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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)
and the Belfast Clinical and Pathological Society (founded 1853)

THE ULSTER MEDICAL JOURNAL

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THE ULSTER MEDICAL SOCIETY

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

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The Ulster Medical Journal, Volume 72, No. 1, pp. 1-1, May 2003.

Editorial

http://www.ums.ac.uk

For the past few months the Ulster Medical Society has had a presence on the world-wide web. It was not launched with any ceremony and so far it is not listed by a Google search but it is there. The site has been kept simple to ease construction and the pages have been kept small to reduce loading times. Only 50% of web surfers will wait more than 8 seconds for a page to download and while we would hope and expect that the Fellows and Members of the Ulster Medical Society would be prepared to wait longer than that to access their society's website, we would not wish to put off non-members who might happen by.

So what will the members and the non-members find at ums.ac.uk? There are four main sections which deal respectively with the Ulster Medical Society, the Ulster Medical Journal, local medical history, and other local medical societies. The first section is more or less complete and contains a brief description of the Society along with more detailed information about the annual programme, membership, administration and contacts. This section and the others will be kept up to date as necessary. The second section is very similar but there is one major innovation – starting with that from the last issue (Vol 71 No. 2) the editorial content of the journal has been made freely available for download article by article. The downloads use the portable document format (PDF) which means they can be viewed and printed in a consistent manner on many different types of computer. The third section currently contains a few pages dealing with people, places and organisations but clearly this section could be expanded enormously. Some articles are complete but longer ones are offered as a précis on the website with the whole being available for download. Very long items such as the Transactions of the Belfast Clinical and Pathological Society are offered as a download only. Local medical historians are welcome to contact the site maintainer to coordinate the development of this section. The fourth section has not really got off the ground but a framework is in place and if local medical societies would like to submit some information about themselves it can be considered for publication. Details are on the website.

The Society's site should be useful and be used. You are invited to view it and offer your criticisms and comments as to how it could be improved. Unlike a book or journal, a website can be changed frequently both in terms of the design and content and if there is a demand for a particular feature the site maintainer will endeavour to provide it.

J. I. Logan, Honorary Archivist,
Ulster Medical Society.

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Editorial

The future of the Ulster Medical Society?

It is over 25 years since Professor D A D Montgomery gave his presidential address to the Society – "The Ulster Medical Society: Quo Vadis". I was then the Honorary Secretary, trying to record some minutes, and the platform party was all correctly attired in dinner jackets, so I do not now recall much of the lecture. But I was recently stimulated to go back to the published address in the Ulster Medical Journal, and much of what he said then is even more relevant today[1].

So where have we come from, and where are we going? It will soon be 200 years since 19 of "the most respectable physicians, surgeons and apothecaries, not merely of the town but of the vicinity like-wise" enrolled under the designation of the Belfast Medical Society.[2] That was in 1806, and in 1862 we amalgamated to become the Ulster Medical Society. "Those responsible were activated by a spirit for mutual improvement in their common profession . . .". Desmond Montgomery charted the historical developments in medicine and society which led to the incorporation of Colleges as professional guilds to safeguard the status as well as the practice of their Fellows: – Physicians in London in 1518, Barber-Surgeons in 1540, and their many successors in similar and evolving specialities. But a college was, and still is, different from a medical society where the desire for collective education and mutual self-help between *all* members of the profession is paramount. Such medical societies did arise, and still exist in various forms – the Manchester Medical Society, the Royal Liverpool Medical Institution, the Royal Academy of Medicine in Dublin, and smaller more local groups which have come and gone with the years. The Ulster Medical Society has survived for nearly two centuries with the unwritten mission statement of unity of purpose, friendship and the opportunity for professional education [3].

In London, similar things were happening, though on a somewhat larger scale. The Medical and Chirurgical Society of London was founded only one year earlier, in 1805, and after various vicissitudes eventually merged with 15 established specialized London societies to become the Royal Society of Medicine in 1907. These specialist sections remain active today, as sections for Pathological, Epidemiological, Odontological, Obstetrical, Clinical, Dermatological, Neurological, Laryngological, Otological, Electro-therapeutic and other interests. Thirty other more recent specialities such as Endocrinology, Anaesthetics, General Practice and Occupational Medicine have followed, and new sections are continuously in evolution [4].

