each case". The surgery was presumably carried out by Dr H C Manley and there were rarely more than 20 operations per year. Manley, who was appointed medical officer when the hospital opened, retired in 1900 and was replaced by surgeon Thomas Sinclair Kirk, assisted by Robert Reid as medical officer. Kirk was appointed Attending Surgeon to the Royal Victoria Hospital in 1902 and from this date all operations were carried out by Howard Stevenson although he was not officially appointed as Kirk's assistant until 1909. The hospital which then was known as the Martin Children's Hospital was mainly engaged in the management of patients with tuberculosis.

Theatre records are available from 1901. The numbers of operations vary from 50-150 per year and most of these were performed on children and young adults with tuberculosis e.g. psoas abscess, curettage, gland drainage, joint excision

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and amputation. Mr Stevenson remained on the visiting staff of the Royal Victoria Hospital until 1941 and continued to carry out most of the operations in the Throne Hospital. He retired from the Throne in 1944 and there-after no designated general surgeon was appointed to its staff. Anaesthetics were administered by "H S" There was no House Surgeon so presumably the anaesthetic was also given by the same person and I note also that Matron on one occasion gave the anaesthetic.

Tuberculosis, which was the common disease, can be identified in 60% of the procedures in 1902, and many other drainage and abscess operations, not specified, may well have been the same disease. In 1910 the figure was not greatly changed at 50% and in 1924 the figure was less than 20%. In 1935 out of a total of 65 operations, only two were for tuberculosis.

In the late thirties "H S" was still doing most of the operating and I note that in 1938 C J A Woodside performed a number of operations. In the early forties the pattern of activity changed and more readily recognizable names appeared on the operating list. These were Wilfred Brennen, in 1942, Bill Coyle in 1943, Daniel Chapman in 1944, John McKee 1945, Walter Braidwood, John Pyper, Hugh Bailie and Mr Coyle in 1946. Most of the surgery performed by these gentlemen was "radical cure of hernia". The notable event of the war years was a direct hit from a bomb during the air raids of 1941, which fortunately caused no casualties. Over the years 1947-1949 many of the doctors became surgeons. These were Messrs. Arthur Stevenson, Herbie Dales, Ernest Morrison, Ronnie Loan, Smith (?R P) and a separately identified W F (Bill) Smith. The numbers of operations also steadily rose from 175 in 1944 to 220 in 1949. W Lennon is recorded as having manipulated rheumatoid joints on 17.10.49.

In the late forties and early fifties more familiar anaesthetists also appeared including Martin (Mac) Shaw, Harold Jefferson, Stafford Geddis, Charles Reid and Maurice Brown.

The medical side of the Throne Hospital was essentially convalescent and long-stay throughout this century. The physicians-in-charge were general practitioners from Whiteabbey: Robert Reid from 1900 until death in 1937, followed by T Lawrence Ross and David Wilson into the 1940s. William Lennon, consultant rheumatologist at the Royal Victoria Hospital had beds in the Throne Hospital until his retirement in 1966. In addition, of course, the consultants of the Royal Victoria Hospital had over all responsibility for many of the patients who were simply "boarded out" in the Throne Hospital.

The first Plastic Surgical operation recorded was on 3.9.50 when a fractured malar with facial scars was operated on by N C Hughes and on 7.9.50 a cross-leg flap was delayed and on 11.9.50 an abdominal tube pedicle was raised. On 18.9.50 a Dupuytren's contracture was corrected. For the remainder of that year there were 100 plastic surgical operations and a total of 220 general surgical operations performed by most of the forementioned general surgeons. David Gilchrist was the first anaesthetist and Bob Gilmore, who at that time was a senior registrar, replaced him when he moved to London a year later.

In 1951 Johnny Boyd, Paddy Creighton and Myles Gilligan were operating on the general patients with the anaesthetists above-named plus Harold Love and James Sutcliffe. In that year there was a total of 750 operations, 459 plastic and 291 general surgery. In 1952 the general surgeons were Ronnie Dickson, Myles Gilligan, Willoughby Wilson and James Kyle. 0ut of 730 operations 191 were general and 539 plastic. In 1953 the "visiting surgeons" were Willoughby Wilson, Reggie Livingston, Alex. McCalister and John B. Lowry.

In 1953 the newly appointed R I H (Roy) Whitlock's first operation was for osteomyelitis of the mandible. Later that year Dr Kyle had become Mr Kyle and 259 general surgical operations and 577 plastic operations were recorded. Additional anaesthetists included T A (Bertie) Browne and Gerald Black.

On 6.6.54 John Gorman removed impacted wisdom teeth. The general surgeons were Brian Smith, Willoughby Wilson, Myles Gilligan, Reggie Livingston and Millar Bell, and anaesthetists Robert Nicholl, Keith (Tub) Morrow, Bob Gilmore, Hugh Graham and Colin Boyd.

In that year 262 general surgical and 592 plastic surgical operations were performed. In 1955 the general surgeons were Messrs. Kyle, Bell, Livingston, Jack McCready and Cecil Maltby, and the anaesthetic staff was reinforced by Bob Gray. Jimmy Piggot and Kenneth Orr performed

minor surgical operations, giving their own anaesthetic. A total of 695 plastic operations and 190 general surgical operations were accounted for in 1955.

In 1956 a James Blundell was included in the surgical listings and Andrew Scott and J (Mac) Clarke anaesthetised. Registrars Ryan and Costello were also noted to have operated; 707 plastic and 262 general surgical operations were performed.

In 1957 Ernest Kemp and Basil Gray performed minor skin grafting operations and Bill Costello, John Lowry and Reggie Livingston made frequent general surgical appearances as did Ian Murphy and Pat Allen on occasional lists. On the dental side Ian Finlay on various lists removed impacted wisdom teeth. A typical list for Norman Hughes is represented by the elevation of a tube pedicle on the arm for the loss of a nasal columella, the excision of scars on chin, lip and forehead, a wedge resection of a growth of the upper lip and sequestrectomy of a fractured tibia and fibula. A list by Dickie the following day included composite graft for the loss of the right side of the nose, removal of a neurofibroma from a thenar eminence, repair of a palate fistula, amputation of a contracted little finger, the removal of a growth from a foot, and grafting of burns to face, legs and hand. Typical dental lists always included at least two cases with impacted wisdom teeth and usually a fractured mandible. A general surgical list usually included either one or two hernias and at least one set of varicose veins which were stripped or ligated. In that year 762 plastic and 298 general surgical operations were performed. The year 1958 includes references to Joe Kennedy who performed minor plastic operations, and Ivan Johnston (who later that year appeared as Mr Ivan Johnstone) and Stewart Clarke and Dick Tooth who did some of the surgical lists which were again mainly done by Messrs. Livingston and Costello. Brian Sommersgill also appeared frequently in the dental surgical lists. Mr Gorman's name also in the latter part of that year appeared more regularly in the dental lists. For that year there were 1050 plastic cases and 243 general. In 1959 Hume Logan and Donal McWilliams, and Donald Hancock, appeared as occasional alternatives to Livingston in doing the general surgical lists. The total of plastic and dental procedures was 1138 and general surgery 180. The following year (1959) saw the introduction of an Australian, Jim Poate as a plastic surgical registrar and thereafter his name appeared regularly in the plastic surgical operating lists. The additional general surgical operators included James Milliken and Ivor Heath; George Emerson also appears for the first time on the oral and maxillo-facial side. David Hadden, who was a houseman, also performed a number of minor skin grafting operations. For 1960, 1284 plastic and dental, and 157 general operations were performed.

In 1961 Professor Rodgers is noted to have repaired a left inguinal hernia on 8.2.61. Owen Tuohy also appears in the oral maxillo-facial lists and W J H (Billy) Graham on the plastic surgical lists. In September, 1961 John Robb appears on the general surgical lists and alternated with Livingston in that capacity for the remainder of the year. The new anaesthetists included Michael Lewis and Moira Hainsworth. The total for 1961 were plastic 686, dental 502, combined 19 and general 128, and emergencies (for the first time identified) 37. 1962 saw the inclusion of Peter Baskett as an anaesthetist and Roy Gibson and John Robb as a plastic surgical registrar and Dr Watson appears in the general surgical list. The numbers were plastic 778, dental 487, combined 24, general 155 (1962).

In 1963 Claire McWilliam and Morrell Lyons appeared in the anaesthetic registrar list. George Emerson appears on the oral surgical side (as senior registrar) and Vance Mitchell appears on the plastic side as S H O. John Robb was replaced by John Colville (senior registrar). The totals for that year were 779 plastic, 562 dental, 26 combined, 180 general and 22 emergencies. In 1964 Douglas George is noted on the general surgical lists and John Cronhelm and Brian Nixon appear as anaesthetic registrars. Ronnie Slater joined the Unit as senior registrar in February 1964 and from then onwards the senior registrars undertook first call for emergencies on alternate weeks until 1968. One emergency comes to mind on 31.3.64, the patient (T M) aged 69 years was admitted with multiple injuries following a road traffic accident. His surgery included laparotomy with repair of multiple perforations of the large bowel, supra-pubic drainage for a bladder injury, reduction wiring of a Le-Fort III facial fracture plus repair of multiple facial lacerations. This was all done without recourse to x-ray or blood and the patient was admitted to the Throne Hospital rather than to the Royal, (where most of the emergencies were done) on account of the

apparent predominance of the facial injuries. In the latter part of 1964 Terry Shaw joined the Unit as a rotating general surgical registrar and Mr Prasad joined as an oral surgical registrar. The 1964 figures were 897 plastic, 643 dental, 20 combined and 157 general surgical most of which were done by Mr Livingston. There were 39 emergencies. In 1967 J A (Alfie) Moore joined as a consultant anaesthetist and Roy Millar was one of the housemen on rotation from the Royal. Hume Logan was a general surgical senior registrar on rotation for a period. The 1967 figures were 1308 plastic, 653 dental, 14 combined, 164 general surgery and 75 emergencies.

Before continuing with the Plastic Surgery Unit's development at the Ulster Hospital, it is worth mentioning a few other developments and milestones at the Throne.

Until 1954 all surgery was conducted in a small theatre sited midway between the two floors. Patients were manhandled up and down stairs to and from this little theatre. This rapidly became unsatisfactory due to the increase in numbers and also the complexity of the surgery. A gift of £15,000 from the Royal Victoria Hospital Ex-Patients' Guild made possible the building of a new twin-theatre suite plus sterilizing areas and changing rooms. The Northern Ireland Hospitals' Authority contributed a further £10,000 to complete this and to provide air conditioning. The old theatre became a dental surgery and even for that it was comparatively inadequate. It was not until 1964 that a bed-lift was installed enabling patients to be brought to and particularly from theatre in their own bed.

In that same year most of the R V H convalescent beds were reallocated to Plastic and General Surgery, providing 57 plastic surgical beds and 12 general surgical beds.

In 1964 a training school for State Enrolled Nurses was opened and in the same year an electric hoist for the transfer of severely burnt patients from their beds to a saline bath greatly facilitated the otherwise very painful handling of these patients and saved the nurses a lot of heavy lifting.

In 1962 the Working Men's Committee paid for a Dental Laboratory, staffed by Mr Walter Hamilton and an assistant technician.

The author who had been introduced to microsurgery in Pittsburg in 1966 continued with the adaption of the operating microscope to clinical needs. The absence of bureauocratic red tape allowed a very expensive operating microscope, designed for the Plastic Unit in the Ulster Hospital (to be opened two years later) to be delivered to the Throne Hospital. Small animals had to be transferred to the Throne (in the boot of the author's car) and used in the familiarisation with small vessel anastomosis. These were transported from the Department of Clinical Science Animal House and back again if they survived the kidney transfer that was the index of successful small vessel anastomosis. This was followed the next year by clinical application to revascularisation and nerve repair.

No history of the Throne Hospital would be complete without special reference to "Mac", Miss F E McKenzie, a New Zealand nurse who worked in East Grinstead with Norman Hughes, and who came to Belfast at the inception of the Unit as the Plastic Surgical Ward Sister. With only the interest of the patients at heart she was the bane of all who came under her influence, housemen and consultants alike. Her professionalism and clinical judgement were highly respected. Many young girls started their nursing career as probation nurses at the Throne prior to commencing their formal Nurse Training at the Royal. Mac's regimental style tempered with kindness was a memorable introduction to Nursing for many young women in their formative years.

The final plastic surgical operation on 29.11.68 was the removal of an impacted wisdom tooth under general anaesthesia by John Gorman; the patient was anaesthetised by Bob Gilmore. On 4.12.68, Plastic Surgery was transferred to The Ulster Hospital Dundonald. General surgery on a reduced scale continued for some years until eventually the hospital reverted to a convalescent unit. It was finally closed on 4 November, 1992.

ACKNOWLEDGMENT

I am indebted to my colleague Richard Clarke who advised on some details and particularly with reference to anaesthetic personnel.

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The Ulster Medical Journal, Volume 67, No. 2, pp. 121-123, November 1998.

Association of Clinical Pathologists. Irish Branch Meeting 27 - 28 March 1998

THE MOLECULAR DETECTION OF GRAM NEGATIVE PATHOGENS IN SPUTUM OF PATIENTS WITH CYSTIC FIBROSIS (CF)

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In the past conventional bacteriological techniques have misidentified Gram negative organisms such as *Stenotrophomonas maltophilia* as *Burkholderia cepacia* due to colonial and phenotypic similarities. Identification is extremely important as *B. cepacia* has severe consequences for CF patients which ultimately lead to death. Categorisation with *B. cepacia* has implications for infection control, psychosocial issues and patient management.

The aim of this study was to provide a faster and more specific technique for the detection of *Pseudomonas species*, *Pseudomonas aeruginosa*, and *B. cepacia*. The techniques employed were split into conventional and molecular.

Conventional methods involved using *Pseudomonas* Isolation Agar Medium, which supports the growth of *Pseudomonas* species and also *B. cepacia*. MAST *cepacia* agar was also used which is specific for the growth of *B. cepacia*. However false positives may occur and can include *Ralstonia spp.*, *Alcaligenes spp.*, and *S. maltophilia* which maybe misidentified as *B. cepacia*. The molecular method employs sequence specific primers for *Pseudomonas spp.*, *P. aeruginosa* and *B. cepacia* to amplify the bacterial DNA by; PCR. The DNA is then visualised using a 2% (w/v) agarose gel stained with ethidium bromide.

Sputa samples from 66 adult CF patients were examined using both techniques. For *Pseudomonas spp.* conventional methods detected 41 positives compared to 47 strong and 6 weak positives by PCR. For *P. aeruginosa*, conventional methods detected 38 positives and PCR detected 40 strong and 7 weak positives. Conventional methods detected 20 positive *B. cepacia* patients compared to 25 strong and 12 weak positive by PCR.

PCR provides rapid and specific detection of small number of these Gram negative organisms. Conventional methods can be slow and sometimes it can be difficult to grow the organism at it is extremely difficult to mimic the *in vivo* growth conditions. Presently the clinical significance of PCR weak positive/culture negative patients is being assessed.

WHY FORMALIN? LESSONS FROM BOUINS FIXED BONE MARROW TREPHINE BIOPSIES

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Bone marrow biopsies were divided and fixed in 10% formalin and Bouins solutions. Morphology and immunocytochemical reactivity with various antibodies using the Avidin Biotin technique for visualisation of reactions was assessed on sections from each.

Lymphoplasmacytoid morphology was clearly demonstrable in the Bouins fixed portion of one biopsy, whereas the only diagnosis possible in the formalin fixed portion was non-Hodgkin's lymphoma. Reactions with anti IgG, A and M heavy chain and IgK and L anti-immunoglobulin antibodies were far stronger in Bouins fixed samples whereas equivalent staining for both fixatives was obtained with anti CD15, muramidase, CD3, CD19, VIII and glycophorin A.

We conclude that definition of monoclonality and quantitation of plasma cell subsets is more satisfactory when Bouins fixation is used, and that its use is more likely to permit accurate morphological subtyping of non-Hodgkin's lymphoma in trephine biopsies.

DEVELOPMENT OF AN ELISA ASSAY FOR THE DETECTION OF ANTIBODY TO *CAMPYLOBACTER* INFECTION

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Campylobacter jejuni is the most common cause of bacterial gastro-enteritic infection within the Northern Ireland population. The present study involves the controlled epidemiological determination of the levels of *Campylobacter jejuni* antibody in the aforementioned Northern Ireland population. Previous research (Lafong & Bamford, 1986) has indicated the lower incidence of the disease within this population; with higher incidence found in England and Wales.

The present study of seroprevalence involves the development of a serological sandwich ELISA (enzyme-linked immuno-sorbent assay) test to determine antibody levels by use of a selective monoclonal antibody. The 5A7 monoclonal has been developed using the OMP 18 antigen and following bulk growth of clones, ascites has then been produced. It is this caprylic acid purlfied ascites of the 5A7 monoclonal that is used for plate coating.

From initial determinations using preliminary ELISAs with coating of 1/100 of the purlfied monoclonal for capturing the antigen and the use of crude *Campylobacter* antigen it is possible to detect the test positive human sera at a dilution of 1/400. It is hoped that with further screening of a selection of sera obtained from blood samples provided from the NIBTS a comparative picture of the levels of antibody present within the population can be determined.

Further investigations under consideration include the use of different conjugates in order to classify the infection leading to the presence of antibody in the sera samples as being recent infection (IgM), current infection (IgA) or previous infection or a secondary exposure (IgG) to the bacterium.

DIRECT MOLECULAR DETECTION OF *MYCOBACTERIUM SPP.* FROM SPUTUM OF ADULTS AND CHILDREN WITH CYSTIC FIBROSIS BY 16S rRNA BASED PCR

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Mycobacterium other than tuberculosis (MOTT) is frequently found in patients with cystic fibrosis (CF) and culture and identification of MOTT is sometimes difficult using conventional bacteriological techniques. It was therefore the aim of this study to investigate the incidence of *Mycobacterium spp.* in adults and children with CF directly from sputum by 16S rRNA PCR. Fresh expectorated sputum from 207 patients (66 adults, 118 children and 23 adult patients with pulmonary exacerbations) were examined. Microbial genomic DNA was extracted from sputum following treatment with sputasol and was examined with specific oligonucleotide primers which amplify a homologous 1,026bp DNA fragment of the 16S rRNA gene, which is unique to *Mycobacterium spp.* In all, 17/207 (8.2%) of sputa were found to contain *Mycobacterium spp.*, i.e. 4/66 (6.1%) adult specimens, 11/118 (9.3%) children's specimens and 2/23 (8.7%) adult pulmonary exacerbations. Further characterisation of species was achieved by single stranded conformational polymorphism (SSCP) of PCR amplicons, demonstrating the existence of several species, and in two patients, the co-existence of two *Mycobacterium spp.* Initial sequence analysis confirmed one amplicon to be either *M buckeii* or *M hassiacum* and further sequencing is presently being undertaken to confirm the species of the other positive specimens. Overall this technique which does not require the ability to grow *Mycobucterium spp.*, enables the rapid detection and identification of *Mycobacterium spp*, including *M. tuberculosis*, which otherwise may be difficult to identify conventionally by culture and phenotypic analysis. The significance of these unusual MOTT detected by this method is still unclear and requires further study.

ACINETOBACTER SPECIES AND CULTURE-NEGATIVE ENDOCARDITIS: DETECTION AND SIGNIFICANCE

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Although various clinical symptoms e.g. pyrexia, vegetation demonstrated by echocardiography, may aid in the diagnosis of infective endocarditis, bacteriological blood culture is still the most important laboratory investigation that is carried out. In approximately 4-24% of cases the blood culture investigation is negative, and hence no microbiological causative agent is identified and therefore appropriate antimicrobial chemotherapy can not always be implemented, thereby compromising patient management. The aims of our current research is to identify aetiological agents of culture negative endocarditis by molecular technology, namely polymerase chain reaction (PCR) and subsequently by sequencing of the amplicon. DNA is isolated from blood culture material and subsequently amplified using appropriate primer pairs. All patients who enter the study are classified as having suspected endocarditis (SBE) due to the fact that they fulfil Duke's criteria. Universal primers for bacteria are used based on the 16S rRNA gene and yeasts and fungi based on 18S rRNA and 28S rRNA genes.

Case Report

Blood cultures were taken from a male patient, 75 years of age with SBE. Trans Ocsophagial Echocardiography demonstrated vegetation of the mitral valve leaflet.

All blood culture material was culture negative. Sixteen samples were analysed from admission I and all were negative by PCR. All samples available for molecular diagnosis during admission I were following decline of the patient's elevated CRP levels and following antimicrobial chemotherapy with imipenem and netilmicin *or* teicoplanin and ciproxin. Thirteen culture-negative bottles from admission II were analysed and 12 were positive by PCR. During this period the patient's CRP levels remained >100 and the patient was on teicoplanin and rifampicin. Sequence data from some of the PCR positive samples demonstrated the presence of the Gram-negative organism *Acinetobacter spp.*, which has been previously implicated in endocarditis.

There is a role for the molecular diagnosis in cases of culture-negative endocarditis.

RAPID MOLECULAR DETECTION OF MRSA IN ICU

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Acquisition of Methicillan Resistant Stuphlococcus Areas (MRSA) and other nosocomial infectious agents continues to be of major concern in relation to infection control, particularly with certain hospital patient groups e.g. neutropenic and immunocompromised patients. Conventional detection of MRSA may take approximately four to five days to confirm, during which time there may be the opportunity for cross-infection of MRSA to susceptible patients in either Intensive Care Unit (ICU) or High Dependency Unit (HDU) areas. The aim of this study was to employ rapid PCR-based detection techniques in order to screen all patients in ICU for MRSA and subsequently to take appropriate infection control procedures to prevent MRSA acquisition to new ICU/HDU admissions. From January - March 1998, all admissions to ICU (n=70) were examined both conventionally and by PCR for the presence of MRSA. Swabs were taken from various sites (axilla, nose, lesions, throat, perineum) and were incubated overnight in Salt Meat Broth and were subsequently plated on to Mannitol Salt Agar containing oxacillin (2 μg/ml). PCR detection employing the *mec*A and *fem*B locus, as indicators of the presence of MRSA was carried out on all broths post enrichment. Results showed that two patients were positive for MRSA, and such screening data was available within 24 hours following admission. We propose that all patients on entering either ICU or HDU, should be screened by PCR for the carriage of MRSA. Adoption of such protocols will aid in the control of transmission of MRSA in these units.