But there are problems in even the best ordered societies. In London and elsewhere, some of the older sections and societies languished and many meetings were poorly attended, largely by retired members. Specialization under the National Health Service had encouraged the proliferation of postgraduate institutions, colleges and associations throughout the country whose activities tended to detract from the local medical societies and the London-based sections. Even colleges were not immune to "malignant infiltration by the cancer of complacency"[5]. We are aware of this problem in the Ulster Medical Society, even though we have a successful programme devised and supported by an enthusiastic President each year. Attendances are relatively poor, and thus the basic aims of mutual introduction and friendship between specialists, as much as between primary and secondary care practitioners, are frustrated.

Professor Montgomery – forward looking as usual – proposed an audit, a programme committee, reorganization of the annual dinner which had become fossilized, and moves to recruit membership from within the ranks of the specialist societies. He asked "who speaks for medicine in Northern Ireland today? Certainly not the BMA, with its increasing involvement with medical politics, nor the postgraduate centres, nor the specialties. Only we – the Ulster Medical Society – who hold all the strands together in the manner of the skilful coachman holding the reins, are

capable of giving the right lead. In recent years we have not been consulted on the big issues, as we were formerly. Have we lost our prophetic role and failed to recognise the authority that we possess? With our unique blend of family doctor, specialist, community physician, laboratory worker, academic and many others, we are better placed to give the opinion of all the forces that maintain and foster the best that is in the profession. We possess the real voice of medicine today. Let us hope that in the future it will be heard."

Stirring stuff. But is it relevant in 2002? If Sir William Whitla's dream had come true the Whitla Medical Institute in College Square North would have evolved into an Ulster Medical Institution which could now provide a medical spokesperson on all the issues of the day. Who is to advise our devolved Assembly on local opinion? In Scotland the proposed Quality and Standards Board for Health, in England, the Medical Education Standards Board, threaten some of the entrenched perogatives of the Colleges. In Stormont similar thoughts are awakening. But our little Society does not have the administrative and secretarial power to take on the might of the government. Even reading the multitudinous reports and consultation papers is too much, let alone developing a coherent professional response. In other places or at other times, large subventions of central funds have been made available under the umbrella of a College, (as the SIGN guidelines (Scottish Intercollegiate Guidelines Network) brought its own organization and finance to the Royal College of Physicians in Edinburgh), or the establishment of the Northern Ireland Council for Postgraduate Medical Education under Sir John Henry Biggart. Is it time for the Ulster Medical Society to shake itself from a comfortable and enjoyable slumber, to raise its membership subscription, to initiate a process so that all trainees in all medical disciplines are required to attend at least one meeting outside their specialty each year, and to involve a number of wise and articulate doctors with an enlarged secretariat to inform and instruct our President and Council on responses to important medical matters in the public arena? We do not run an examination to provide a financial base – nor do we want to. The Ulster Medical Journal continues to maintain its international standard for medical publishing, but has been bypassed by the local commercial world. We must seek other sources of funding.

There are three options if we want to go forward. To develop a Collegiate structure in association with all the various Royal Colleges – as the Northern Ireland Office of the Royal Colleges of Physicians of the UK has already initiated. Or to develop a larger all-inclusive society with specialist sections with Ulster and Irish roots, perhaps linked to the Royal Society of Medicine in London, or to the Royal Academy of Medicine in Dublin, or both. Or to merge with the Postgraduate Council and Postgraduate Centres in a larger, more disparate, educational forum. It is time to discuss this. Professor Montgomery remarked at the close of his address in 1975, "Some of you who are here tonight will be able to greet the year two thousand with most of your facilities intact... if we are truly men and women of vision and integrity and dedication we shall not fail to hand on a Society worthy of those who follow us".

Dr Henrietta Campbell has inspired us again with her address on "Public Health – a bond between government and its people"[6]. If "health is a bridge to peace, an antidote to intolerance and an assurance of shared security", the Ulster Medical Society must rise to the challenge as we approach our bicentenary.

David R Hadden
Honorary Secretary, Ulster Medical Society 1973-77
President 1995-96
Council Member, Royal College of Physicians of Edinburgh
Regional Sub-Dean for Ireland, Royal Society of Medicine.