The Ulster Medical Journal, Volume 67, No. 2, pp. 124-125, November 1998.

Case Report

Apnoeic episodes in a patient with Chiari type I malformation

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Accepted 6 April 1998

The Chiari type I malformation is a rare condition that generally occurs in young adults. It consists of a caudal displacement of the cerebellum and brain stem to a variable extent through the foramen magnum.[1]

There can be a wide variety of symptoms in these patients, including headache, weakness, numbness of the limbs, unsteadiness and loss of balance.[2] A variety of respiratory disorders have been described including acute respiratory failure,[2] respiratory arrest [3] and sleep apnoea.[1] It is extremely unusual for a patient with the condition to have no abnormal neurological signs on presentation, if apnoeic problems are a feature.

We describe such a patient in whom, curiously, a transient pyrexia accompanied his apnoeic episodes.

CASE REPORT A 31 year old farmer arrived in Casualty at Mid-Ulster Hospital with a history of several apnoeic episodes associated with unresponsiveness, witnessed by his wife. Rectal diazepam had been administered about an hour prior to admission by the general practitioner, as the patient had appeared to be anxious and shivering on coming round from the apnoeic episodes.

There was a past medical history of similar symptoms, also with a high initial temperature, 18 months and two years previously, requiring hospital admission for two days on each occasion. The diagnosis on each admission was "viral illness". Hyperventilation had been noted on a couple of occasions. Arterial blood gases during one of these episodes showed a pH of 7.64, (normal range 7.36-7.44kPa) pO2 13.7, (normal range 11.3-14.6 kPa) and pC02 2.42,(normal range 4.7-6.0 kPa).

On examination on his third admission, his temperature was 38.6 degrees centigrade. He had 10 apnoeic episodes in Casualty associated with loss of consciousness, during which he was noted to be haemodynamically stable. Full neurological examination revealed no significant abnormalities, apart from his unresponsiveness whilst apnoeic.

Investigations showed that full blood picture, urea and electrolytes, thyroid function and blood sugar were normal. ECG and chest x-ray were

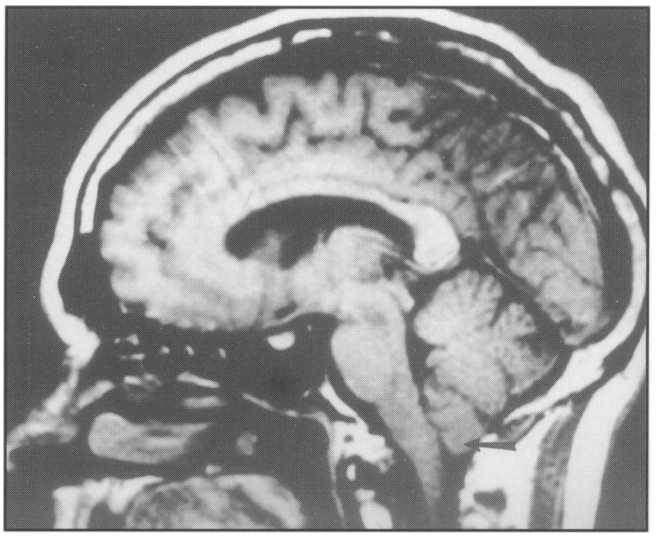

Figure MRI image showing ceribillar tonsilar discent (Chiari type I malformation).

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normal. CT scan brain and EEG with hyperventilation were normal.

He was readmitted one week later with further apnoeic episodes, and two weeks later with severe generalized headache. Full neurological examination was invariably normal.

MRI scan was performed in order to evaluate the brain stem more accurately than CT scanning permits. This showed a Chiari type I malformation with herniation of the cerebellar tonsils through the foramen magnum to the level of the upper border of the posterior arch of C1. (Figure) MRI of the thoracic spine was normal.

He was transferred to the Regional Neurosciences Unit for assessment with a view to foramen magnum decompression. It was decided to proceed with surgery. A sub-occipital craniectomy was performed and the posterior arch of C1 was removed. The dura was then opened and the tonsils were found to have herniated to just below the level of the foramen magnum, but they did not reach the arch of C1. Some fine adhesions between the tonsils and the brainstem were noted; these were divided by sharp dissection. The fourth ventricle was entered and a Surgicel patch was placed over the dural opening. Post-operative recovery was unremarkable apart from some headaches, which gradually resolved. There have been no further problems with apnoeic episodes in the 30 months that have elapsed since surgery.

DISCUSSION

Although the original description of the Chiari malformations was in 1891,[4] respiratory failure as a presenting feature in adults has only been described in the past decade.[2, 3, 5, 6]

Conventionally, the diagnosis should be considered in adults when symptoms and signs of damage to the cerebellum, medulla and lower cranial nerves appear.

Our case illustrates that it is important to think of the diagnosis in any patient with unexplained apnoeic episodes, even though neurological examination may be normal.

The exact pathogenesis of the apnoea is not fully understood – possibly compression of the medulla or compromise of the vascular supply to the brain stem may be responsible.[7]

Chiari type 1 malformation is a condition that is potentially treatable by surgical decompression.[3] The fact that our patient has not relapsed during the 30 month follow-up period is encouraging.

The unusual features in this case are the absence of neurological signs or florid evidence of respiratory failure, and the presence of pyrexia with the apnoeic episodes.

ACKNOWLEDGEMENT

We thank Mr John Gray, Consultant in Neurosurgery, Department of Neurosciences, Royal Victoria Hospital, for permission to publish this case, and for his help with the manuscript.

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The Ulster Medical Journal, Volume 67, No. 2, pp. 126-128, November 1998.

Case Report

A rapidly enlarging neck mass

A Paterson, P S Thomas

Accepted 7 April 1998

Neck masses in children are a frequent occurrence and can often create a diagnostic dilemma. In such a situation the clinical history and physical examination are important. A thyroid lesion which is rapidly enlarging, firm and non-tender, associated with additional symptoms such as hoarseness, stridor, dyspnoea or dysphagia should alert the clinician to a potentially malignant lesion, particularly in the euthyroid patient.

The case presented illustrates many of these primary features; however there was a strong family history of autoimmune thyroid disease which could have been misleading. The imaging findings suggested the need for urgent histological investigation which led to a prompt diagnosis being made.

CASE REPORT. A thirteen year old boy noted a swelling in the left side of his neck upon waking one morning, whilst on holiday. He attended the Accident and Emergency department of the nearest hospital and he was referred for an ultrasound scan. His parents were informed that his thyroid gland was "enlarged" and they were advised to seek further help on their return from holiday. A week later he attended the Rapid Response Clinic at The Royal Belfast Hospital for Sick Children. His neck swelling had not changed in size appreciably during this time and he did not complain of any systemic symptoms. The patient's mother stated that there was a strong history of autoimmune thyroid disease in the family, with three maternal relatives having hypothyroidism and the patient's maternal grandfather having suffered from hyperthyroidism. Clinically and serologically the patient was euthyroid, and his thyroid antimicrosomal antibody levels were not elevated. A repeat ultrasound scan was requested (see figure 1). The scan showed an heterogeneous, solid mass arising in the left lobe of the gland, which was surrounded by a compressed rim of more normal thyroid tissue. The mass measured

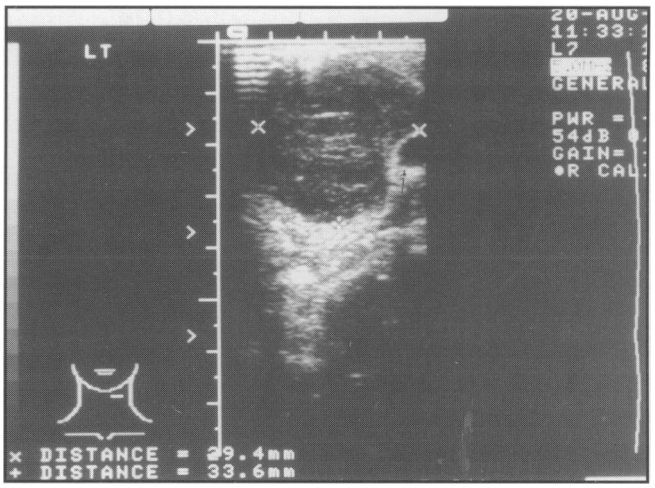

Fig 1. Transverse ultrasound scan through left lobe of the thyroid gland, showing mixed echogenicity mass displacing the carotid sheath (arrowed) and compressing normal thyroid tissue posteriorly.

2.7 x 4.0 x 3.4cm. The left carotid sheath was partly encased by the mass and was displaced posterolaterally. An enlarged lymph node was present along the left internal jugular chain. Radiologically the diagnosis was thought to be lymphoma or carcinoma. An adenoma was felt to be less likely, given the clinical history and the short time period involved.

An isotope study was suggested (see figure 2). This revealed a large "cold" area corresponding to the tumour mass. A chest x-ray showed deviation of the trachea to the right by the mass. The lungs were clear.

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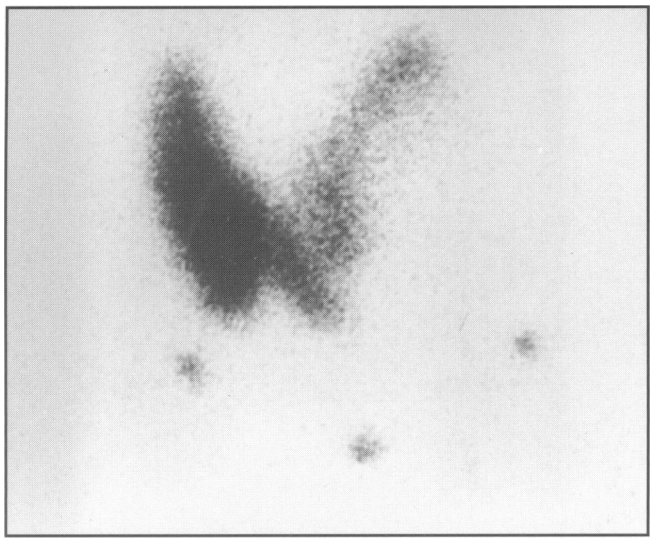

Fig 2. Isotope scan using $^{99m}TcO_4$ showing a cold lesion occupying most of the left lobe of the thyroid gland.

A fine needle aspiration of the lesion was inconclusive, and surgical biopsy was undertaken. This confirmed the diagnosis of non-Hodgkin's lymphoma stage IIA, with involvement of the previously-noted cervical lymph node.

Computerised tomography of the chest, abdomen and pelvis did not show any further evidence of disease progression. The patient was referred to the care of the paediatric oncologists and he was commenced on chemotherapy. Five months later he is well and responding to treatment.

DISCUSSION

The differential diagnosis of thyroid enlargement in childhood is wide and includes Hashimoto's thyroiditis, subacute (presumably viral) thyroiditis, abscesses, cysts, thyroid dysgenesis with residual and/or ectopic functioning tissue, benign adenomas and carcinoma.[1] To differentiate between them, historical details relating to the mass itself; whether it is tender to the touch, how fast it has grown and whether or not it is associated with any systemic upset should be ascertained. Any family history of thyroid or other autoimmune disease or an history of previous head or neck irradiation must also be documented. Attention to the thyroid status of the patient is important during the clinical examination.

In this situation an ultrasound scan is often requested to help to define the lesion. An ultrasound examination of the neck requires no preparation or sedation, and does not involve the use of ionising radiation. The technique can be used to define the precise location of a lesion and its relationship to other anatomical structures. It can distinguish solitary from multiple lesions and solid from cystic lesions. The additional use of colour Doppler demonstrates those lesions which are predominantly vascular in nature.[2, 3, 4]

Thyroid scintigraphy reveals functional rather than anatomical information. The studies can be performed either with isotopes of radioiodine or using technetium-99m in the form of sodium pertechnetate ($NaTcO_4$). In both the monovalent anion involved is actively taken up in the thyroid. Radioiodine is oxidised and utilised for hormone synthesis as with dietary iodine. Pertechnetate is not organified. Resultant images classify thyroid nodules as either hot, warm or cold according to the degree of radionuclide accumulation. A hot nodule nearly always indicates a benign functioning adenoma.[5] The majority of cold nodules will also be benign and would include, for example, cysts, abscesses and haematomas. The proportion of solitary cold nodules that are malignant varies widely, but is generally quoted as lying between 12-35%.[6]

Primary carcinoma of the thyroid gland presenting in childhood is uncommon, accounting for only 1.5% of all malignancies before the age of 15 years. Two thirds of these tumours occur in girls between seven and 12 years. The major types of thyroid cancer in childhood are papillary (70%), follicular (20%) and medullary (5-10%). Lymphoma of the thyroid is an unusual condition that has been described almost exclusively in elderly Caucasian females.[2, 7, 8]

This case is both rare and unusual, in that it describes primary non-Hodgkin's lymphoma of the thyroid gland in a thirteen year old male child. Less than a dozen cases of this condition in childhood have been described in the world literature and the majority of these have been in girls.[9] Thyroid malignancy should be considered in the differential diagnosis in children who present with a rapidly enlarging neck mass.

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The Ulster Medical Journal, Volume 67, No. 2, pp. 129-131, November 1998.

Case Report

Late presentation of branchial cyst

M J McClure, C S McKinstry, R Stewart, M Madden

Accepted 1 May 1998

Branchial cyst is a common cause of a soft tissue swelling in the neck of a young adult. In older adults, with this presentation, it is important to exclude metastatic lymphadenopathy, lymphoma or tuberculosis. We report a branchial cyst which presented in a fifty nine year old male, with typical ultrasound and magnetic resonance (M.R.) appearances leading to the correct radiological diagnosis.

CASE REPORT A fifty-nine-year-old man was referred with a twelve month history of a swelling in the left side of his neck. He reported that the swelling varied in size with time. It was never painful nor inflamed. He had occasional pains in his left shoulder radiating into his neck, but this was relieved with anti-anginal medication. He was a non-smoker. There was no associated hoarseness, dysphagia, dizziness or blackouts and he had no intraoral pain or ulceration. His general health otherwise was unremarkable.

On physical examination, the neck lump was soft, fluctuant, non tender and pulsatile measuring 4x5 cm in size. It was situated in the left anterior triangle, inferior to the angle of the mandible, superficial to the left carotid artery and anterior to the upper third of the sternomastoid muscle. There was no associated submandibular or parotid swelling and it was not related to the thyroid gland. Examination of the mouth, nose, sinuses, pharynx and larynx was normal.

Biochemical and haematological blood profiles, including an erythrocyte sedimentation rate, were normal. A doppler ultrasound scan (7.5 MHz, 5.5 cm, linear array) of the neck showed a normal left carotid artery. The jugular vein was displaced laterally, and compressed, by a mass 4.2 cm in length and 1.5 cm in depth. The mass was of low to medium-level echogenicity and appeared cystic rather than solid.

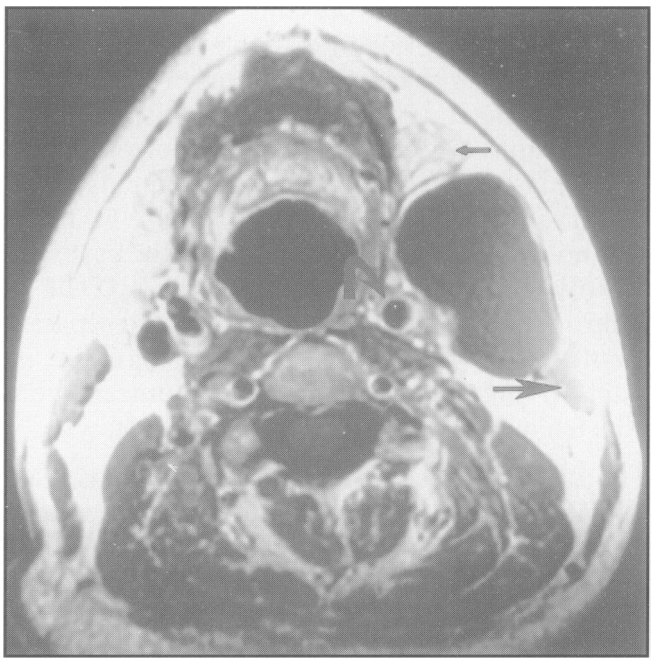

Fig 1. Axial T1 weighted MR image. Note submandibular gland (short arrow), sternomastoid muscle (long arrow) and carotid sheath (curved arrow). The cyst fluid is characteristically of low intensity on T1 weighted images. The cyst wall does not enhance following Gadolinium-DTPA.

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An M.R. scan (1.5 Tesla magnet) was then requested to identify more clearly the margins of the mass and it's relationship to the underlying vessels. Coronal and axial T1 weighted (Repetition time (TR) 640 ms/Echo time (TE) 11ms) images were obtained followed by axial STIR (Short Tl inversion recovery; Time from inversion (TI) 150 ms/TE 85 ms/TR 6000 ms) images. Following intravenous Gadolinium-DTPA (Diethylene triaminepentacetic acid) contrast enhancement, axial T1 weighted images were obtained.

These confirmed the presence of a large, well-defined, rounded mass in the posterior submandibular space, the contents of which were of fluid signal intensity. There was displacement of the submandibular gland anteriorly, the sternomastoid posteriorly and the contents of the carotid sheath postero-medially (Figure 1). There was no evidence of enhancement of the cyst wall following intravenous Gadolinium-DTPA. Inferomedially the mass was difficult to separate from a displaced, compressed and thrombosed internal jugular vein. The appearances were consistent with a second branchial cleft cyst.

The cyst was surgically excised. A sinus tract extended superiorly between internal and external carotid arteries and was ligated. The left tonsil appeared to be inflamed and was removed. Histopathological examination confirmed a branchial cyst lined by squamous epithelium and containing copious lymphoid tissue in the wall, and an inflamed tonsil (Figure 2). No granuloma formation, caseation necrosis or atypical cells were evident.

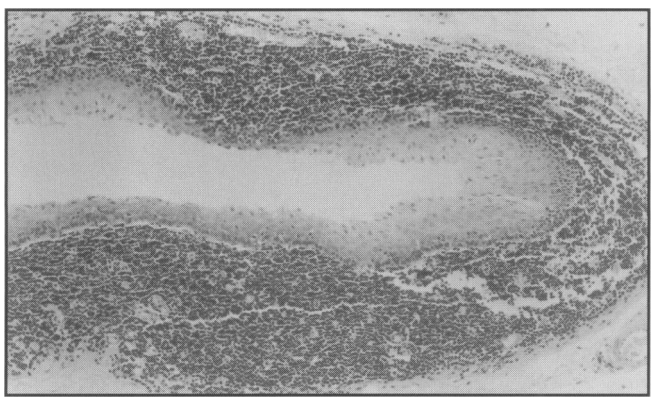

Fig 2. Histopathological section of cyst wall. The branchial cyst is lined by squamous epithelium and contains lymphoid tissue within the wall. There is no evidence of cellular atypia or granuloma formation.

DISCUSSION

Branchial cyst is the commonest cystic lesion occurring in the neck. There are four theories of origin of branchial cysts.[1] Embryologically, they may represent remnants of pharyngeal pouches or branchial clefts or a fusion of these two elements (present in a two to nine week embryo). Alternative theories include remains of the cervical sinus of His, formed when the second arch grows down to meet the fifth arch, hence "lateral cervical cyst". The "Thymopharyngeal duct theory" is less convincing.

King *et al* proposed the "Inclusion theory" that cyst epithelium arises from lymph node squamous epithelium.[2] Much evidence supports the latter. For instance, most branchial cysts contain lymphoid tissue with no internal opening, the peak age incidence is later than expected for a congenital lesion, and a branchial cyst in a neonate is almost unknown.

The peak age incidence for branchial cysts is in the third decade. Typically they present as a swelling in the anterior triangle of the neck adjacent to the angle of the mandible. Sixty percent are in males, sixty percent on the left side. A few cysts have a definite tract to the posterior pillar of the tonsil, but most do not. A sinogram is of value in the former.[3]

In patients over the age of forty years a cystic metastatic node from a primary neoplasm must be excluded.[4] Differential diagnoses include lymphoma, tuberculosis, and, less frequently, lipoma, nerve sheath tumour or carotid body tumour. Branchiogenic carcinoma is also well documented in the literature. In this condition, neoplasia occurs within squamous epithelium of the branchial cyst, in a patient where an undiagnosed primary has been completely excluded.[5]

Branchial cysts typically contain straw coloured fluid consisting of cholesterol crystals and squamous epithelial cells on fine needle aspiration cytology. Histopathologically, these cyst walls contain lymphoid tissue with evidence of germinal centres, which supports the "Inclusion Theory".

Ultrasound of branchial cysts has been reported. Bedami and Athey *et al* describe echogenic layering in the dependent portions of branchial cysts.[6] More recently Reynolds and Wolinski *et al* describe uniform low to medium level echogenicity in cysts which they postulate

represent cholesterol crystals and cellular material.[7] Our documented case conforms with these features, demonstrating low to medium-level echogenicity, but does not show dependent layering. Its relationship to the underlying carotid sheath is well demonstrated by Colour Doppler methods. Computerised tomography confirms the cystic nature of branchial cysts and determines the extent and anatomical relationship.[8]

At present, M.R. scanning provides the optimum diagnostic imaging modality available for patients presenting with lateral neck masses, due to greater inherent tissue contrast resolution and multi-planar imaging techniques.[9] Gadolinium-DTPA contrast is useful in excluding differential diagnoses. Typically, cyst wall enhancement occurs with neoplasia and infective causes such as tuberculosis. Absence of contrast enhancement of the cyst wall, and its site in the posterior submandibular space with characteristic displacement of adjacent structures[10] permitted the correct radiological diagnosis to be made in this case, despite the late age of presentation.

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The Ulster Medical Journal, Volume 67, No. 2, pp. 132-133, November 1998.