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Public health – a bond between a government and its people

(The health of the people – a responsibility governments cannot choose to ignore)

Presidential Address to the Ulster Medical Society 10th October 2002

Henrietta Campbell, Chief Medical Officer

Public health is the concerted action taken to promote health and prevent disease, with a focus on society rather than individuals. There is much that we as individuals can do to protect and promote our own health. However, as a society, we recognise that actions taken by Government may affect our health. We expect Government to take responsibility for ensuring better health and well-being for its people, and we are often suspicious that poor or short-sighted decision-making by politicians may harm health.

A society which has poor health is not a sustainable society and poor health is linked in a vicious circle with poor economy. On the other hand, a wealthy society tends to be a healthy society. Public health, or the promotion of health and the prevention of disease, is therefore a bond between a people and its Government. The concept of public health and its relationship with politics and governance has been a recurring theme throughout modem history. The study of the successes and failures of governments in tackling public health issues provides valuable lessons as to how today's modern diseases may be confronted.

The history of infectious diseases, and particularly of the great epidemics, has been well documented.[1] The earliest records show leprosy being introduced into Europe and subsequently being spread by the Roman Army wherever it went. Throughout history it has been a recurring theme that the movement of troops across continents caused many of the great pandemics. Most historians however credit Christopher Columbus's arrival in America in 1492 as a critical catalyst of infectious disease, with the subsequent death of many thousands of people on both sides of the Atlantic. It has been dubbed as the "Columbian exchange", the intercontinental flow of microbes and the first global pandemics. Measles, typhoid and smallpox were imported to the Americas, with profound consequences for the indigenous people who had no immunity at all. Later years saw huge recurring epidemics of influenza, the spread of smallpox, tuberculosis and bubonic plague, all with such devastating impact that for centuries the population of Britain and Ireland increased only slightly.[2]

In 1842 Edwin Chadwick reported on the "Sanitary Conditions of the labouring population of Great Britain".[3] He concluded that insanitary conditions caused social as well as biological disease – a psychological degradation that led desperate people to invest their hope in alcohol, or worse in revolution. Chadwick's report was so compelling that six years later the 1848 Public Health Act was passed. The delay of 6 years between the report and subsequent legislation was due apparently to the controversy over the Corn Law of 1846 and a preoccupation with the Irish Famine [1845-48]. Central to the Public Health Act was a clean and secure water supply, together with the separate disposal of sewage and waste. It also began to address all the other major issues of the time – poverty, housing, the environment, safety and food.

The vision and energy of Edwin Chadwick ushered in a new era of social reform throughout England and Wales.[4] The Public Health Act in 1848 was the first major piece of legislation in which

Department of Health, Social Services & Public Safety, Castle Buildings, Upper Newtownards Road, Belfast BT4 3SJ.

H Campbell, Chief Medical Officer

Government positively intervened to prevent disease and promote health.

Belfast was not without its great visionaries at that time. In 1852 evidence was presented to a meeting of the Statistical Section of the British Association by Henry McCormac and A G Malcolm which was to begin a process of great change in Belfast.[5,6]

The evidence given detailed the sanitary characteristics of Belfast and showed the link between successive epidemics in Belfast and poor sanitation. Malcolm calculated that due to the extremely high infant mortality the average life expectancy in Belfast at that time was nine years. He set out clearly the remedial measures which needed to be taken, along the lines of the Chadwick reforms and also called for the establishment of a permanent Board to superintend and regulate all sanitary matters for the Borough.

The scientific papers presented by Cormac and Malcolm however were not enough. In order to bring about change another great force was needed, and it came in the unlikely form of a Congregationalist Minister, the Rev W M O'Hanlon, who received a call to Upper Donegal Street Church in 1849. He very soon made his name through writing a regular column for the Northern Whig on all the burning social issues of the day.[7] The nature of his writing however made him very unpopular with the Evangelical Society who happened to be his employer.