Case Report

Bronchobiliary fistula complicating open cholecystectomy

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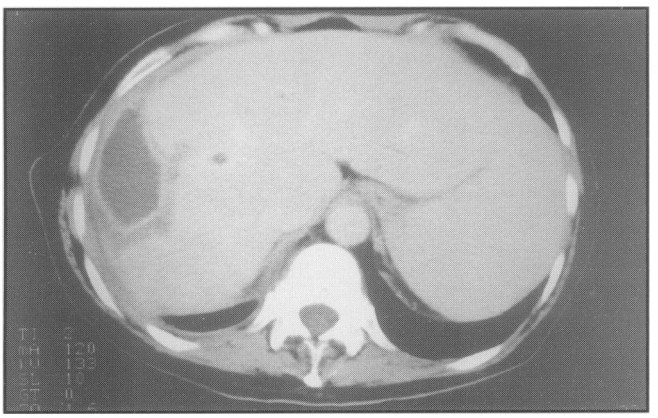
Accepted 15 August 1998

We report a case of a bronchobiliary fistula following an intrahepatic abscess as a result of a bile leak after an elective open cholecystectomy.

CASE REPORT A 64 year old woman with history of scleroderma had an elective open cholecystectomy. One week later she developed a subhepatic bile collection. A subhepatic drain was inserted but she developed a persistent bile fistula. Endoscopy revealed a leak from the cystic duct. A 10 French gauge stent was inserted into the common bile duct beyond the level of the cystic duct.

The bile leak resolved, but two months following discharge she developed right upper quadrant pain, rigors and bilioptysis (a cough productive of bile). Chest radiograph showed a right sided pleural effusion and CT scan demonstrated a large abscess in the right lobe of the liver (Fig).

Percutaneous drainage was unsuccessful so a laparotomy was performed. A large area of the right lobe of the liver (most of segments VII and VIII) was found to be necrotic, and a defect was noted in the dome of the diaphragm, which appeared to communicate with the right chest cavity. The necrotic parenchyma was excised and two large sump drains were inserted, one into the abscess cavity and the other into the defect in the diaphragm.



Contrast CT scan demonstrating large subcapsular hepatic abscess in segments VII and VIII.

Post operatively she developed an air and bile leak. A subsequent ERCP was performed and the plastic biliary stent removed from the bile duct. There was a suspicion of contrast in the bronchial tree on this examination. A further CT scan demonstrated a pleural effusion, diaphragmatic disruption and a collection under the diaphragm consistent with bronchobiliary fistula. Her bilioptysis settled when the drain from the defect in the diaphragm was connected to an underwater seal. The air and bile leak slowly diminished allowing removal of the drains. She remained well at follow up two months later.

DISCUSSION

Bronchobiliary fistula is a rare complication of disease of the biliary tract. Peacock first highlighted the complication in a patient with a hydatid cyst in 1850.[1] It is most frequently associated with necrotizing hepatic infections, such as amoebiasis and echinococcosis.[2] Other causes include subphrenic abscess, thoraco-abdominal trauma including iatrogenic percutaneous biliary injury[3] and suppurative complications of biliary tract obstruction. The two major aetiological factors are, therefore, infection (subphrenic or intrahepatic abscess) and mechanical bile duct obstruction with the

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latter being more common in Western countries.[2,4] In this case there was no evidence of biliary obstruction but the patient did have an intrahepatic abscess. The coexistence of scleroderma may have contributed to poor healing resulting in leakage from the cystic duct and subsequent abscess formation.

Presentation of a bronchobiliary fistula may range from chronic episodes of bilioptysis to a severe bronchopneumonitis. Bilioptysis is pathognomonic of bronchobiliary fistulae and, in one review of non-traumatic bronchobiliary fistulae, was present in all the patients studied.[4] The triad of symptoms of right upper quadrant pain, fever and bilioptysis, as noted in this case, was reported in 11 of the 16 patients reviewed by Gugenheim et al.[4]

Bile stained sputum can be analysed for bilirubin concentration and in true bilioptysis it may contain up to 8 mg/dL of bilirubin. Chest X-ray findings of a right pleural effusion and a raised hemidiaphragm, as seen in this patient, are common in this condition. The finding of a diaphragmatic disruption secondary to an abscess or laceration at the liver dome with associated right pleural effusion in a patient with bilioptysis strongly suggests a bronchobiliary fistula.[5] Cholangiography, either percutaneously or endoscopically, should be performed.[6] Large amounts of contrast may be required at ERCP to demonstrate the fistula and the detail may not be as clear as with percutaneous imaging.[7] Isotope scanning with HIDA may also be used,[8] but bronchoscopy is generally unhelpful.[4]

Drainage of any abscess and relief of bile duct obstruction are the two key principles of management. Drainage of an abscess may be carried out either percutaneously or surgically. This case required surgical drainage as the necrotic material was too viscous to drain percutaneously. In patients with associated biliary tract obstruction the priority of management is towards decompression of the bile duct by means of a stent or a surgical procedure such as a Roux-en-Y hepaticodochojejunostomy.

Bronchobiliary fistulation is a rare complication of biliary disease. Diagnosis with CT scan and cholangiography followed by drainage of abscesses and biliary decompression are the key elements in the management of this potentially life threatening condition.

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The Ulster Medical Journal, Volume 67, No. 2, pp. 134-136, November 1998.

Case Report

Orthotopic liver transplantation for Hepatitis C infection: the best Christmas present?

S D Johnston, O McNulty, E Mayne, M E Callender

Accepted 4 September 1998

SUMMARY

We report the case of a 60-year-old man with mild Christmas disease, Factor IX 10% of normal, who developed chronic hepatitis C infection after receiving coagulation factor concentrates. Subsequently he developed encephalopathy and liver failure and was referred for liver transplantation. Following transplantation, Factor IX levels rapidly normalised and have remained so, representing a phenotypic cure of his Christmas disease.

CASE REPORT

The patient originally presented in 1971 (aged 35 years) with an episode of prolonged bleeding from the site of a dental extraction. Investigations led to the diagnosis of mild Christmas disease (Haemophilia B). Over subsequent years he was given fresh frozen plasma and then intravenous coagulation factor concentrates. In 1978, as part of pre-operative management prior to haemorrhoidectomy he was given coagulation factor concentrates, and two weeks following this he developed clinical jaundice with the maximum bilirubin concentration rising to 100 mg/l. It is assumed that the coagulation factor concentrates were infected with hepatitis C virus. Liver function tests were normal pre-operatively. The jaundice rapidly resolved although his liver function tests remained abnormal. He had no other risk factors for hepatitis C infection or for the development of end-stage liver disease.

In May 1995 he presented with haematemesis and melaena. Splenomegaly was noted on examination, and upper gastrointestinal endoscopy revealed large oesophageal varices which were treated by a course of injection sclerotherapy. He suffered several episodes of encephalopathy without evidence of further gastrointestinal bleeding, electrolyte imbalance or infection. In 1996 he developed further episodes of encephalopathy and bleeding varices which were again treated by injection sclerotherapy. His clinical course was complicated by the development of ascites which resolved with spironolactone. He continued to have episodes of intermittent confusion and poor energy and was managed with oral spironolactone, neomycin and lactulose. Liver biopsy was not performed. He was unable to tolerate alpha-interferon treatment on account of side-effects.

Hepatitis C antibody testing was positive and hepatitis C RNA by PCR (Polymerase Chain Reaction) was persistently positive with viral subtype 3a. *HbsAg* negative; *HbeAg*, *HbeAb* were negative. *HBV* core *IgG* was not performed. HIV antibody test was negative. Autoimmune screen revealed anti-smooth-muscle antibody in low titre. Haemoglobin was reduced at 10.0 g/dl, white cell count 4.1 x 10^9/l, platelets 163 x 10^9/l. Liver function tests were as follow: albumin 29 g/1, *AST* 56 U/1, *ALP* 216 U/l, bilirubin 28 mg/l, alpha-fetoprotein normal. Creatinine clearance

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was normal (86 mls/min). Pulmonary function tests and echocardiogram were normal. Aminoacid profile at the time of encephalopathy revealed increased levels of tyrosine, phenylalanine and methionine, and normal levels of valine, leucine and isoleucine. Copper studies and alpha-1-antitrypsin were normal. Ultrasound of the abdomen revealed patency of the portal vein. CT brain scan was normal. Electro-encephalogram revealed mild generalised abnormality with slight temporal preponderance.

He was referred to King's College Hospital, London, where he underwent an orthotopic liver transplantation in October 1997. On the second post-operative day he was found to have normal Factor IX levels. He was subsequently treated with cyclosporin, azathioprine, prednisolone and sucralfate and remains well at six-month follow-up. Hepatitis C RNA detected by PCR is positive post-transplantation, and Factor IX levels remain normal.

DISCUSSION

It is well-recognised that most haemophiliac patients who have been given coagulation factor concentrates prior to 1985 are at risk of hepatitis C infection. Interferon is the main treatment currently available for chronic hepatitis C infection and is commenced after a liver biopsy confirms significant inflammatory changes combined with evidence of active viral replication. The risks of liver biopsy, in particular haemorrhage, obviously are accentuated in haemophiliacs who require coagulation factor concentrates prior to the procedure, therefore interferon treatment is often given without a biopsy being undertaken. Liver biopsy may be carried out in haemophiliacs who are empirically treated with interferon but who are unable to tolerate the full course of treatment or if the patients' symptoms suggest that they may have significant liver disease which is not indicated by liver function tests. The main limitations of interferon treatment are adverse effects including poor energy and flu-like symptoms as in this case. Combination treatment is a possible treatment option for the future and further studies are currently underway with amantidine and ribavirin with interferon.

Haemophiliac patients with chronic hepatitis C infection have a cumulative risk of progressing to liver cirrhosis in 1.7% at 10 years and 19.8% at 20 years[1] and liver transplantation may be required. Successful liver transplantation in humans with haemophilia was initially described in one patient with severe haemophilia A (Factor VIII deficiency) in 1985.[2] The procedure is safe providing that adequate intra-and immediate post-operative coagulation factor replacement is given to avoid bleeding complications and there does not appear to be an excessive transfusion requirement.[3] There are reports of three patients with Haemophilia B (4-6), 10 patients with Haemophilia A (3, 4, 7-9) and one patient with combined factors VIII and IX deficiency[10] who have received liver transplants in the literature. Data on the survival and length of cure of such patients is limited. One report documents survival of 12 months post-transplantation and sustained factor concentrations.[4] There is one report of a patient who died intra-operatively which was related to technical difficulties of graft insertion[9] and one late mortality due to the development of acquired immunodeficiency syndrome,[8] another complication of multitransfused haemophiliacs.

Liver transplantation has been used in the treatment of genetic diseases in patients with no significant liver disease.[11] A case can be made for liver transplantation prior to the development of liver failure in haemophiliac patients with hepatitis C infection in view of the additional benefits of a phenotypic cure of the clotting abnormality.[3] However, this must be viewed in the light of the present shortage of organ donors and the impact on other patients with end-stage liver disease. The mechanism of cure of the coagulation deficiency relates to the fact that the liver is the source of synthesis of the vitamin K dependent coagulation factors (including Factor IX) and since the graft originated from a non-haemophiliac patient there is a phenotypic cure of the coagulation deficiency.