In one essay O'Hanlon wrote:

> *"Permit me to call the earnest attention of the more affluent, respectable and especially the Christian public of Belfast, to the deplorable condition of the poor who inhabit the back streets, courts, and alleys of our rapidly expanding and populous town. This is a subject which may yet be pursued apart altogether from sectarian principles, either in religion or politics."*

In letter after letter to the Northern Whig O'Hanlon spelt out in emotive language the misery, squalor and poverty which existed for a large part of the population in Belfast. In doing so he presented a qualitative study of life for the poor in Belfast. Whilst Cormac and Malcolm might have been ignored, the need for action was brought clearly into public view by O'Hanlon's writings in the Northern Whig. He spoke of the contrast between the poor and the salubrious spirit stores, one of which boasted that it had sold 9,380 gallons of whiskey over a four month period. O'Hanlon called whiskey *"liquid fire and damnation"*. Whilst some of this language might have resonated with the Evangelical Society he was informed that he was not *"adapted to the work"* and his salary was promptly withdrawn. O'Hanlon however stayed on in post for four years and continued to harangue the ratepayers and politicians to take positive action, and the wealthy to become benefactors.

Thus was born Belfast's first Public Health reformer. The Public Health Act was duly applied to Belfast and in 1852 Samuel Browne was appointed as medical officer for health. Samuel Browne and A G Malcolm are credited with driving through the first reforms. Implementation however, was slower in Belfast than in some of the other great industrial cities throughout England. But throughout the latter part of the 19th century and in the early decades of the 20th vast amounts of public money and benevolent funds were spent in building a huge infrastructure for clean water and sewage disposal in Belfast – much of it still in existence today.[8]

The Government of Ireland Act 1920 paved the way for the establishment of Northern Ireland but there was much still to be done to improve health. It is difficult for us today to comprehend how tenuous life must have seemed in those days. Expectation of life was only 52 years of age, the pandemic of influenza in 1918/1919 had claimed almost 6,000 lives. In 1916 more than 2,000 men of the 36th Ulster Division were killed in one day alone at the Somme. All the indicators showed that the health of the people was still much worse than elsewhere in these islands. Death rates were higher and in particular deaths from tuberculosis were 50% higher than in England and Wales.[9] Looking at the legislative programme in the early years of Stormont there is little evidence however that health was high on the agenda.

By 1941 the death rates from tuberculosis in Northern Ireland were still far higher than elsewhere and, much later than would have been wished, the Tuberculosis Authority was established. As a public health measure it proved to be such a success that within a few years its work was almost complete. But as always seems to be the case with our health establishments, the Authority proved extremely difficult to dismantle and remained in existence for many years.

In 1942 the Beveridge Report was published. It proved to be a far-reaching report which set out the vision of the welfare state, tackling the 5 giants: Want, Disease, Ignorance, Squalor and Idleness. The public reception of the Beveridge Report was ecstatic. One journalist is reported as saying *"Beveridge has put the ball in the scrum all right. I wonder what shape it will be when it comes out"*. The shape is still there to be seen to this day. The welfare reforms which took place during that period still form the central core around which all our welfare structures are built.

The consolidation of those reforms led to an era of optimism and a sustained period of economic growth – prompting the statement by Harold MacMillan in 1957 *"most of our people have never had it so good"*. But it was to become evident that not everyone was having it so good, and the safety net was not catching everyone.

In 1980, the Black Report was published, the author being Sir Douglas Black, at that time President of the Royal College of Physician[10]. The Black Report showed clearly that major inequalities in health existed in our society, inequalities between social classes, across ethnic divides, and between the North and the South. The Black Report was published in 1980 during a bank holiday weekend, with a brief introduction by the Secretary of State saying it was unrealistic. Only a very few copies were printed but it attracted a great deal of interest both in the UK and abroad. After the publication of the Report pressure was brought to bear constantly upon Government to recognise the issues which it had raised. In Whitehall the phrase "inequalities in health" was deemed unacceptable and in its place the phrase used was "variations in health". A change of Government finally allowed "inequalities in health" and "poverty" to enter into the vocabulary of the policy-makers.

The public health agenda in most developed countries is now one which focuses on the determinants of health. In Northern Ireland there is a recognition that Government action is needed to tackle inequalities in health and that it must do so by focusing on the determinants of health.

Last year in Northern Ireland there were 3,000 deaths in people under the age of 65, two thousand men and one thousand women. Two thirds of these deaths due to entirely preventable causes. The greatest burden of preventable deaths are carried by the lower social classes who have twice the risk of dying before the age of 65.

Heart disease remains the major cause of death. Barker and his colleagues showed that the variables associated with heart disease were: low birthweight, low weight at one year, low social class of father, low level of education, low adult social class and low income in adult life.[11] In Northern Ireland last year almost 5,000 children were born to parents of social classes 4 and 5. According to Barker they may be doomed already. If we are to tackle these inequalities in health there needs to be concerted action across all Government departments.

Inequalities in health are likely to be with us for some time. There is every prospect that the near future will be even more challenging than the past 100 years. It may be that we will require to be as energetic and forceful as Edwin Chadwick if we are to secure the health of future generations.

Smoking will remain a major threat to health. If everyone stopped smoking today we would still see the impact of tobacco on health for the next 30 years. In Australia and in some states in the US tough action by Government has reduced the levels of smoking to well below 20%. In the UK, belatedly, action is being taken on tobacco advertising. It may be of some significance that the UK is the fourth leading importer of raw tobacco and the third largest exporter of cigarettes. On the other hand it is estimated that up to one third of cigarettes smoked in UK is illegally imported.

If poverty and smoking are currently the two main causes of poor health then they are closely followed by the modem epidemic of obesity. In the US the Centre for Disease Control and Prevention estimate that obesity causes 300,000 deaths in the US each year and Type 2 diabetes in children is now an emerging epidemic. The American Health Association this year stated that from four years of age every child should have its blood pressures, blood cholesterol and anti-insulin factor checked.[12] Recent studies have shown that over 20% of young people are overweight and almost 8% are obese.[13] A newspaper headline a few months ago put the message over very clearly – "our children are eating themselves sick". As for our adult population, instead of five portions of fruit and vegetables every day the average diet in NI consists of 800gms of fresh fruit and vegetables

each week – the equivalent of a large apple.

It has been predicted that based on these trends the prevalence of diabetes will double by 2020. In addition obesity and lack of exercise is a major factor in cancers of colon, breast, kidney and digestive tract. So it is likely that the incidence of cancer is set to rise significantly. Today more than ever before concerted Government action is needed to tackle the risk factors of smoking, diet and exercise. The traditional health education campaigns have had limited success and are no longer valued by an increasingly sceptical public.

Multi-national enterprises now determine diet and lifestyle and the WHO warns that Governments have lost their sovereignty or control over the determinants of health. In America it has been calculated that 10 billion dollars are spent each year by the food industry on targeting the advertising of their products at schoolchildren. The number of hours spent by children watching television is directly related to their risk of becoming overweight. This is due not only to the inactivity but also to constant bombardment with junk food commercials.

These matters have been hotly debated in the newspapers and journals recently. On the one hand there are those who argue for regulation of the food industry with, for example:

a tax on fast food and soft drinks;

a subsidy on nutritious food;

a ban on vending machines in schools; and

a ban on "junk" food advertising aimed at children.

On the other hand there are those who say that people should simply be given the information and then allowed to choose for themselves.

In summary therefore poverty, smoking and obesity can be seen as the three major plagues of our modem age. But there may be a fourth. It may well be that the greatest threat facing us in the next few decades is one which will take us back to the times of Edwin Chadwick, the re-emergence of infectious diseases.

Over the centuries as we look at the history of infectious diseases we have seen that, with epidemics, timing is everything. The Black Death in 1346, the Spanish Lady in 1920 and HIV, now infecting more than 36 million people worldwide. All these occurred because the time and the conditions were right.

Today we have all the ingredients for the next great pandemic. The world's population is now 6 billion with the majority living cheek by jowl in large cities. Every day there are millions on the move. Every day there are vast quantities of crops, animals and processed food being shipped from place to place. Think of the mayhem which would have been caused last year if foot and mouth had been pathogenic to man.

In the 19th century the ascendance of the British Empire placed Britain at the epicentre of the movement of people and goods. Now – at the beginning of the 21st century the expansion of Heathrow puts the British Isles again at the epicentre.

In her book "Betrayal of Trust, the Collapse of Global Public Health", Laurle Garret illustrates how our global public health system has been systematically eroded and that no person is safe from infectious disease.[14] The threats arise from antibiotic resistant bacteria, epidemics from new and re-emerging organisms and the very real threat of bio-terrorism.