The main long-term problem with liver transplantation for hepatitis C induced cirrhosis is allograft reinfection with HCV, which usually runs a benign course[12] although it may progress to cirrhosis within 1-2 years.[13] The time taken for the restoration of normal coagulation factors may be as short as 12 hours[4] and a sustained response at 72 hours confirms de novo synthesis of clotting factors by the graft. Further follow-up is required to determine if there is a sustained cure of the haemophilia and to see the outcome of the continuing HCV infection.

ACKNOWLEDGEMENT

The authors are grateful to Dr J O'Grady, Director of the Liver Unit, and the hepakobiliary surgeons, King's College Hospital, London, for permission to publish this case report.

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The Ulster Medical Journal, Volume 67, No. 2, pp. 137-138, November 1998.

Case Report

Acute presentation of ascites in association with colon cancer

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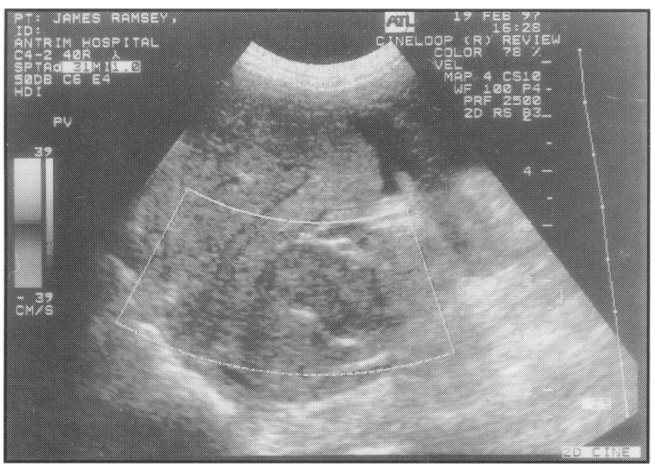
Accepted 1 August 1998

Portal vein thrombosis is a relatively rare condition in western countries. In adults it is often related to cirrhosis or hepatocellular carcinoma and does not usually have any acute manifestations other than complications of portal hypertension. We report a patient with portal vein thrombosis presenting as acute ascites associated with a colonic carcinoma.

CASE HISTORY An 80 year old man presented with gross ascites and altered bowel habit. Investigations, including a barium enema and Duplex Doppler ultrasound, revealed a colonic carcinoma and a portal vein thrombosis (figure). The ascites was a transudate and did not contain any malignant cells. The ascites responded satisfactorily to treatment with spironolactone and he then underwent a left hemicolectomy. The ascites recurred a few days after his surgery, and this had to be aspirated. He made a good recovery and was discharged to continue treatment with spironolactone.



Dupplex Doppler showing the walls of the portal vein (white lines within the boxed area) with no blood flow within it.

DISCUSSION

The acute presentation of ascites in association with colonic carcinoma could easily have been attributed to metastases. However, it was in fact probably secondary to the portal vein thrombosis. Portal vein thrombosis is a rare condition which affects both children and adults. The overall incidence at autopsy ranges between 0.05% and 0.5%.[1] It does not usually have any acute manifestations, but patients often present with complications of portal hypertension, notably haemorrhage from varices. When it does present acutely, it is usually with sudden onset of ascites,[2] which tends to resolve spontaneously when a collateral circulation develops. In this case, radiological investigation did not show any collateral circulation.

The commonest causes of portal vein thrombosis are cirrhosis, infection, intra-abdominal inflammation (pancreatitis, appendicitis, cholecystitis, diverticulitis), trauma (including surgery), neoplastic disease (notably hepatocellular and pancreatic carcinoma), myeloproliferative disorders and inherited and acquired hypercoagulable states. Idiopathic cases also occur.[1] In the case presented the first six causes were ruled out by clinical examination, investigation and laparotomy. It was therefore suspected that the underlying factor could have

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been a hypercoagulable state. The patient had no history of thrombosis in the past and was therefore more likely to have an acquired condition. The association of malignancy with hypercoagulable states and thrombosis has long been recognised, and these have been reported in as many as sixty percent of cancer patients.[3] Possible contributory causes for thromboembolic disease in cancer include the capacity of tumour cells and their products to interact with platelets, clotting and fibrinolytic systems, as well as their interactions with endothelial cells and tumour-associated macrophages.[4]

If portal vein thrombosis is suspected clinically, ultrasound scanning (preferably with colour Doppler) is the radiological investigation of choice. If this is unhelpful, the next step is to proceed to MRI or CT scanning with intravenous contrast enhancement. If these non-invasive tests are inadequate then portal angiography should be carried out.

Management is often centred around treatment of complications, in this case the treatment of ascites by diuretics. The role of anticoagulation in patients with portal vein thrombosis has not yet been established. There is little evidence that it is of any benefit[1] and it increases the risk of bleeding if varices are present.

This case emphasises the importance of routine ultrasound in the presence of ascites. It should not be presumed that ascites in the presence of a neoplasm is secondary to metastatic disease, as dual pathologies can often coexist.

ACKNOWLEDGEMENT

We thank Mr T Diamond for his critical reading of the manuscript and helpful suggestions.

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The Ulster Medical Journal, Volume 67, No. 2, pp. 139-141, November 1998.

Case Report

The use of transcatheter embolisation to treat uterine fibroids

P K Ellis, I M G Kelly, P P Fogarty

Accepted 26 June 1998

Uterine leiomyomata (fibroids) are the commonest benign pelvic tumours. Therapeutic options include hormone manipulation or surgical management, myomectomy if the patient wishes to retain fertility, or hysterectomy. We describe the use of transcatheter arterial embolisation in a patient who presented with a large uterine fibroid and pressure symptoms.

CASE REPORT A forty-two year old female patient presented with acute urinary retention. She was admitted to hospital where a urethral catheter was passed. She described a several month history of occasional difficulty commencing the flow of urine but was otherwise well with no relevant past medical history.

Initial assessment included ultrasound, which showed a large uterine fibroid lying at the posterior aspect of the uterus, with a diameter in excess of ten centimetres. Hypervascularity was observed on colour doppler imaging. After discussion of therapeutic alternatives with the patient, we decided on transcatheter percutaneous embolisation of the uterine arteries.

Prior to the procedure a prophylactic iv bolus of cefuroxime (750 mg) and metronidazole (400 mg) was given. The procedure was performed under conscious sedation (midazolam and fentanyl) with physiological monitoring.

An initial puncture was performed at the right common femoral artery and a 5-French arterial sheath was placed. A 5-French pigtail catheter was placed in the aorta, and pelvic angiography demonstrated enlarged uterine arteries with multiple dilated abnormal tortuous vessels, corresponding to the uterine fibroid (fig 1).

The aortic bifurcation was then crossed using a 5-French Cobra II catheter, (Cordis, Roden, the Netherlands). The internal iliac artery was selected and subsequently the left uterine artery was cannulated using the road mapping facility available on angiographic equipment. Polyvinyl alcohol (PVA) foam particles of size 500 to 710 microns (Cook, Bloomington, In) were mixed

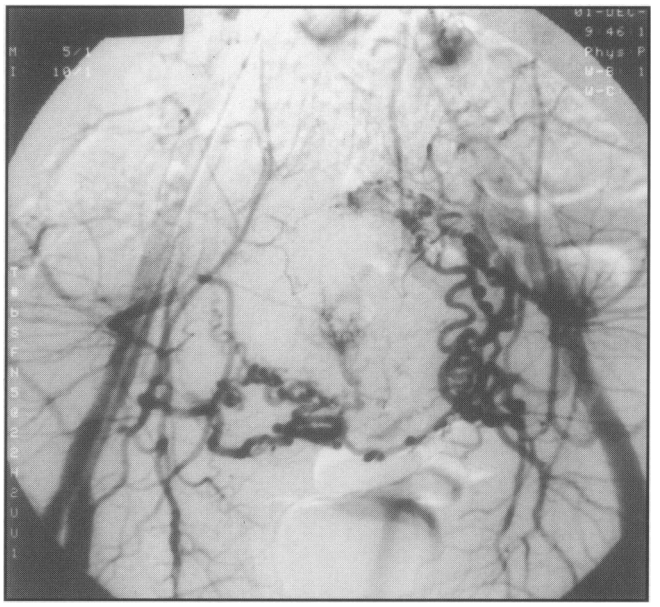

Fig 1. Pelvic Arteriogram: Multiple, dilated, tortuous vessels are identified centrally within the pelvis corresponding to the large uterine fibroid.

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with dilute contrast media and were slowly injected under fluoroscopic guidance until flow in the left uterine artery was abolished.

A 5-French Sos-Omni selective catheter (Angio-Dynamics, Queensbury, NY) was then used through the arterial sheath to select the ipsilateral right internal iliac artery. A guidewire was placed distally within this artery and an exchange was performed for a Cobra catheter. Again PVA particles were injected slowly with dilute contrast medium, until flow in the right uterine artery was also abolished.

A repeat pelvic angiogram was performed and this demonstrated continued minimal filling of both uterine arteries. The procedure was then performed for a second time in each artery with further embolisation using PVA particles. A small pledget of Gelfoam (Upjohn, Kalamazoo, MI) was placed at the origin of each uterine artery. Following this procedure pelvic angiography demonstrated occlusion of both uterine arteries, with no evidence of filling of the abnormal uterine fibroid vessels. (fig. 2)

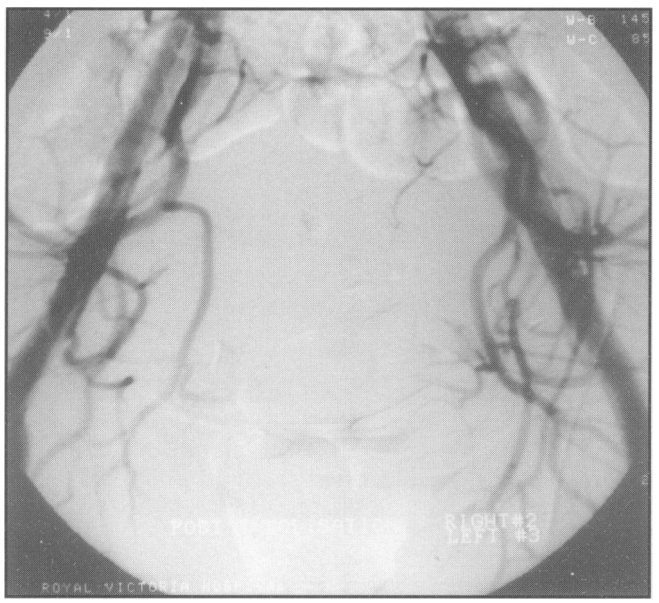

Fig 2. Pelvic Arteriogram (post embolisation): No filling of the uterine arteries is identified.

Ultrasound examination, immediately following the procedure, demonstrated no evidence of flow within the fibroid on colour Doppler imaging, and multiple echogenic foci within the fibroids, representing aggregations of embolic material (fig. 3).

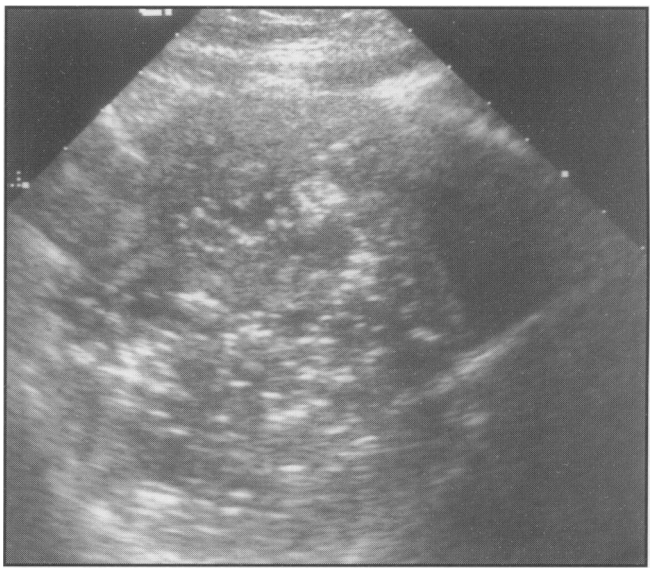

Fig 3. Ultrasound of pelvis: The large uterine fibroid is well seen. Multiple echogenic (bright) foci represent aggregates of embolic material.

Approximately one hour following the procedure the patient developed episodes of sweating and shivering due to the post embolisation syndrome; she was treated using diclofenac sodium, 50 mg suppository. These symptoms resolved over two hours and the patient was discharged the following morning.

At six weeks, ultrasound examination demonstrated a seventy-five percent reduction in the total volume of the fibroid. She has reported no further symptoms.

DISCUSSION

Initial reports of devascularisation of the uterus detail an effective means of controlling postpartum haemorrhage.[1] High success rates have been described with uterine artery ligation in both postpartum and post-caesarean section bleeding. As a logical extension to this, percutaneous transcatheter embolisation has been used effectively in several situations, including postpartum bleeding, uterine arterio-venous malformation[2] and gynaecological malignancy bleeding.[3] Complication rates for these procedures are low and the option of surgery is still available should success not be obtained.

Uterine leiomyomata (fibroids) are commonly asymptomatic, although uterine enlargement can result in pressure symptoms with heaviness and discomfort. Infarction or torsion may result in pelvic pain. Haemorrhage is a common

complication, presumably due at least partly to the hypervascularity of a uterine fibroid.

In theory, uterine fibroids should be ideally suited to embolisation as they derive their blood supply almost exclusively from the uterine arteries. The vascular patterns of myomatous uteri have been well described previously: essentially there is a peripheral supply of tortuous and dilated vessels from which arise arteries that supply the central part of the fibroid. The peripheral supply results in a dense persistent tumour blush on angiography.[4] As clear anastomoses occur between the left and right uterine artery, both vessels must be embolised to obtain a satisfactory technical result. In addition, there is evidence that there is devascularisation of uterine fibroids in women who respond well to treatment with hormonal agents (including synthetic progestogens and LHRH agonists). Investigation with doppler ultrasound has demonstrated some devascularisation of fibroids in women who have responded well to treatment with hormonal therapy.[5] This further supports the argument for percutaneous embolisation of the uterine arteries.

Few previous reports of uterine fibroid embolisation exist. However, Ravina et al. described a series of sixteen patients, of whom fourteen had heavy and prolonged bleeding, and who underwent uterine arterial embolisation.[6] At a mean follow-up of twenty months, symptoms had entirely resolved in eleven patients and were partially relieved in three. All had been previously treated with hormonal therapy, with only transient success. Goodwin et. al. at the University of California, Los Angeles, described this technique in eleven patients.[7] Eight of nine patients, who they were able to follow up, reported noticeable symptomatic improvement at six months.

One potential benefit of percutaneous embolisation is the preservation of normal anatomical structures and therefore fertility. Most of the patients in the French study, (Ravina et. al.) returned to normal menstruation, and indeed one conceived after fifteen months. It would be prudent to await long-term follow-up in larger clinical trials to fully appreciate the long-term potential benefit, both with respect to the treatment of the uterine fibroids and preservation of fertility.

In conclusion, percutaneous transcatheter uterine arterial embolisation offers a useful alternative to surgery in the treatment of uterine fibroids. Potential benefits over surgery include reduced post-operative complications, lower costs, shorter hospitalisation and the potential preservation of fertility. Although short-term results have been excellent in our case, and in the two previously described short series[6, 7] further work will be necessary with large controlled trials to assess long-term benefit.

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The Ulster Medical Journal, Volume 67, No. 2, pp. 142-144, November 1998.

Case Reports

Testicular epidermoid cyst: a case for conservative surgery

D W Harkin, P Pyper, M Hawe

Accepted 22 July 1998

We present two case reports of benign testicular epidermoid cysts, along with a review of the literature. This rare cause of intra-testicular swelling has often been treated by orchiectomy in the past. Evidence in the literature suggests a more conservative approach can be adopted safely, provided certain diagnostic criteria are observed.

CASE 1

A 24-year-old man presented with a painless 2 cm nodule in the lower pole of his right testicle. Ultrasonography revealed a hypoechoic intra-testicular circumscribed lesion with normal surrounding parenchyma. The levels of serum testicular markers human chorionic gonadotrophin (HCG) and alpha-fetoprotein were normal.

Inguinal testicular exploration revealed a solid intra-testicular lesion. On opening the tunica albuginea a 1 cm solid lesion with calcific exterior was easily enucleated, leaving a normal testicular parenchymal bed. The lesion contained yellow-white keratinous debris. The tunica was closed with preservation of the testicle. Histopathology confirmed a benign epidermoid cyst and the patient remained well at one year follow-up. (Figures 1 and 2).

Fig 1. Testis with non-infiltrating intra-teticular lesion visible on opening the tunica albuginea.

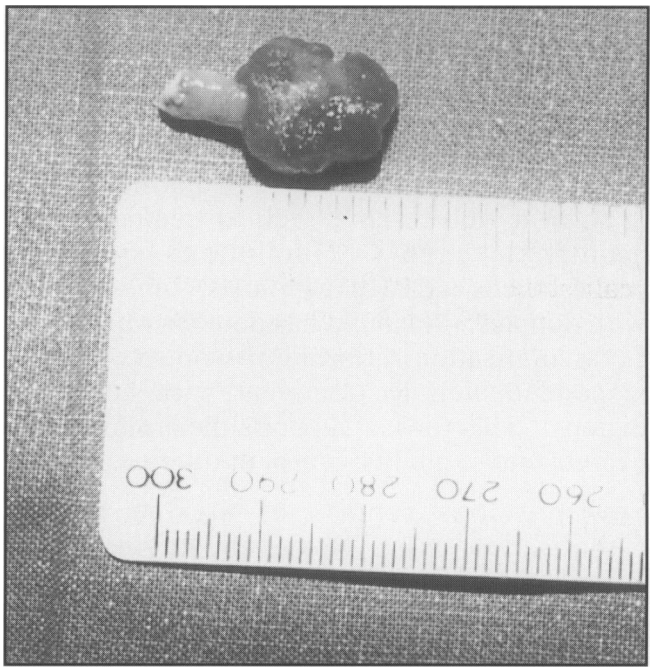

Fig 2. Epidermoid cyst after simple enucleation.

CASE 2

A 23-year-old man presented with a painless 1 cm swelling in his right testicle. Ultrasonography showed a round 1 cm solid intra-testicular lesion with a hypoechoic centre and

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hyperechoic margin. The rest of the testis was normal. Serum markers, HCG and alpha-fetoprotein, were normal. Inguinal testicular exploration revealed a solid intra-testicular lesion. A wedge resection of the lesion with a rim of surrounding parenchyma was analysed; features were in keeping with a benign epidermoid cyst. The testicle was preserved and postoperative paraffin sections confirmed the presumptive diagnosis. The patient was well at one year follow-up.

DISCUSSION

Epidermoid cysts are a rare cause of benign intra-testicular swelling. Dockerty and Priestley[1] first clearly described them in 1942, as benign epidermoid cysts in a normal testis. Since then approximately 300 cases have been reported as small series or retrospective literature reviews. Due to the concern about the malignant potential of intra-testicular tumours, radical surgery is still carried out by many. Price *et al* [2] found 84% (58 out of 69) underwent orchiectomy in their review. This is disturbing for a benign condition of young adults. We present the available evidence and advocate what is a safe, yet still conservative, treatment for these lesions.

The World Health Organisation classifies epidermoid cysts of the testis as a "tumour-like lesion", and there remains debate as to the true histological origin of this lesion. Previously they were believed to be monodermal teratomas, but if so this would suggest they should be found in association with testicular intraepithelial neoplasia (TIN or carcinoma in situ) as with 70-100% of other testicular tumours of germ cell origin, Jacobsen *et al* [3] and Loy *et al.*[4] This in turn would suggest they should have a malignant potential as TIN invariably progresses to germ cell tumour (GCT), Skakkebaek *et al.*[5] Two independent series by Jacobsen *et al* [3] and Dieckmann *et al*,[6] have shown no evidence of TIN in association with epidermoid cyst by immunohistological staining for placental alkaline phosphatase, in a combined retrospective review of 163 cases of true epidermoid cyst. The few isolated reports of disseminated GCT in association with epidermoid cyst have all been due to burnt-out or missed coexistent primary GCT in the testicle. Therefore their indolent benign behaviour, and their propensity to occur in other systems not of germ cell origin would suggest another origin not yet proven.

The Mayo Clinic Series and combined literature review, Malek *et al*,[7] would suggest these cysts are usually solitary, painless, and have a slight propensity for the right side (54% of 154). They have not been reported in negroid races; they tend to present at between 20 and 40 years of age, but have been diagnosed in utero.[8] Dieckman *et al* [6] found their relative incidence to be 2.1%, and Malek *et al* [7] 1%, in relation to testicular germ cell tumours.

Clinically they are impossible to differentiate from sinister intra-testicular lesions. This has prompted a radical approach in the past with inguinal orchiectomy. They have a characteristic if not pathognomonic appearance on ultrasonography: a circumscribed intra-testicular lesion with hypoechoic interior and hyperechoic margin, sometimes calcific, with a normal surrounding parenchyma. Tumour markers human chorionic gonadotrophin and alpha-fetoprotein must also be normal. On inguinal testicular exploration they should be found to be intratesticular but not invading tunica or surrounding parenchyma. They are typically in the region of 1-3 cm often with a calcific capsule containing keratinised debris. Price *et al*,[2] suggested pathological criteria for epidermoid cyst: (1) the lesion is a cyst located within the parenchyma of the testis; (2) the lumen is filled by keratinised debris; (3) the wall of the cyst is composed of fibrous tissue plus or minus lining squamous epithelium; (4) no teratomatous or dermal adenexal elements are present.

Treatment is invariably surgical both to confirm the diagnosis histologically and to remove the cyst. In the past radical inguinal orchiectomy was carried out due to poor knowledge or understanding of the benign nature of the condition, Price *et al* [2] reported 84% orchiectomy rate in their review. However, in the recent past more conservative enucleation and segmental resection have also been used, without associated recurrence or mortality. Despite clinical, ultrasonic, and serum marker evidence of benign disease diagnosis can only be confirmed histologically. Therefore an inguinal testicular exploration is advocated in keeping with indeterminate cancer risk. A frozen section examination can be carried out during the operation to support the diagnosis, but paraffin section is to be preferred for confirmation. With conservative surgery a rim of testicular parenchyma should be taken at wedge resection

to rule out TIN by immunological staining. In our own practice we changed from simple enucleation with the first patient to conservative segmental resection with intra-operative frozen section in the second.

With increased awareness, it is possible to carry out a safe testicle-conserving operation without disregarding the principles of cancer surgery, bearing in mind that, although less common, benign intra-testicular lesions do occur. The indolent clinical presentation, characteristic ultrasonography, and normal tumour markers suggest benign disease. The use of frozen section along with characteristic appearances of the cyst and contents will allow intra-operative reassurance. We would agree with Dieckman *et al* [6] that a rim of parenchyma should be sent to test for TIN. If there are any suspicious features, scars or coexisting lesions however, cancer principles and appropriate orchiectomy must be carried out.

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The Ulster Medical Journal, Volume 67, No. 2, pp. 145-146, November 1998.

Book Reviews

The Royal Belfast Hospital for Sick Children. A History 1948-98. Harold Love. The Blackstaff Press. 1998 IBSN 0 85640 621 X.

Dr Harold Love, his secretary Mrs Vicki Graham and the publishers Blackstaff Press have together produced a most elegant book. The attention to detail seen in the beautiful photographs and line drawings on its cover sets the tone for the painstakingly researched information it contains.

The history of the Belfast Hospital for Sick Children from its foundation in Queen Street in 1873 to its present site on the Falls Road in 1932 and its acquisition of the "Royal" title in 1948 has already been documented in detail by Dr H G Calwell in his book "The Life and Times of a Voluntary Hospital." A brief resume of this period by Dr Love introduces his history from 1948 to 1998. Against this backdrop of the previous one hundred and seventy five years and the introduction of the National Health Service in 1948 the author takes up his brief.

As you read through the book the enormous progress that has taken place in the treatment of ill children in RBHSC in the past fifty years becomes apparent. Intensive care units, techniques such as renal dialysis and transplants, surgical treatment of complicated congenital cardiac anomalies, the prevention of brain damage in children with inborn errors of metabolism by special diets, effective treatment for cystic fibrosis and many forms of malignant disease, and chromosomal analysis are only some of the advances undreamed of in 1948. At that time the only antibiotic available was penicillin G, and IV infusions were given by metal cannulae into exposed veins.

The author also draws attention to how childhood diseases have changed in the period under review. Many infectious diseases, once the cause of infant and child mortality, poliomyelitis, whooping cough, diphtheria and measles have been almost eradicated by immunisation. Tuberculosis in all its forms, rheumatic fever and its complications and severe fatal gastro-enteritis in infants have all disappeared. These changes have resulted in the closure of the large infectious diseases hospital at Belvoir Park and the provision of a new small unit at RBHSC. Rh incompatibility in the new-born, requiring exchange transfusion, a treatment pioneered in the UK by the late Dr Wilfrid Campbell, is also a thing of the past due to anti-D immunisation of the mother.

In all there are eighteen chapters, each introduced by a line drawing. As well as dealing with the birth and development of each specialty, Dr Love takes us through the convoluted bargaining between the medical staff and the NIHA, and later the EHSSB, with clear descriptions of the long gestational periods before necessary new developments were born, sometimes helped and sometimes hindered by the personalities involved. These protracted bargainings were mainly to acquire finance for the appointment of the increasing number of specialist paediatricians required to keep the hospital in the forefront of paediatric practice, and also for the extension of buildings and up-grading of departments. No doctors interested only in general paediatrics now survive at RBHSC.

The foundation of the department of child psychiatry and psychology is interesting. In 1942 Queen Elizabeth (now the Queen Mother) directed that the sum of two thousand pounds, donated by a group in Canada, be used for the children of Northern Ireland, and Dr Muriel Frazer suggested that the money be used to establish a Child Guidance Clinic in the Children's Hospital. In 1946 Dr Douglas Lothian was appointed clinical assistant to run the clinic on a sessional basis. It was not until 1967 that a full time consultant paediatric psychiatrist, Dr William Nelson, was appointed. In 1997 the department had three consultants and an associate specialist.

Dr Love has a very acute insight into the personalities he describes. Nowhere is this more clearly demonstrated than in the description of the characteristics of the three Professors of Child Health, who in turn held that post from 1948 till 1997.

As well as clinical departments the book also details the work of the "Toy Ladies", and school teachers in looking after the welfare of young in-patients.

The chapter on the history of Lissue Hospital ends on a very sad note. After forty years' useful service it was left empty and destroyed by fire in 1996. Many interesting photographs of excellent quality, clinical histories, radiographs, anecdotes and even poems leaven the detail. A paediatric surgeon like Stephen Potts, who is also a poet, must be a rarity!

The information in the appendices is extensive covering the years 1932 to 1997.

Notes record the origin of information referenced in the relevant chapters.

The index is comprehensive on a named basis.

The high quality and accuracy of the writing are reflected in the few errors or omissions recognised. Dr Christopher Green's book has the title "Toddler Taming", not "Toddler Training". (Either an impossible goal!) (Page 19).

Dr Dennis Carson's quote from his time at Johns Hopkins Hospital should read where he had "a little authority and minimal responsibility" (Page 20).

Dr Violet Breakey's resignation in 1958 was due not only to difficulties with her colleagues, but also on account of her imminent marriage to a doctor from the USA (Page 26).

The photograph of Dr Sid Dempsey is not Dr Dempsey (Page 143).

Dr Marie Kennedy's name has been omitted from the index (Page 238).

Dr Love comments on the problems caused by the civil unrest surrounding the hospital during the last thirty years. However it seems to me that even more credit could have been given to the entire staff, ancillary, nursing, and medical. Without their dedication in the face of much personal inconvenience, and at times danger, the hospital would not have been able to provide the uninterrupted service that was given to the sick children of the province.

I thoroughly enjoyed reading this well-written and informative volume. Each specialty is covered in one chapter, so that the book can be put down and taken up again, which makes for easy reading.

I would recommend it highly to all with an interest in the hospital, or indeed in the history of Belfast.

Women's Health and Menopause. Edited by R Paoletti *et al.* Kluwer Academic Publishers. pp. 340. £68. ISBN 0 7923 4697 1.

This multi-author volume consists of the proceedings of an International Symposium on Woman's Health and Menopause held in Florence, Italy, in December 1996. There are 47 short papers from a wide range of specialities providing a comprehensive review of many of the advances in our understanding of the short and long term effects of ovarian failure and their treatments.

The significance of the benefits of hormone replacement therapy in relation to cardiovascular disease are now widely recognised but controversy still surrounds the potential risk of breast cancer. Other topics discussed include osteoporosis prevention and the relation of the menopause to Alzheimer's disease.

The problems of compliance in relation to long term therapy is addressed and in particular the management of vaginal bleeding in older women.

The understanding that the role of the oestrogen receptor is not identical in all tissues has led to a search for new drugs to exploit specific targeting of bone and CVS. In this regard the contributions on dietary phytoestrogens and the new SERM, Raloxifene are of interest.

This book can be recommended as an excellent, well-referenced review of menopause research. However it is worth noting that our knowledge in this field has rapidly advanced since 1996 and hence some of the studies quoting epidemiological data are out-of-date.

W. THOMPSON

Procedures in Hepatogasterentology, 2nd Edition. Edited by Guido N J Tytgat and Chris J J Mulder. Kluwer Academic Publishers. ISBN 0 7923 4352 2. pp 494.

In this multi-author Dutch textbook, the editors have brought together a comprehensive and practical overview of diagnostic and therapeutic endoscopy of the entire gastrointestinal tract, combined with sections on nutrition and hepatology. There is a basic description of all commonly performed endoscopic procedures with text descriptions of pathological lesions. In these sections, one criticism is a lack of colour illustrations. However, very clear and simple line diagrams illustrate techniques, radiological features and equipment while treatment protocols are clearly set out in flow diagrams and algorithms elsewhere in the text.

Minimally invasive surgery is represented in sections on laparoscopic surgery and percutaneous cholangiography. Very recent advances in endoscopic ultrasound and interventional laser therapy with YAG and Argon plasma coagulation are clearly explained. In most sections, the authors set out indications, expected hazards and complications of all the procedures included.

Despite its lack of slide illustrations, this book represents a major European contribution to a rapidly expanding discipline and should be read, mainly as selective reference, by consultants and specialist registrars involved in endoscopic diagnosis. It would be a worthwhile addition to the reference library of all busy endoscopy units.

J S A COLLINS

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The problems of compliance in relation to long term therapy is addressed and in particular the management of vaginal bleeding in older women.

The understanding that the role of the oestrogen receptor is not identical in all tissues has led to a search for new drugs to exploit specific targeting of bone and CVS. In this regard the contributions on dietary phytoestrogens and the new SERM, Raloxifene are of interest.

This book can be recommended as an excellent, well-referenced review of menopause research. However it is worth noting that our knowledge in this field has rapidly advanced since 1996 and hence some of the studies quoting epidemiological data are out-of-date.

W. THOMPSON

Procedures in Hepatogasterentology, 2nd Edition. Edited by Guido N J Tytgat and Chris J J Mulder. Kluwer Academic Publishers. ISBN 0 7923 4352 2. pp 494.

In this multi-author Dutch textbook, the editors have brought together a comprehensive and practical overview of diagnostic and therapeutic endoscopy of the entire gastrointestinal tract, combined with sections on nutrition and hepatology. There is a basic description of all commonly performed endoscopic procedures with text descriptions of pathological lesions. In these sections, one criticism is a lack of colour illustrations. However, very clear and simple line diagrams illustrate techniques, radiological features and equipment while treatment protocols are clearly set out in flow diagrams and algorithms elsewhere in the text.

Minimally invasive surgery is represented in sections on laparoscopic surgery and percutaneous cholangiography. Very recent advances in endoscopic ultrasound and interventional laser therapy with YAG and Argon plasma coagulation are clearly explained. In most sections, the authors set out indications, expected hazards and complications of all the procedures included.

Despite its lack of slide illustrations, this book represents a major European contribution to a rapidly expanding discipline and should be read, mainly as selective reference, by consultants and specialist registrars involved in endoscopic diagnosis. It would be a worthwhile addition to the reference library of all busy endoscopy units.

J S A COLLINS

The Ulster Medical Journal, Volume 67, No. 2, pp. 147, November 1998.

Acknowledgements

We are grateful to the following for their continuing generous support:

Royal Victoria Hospital Medical Staff Committee – £750

Northern Ireland Council for Postgraduate Medical and Dental Education – £400

Mater Infirmorum Medical Staff Committee – £200

Erratum

UMJ 67 (S1) June 1998 p 85

Brian J Rowlands Introduction of the Purce Lecture

Surgeon Purce's Christian names were George Raphael Buick and not as they appeared.

The editor is grateful to Dr G B Purce for bringing this to his attention.