Wealthy countries such as ours fight vigorously against their own infectious diseases but at the same time we allow them to devastate poor countries. But infectious agents do not recognise borders and we are now beginning to see for example that AIDS and tuberculosis can have a direct effect on us because of the movement of populations. Perhaps we should regard the world not just as a global village but also as a global culture medium.

For all of us perhaps the most frightening scenario is that of bio-terrorism. The roots and causes of war, including bio-terrorism, lie in poverty and in political, economic and social inequalities. The priority for peace-makers and politicians will be to redress these issues rather than, by their actions, make them worse. But, whilst we wait for our politicians to deliver world peace, public health has to be the first line of defence. This will mean increasing disease surveillance, professional and public education, stockpiling vaccines and antibiotics and continued research.

The challenges facing the health of our society today are as significant and challenging as in the time of Edwin Chadwick. Inequalities in health still persist and are associated with unacceptable levels of avoidable death. Infectious diseases have not disappeared, instead they have outwitted

modern medicine. In addition the modern lifestyles which we have adopted have brought a huge burden of chronic disease.

And perhaps the greatest threat to health is man himself. There is always the threat of war – and the emerging evidence of a readiness to use biological warfare. As for science and technology we are in a society which is pushing at the boundaries of high technology – some of which is barely understood. We need to be very wary that we do not unleash a monster.

John Wynn Owen of the Nuffield Trust has argued with others that, as in Chadwick's time, there is an urgent need for a new Public Health Act which would provide a legislative framework for the establishment of a strong and accountable public health function.[15] Discussions around our preparedness for bio-terrorism will no doubt strengthen the case for Public Health Legislation.

As a society we are still undecided about the role of the State. Should the State intervene on matters of health with legislation and regulation, or should information be provided and individuals be allowed to make up their own minds. Many would argue that the insidious power and influence of the multi-nationals is so pervasive that regulation is needed.

There are of course other actions which Government could take to protect health. Take for instance very simple measures such as water fluoridation, banning of smoking in public places, folic acid in flour, the reduction of salt in food-proces sing, more time for physical activity in the school curriculum. We could all add to that list.

Now, in an age of devolution and of public participation it is more difficult to envisage decisive Government action being taken on these public health issues. No matter how vigorous the debate may be in medical and public health circles there can be no guarantee of a successful outcome on the floor of the Assembly. It would sometimes appear that we are in a post-professional era and the voice of the popular lobbyist is given the greatest ear.

Political decision-making is not an easy task. It involves a complex assessment of moral, legal, ethical, technical, financial and political issues and inevitably requires compromise. Devolution of power and public participation brings new opportunity in public health. Engaging local communities in the debate about their health encourages local action on health. It might also bring a much-needed diversion from local sectarian issues. In terms of health each community in North or East Belfast has more that binds them to their neighbour than divides them.

Gro Harlem Bruntland, Director General of WHO put it very succinctly when she was recently speaking about the global threat of war – *"Health is a bridge to peace and an antidote to intolerance and a source of shared security."*

The medical profession even in Northern Ireland still enjoys great privilege. But we also need to accept that with privilege comes responsibility and that our corporate responsibility must be advocacy for the health of our people.

Perhaps one way forward is to bring our people to a sense of singular community in which the health of each member rises or falls with the health of all the others. It would be within our power as a profession to bring that about.

Back in the 1840s Edwin Chadwick was spear heading what was to become a public health revolution across England and Wales. At that time our medical fore fathers here in Northern Ireland were busy calling for more and bigger hospitals to be built – apparently incapable of recognising that the root causes of disease urgently needed to be tackled. We need to be sure that we are not guilty of the same omission today.

In the past year two documents have been circulated for consultation. "Investing for Health" set out a cross-departmental strategy to improve health. "Developing Better Services" proposed a rationalisation and modernisation of acute hospitals. There are no prizes for guessing which has excited the most interest within the medical profession.

The Constitution of the Ulster Medical Society states that the object of the Society shall be to improve the care of the sick by widening, improving and developing the education and knowledge of all concerned in the pursuit of medical matters.

This is a very laudable objective and we have all been greatly enriched in our professional lives because of the work of this honourable society. But perhaps it is time to revisit our objectives as a society so that we might also strive to ensure better health for our society. In these days of devolution of political power and public consultation this society might become a powerful

advocate for the health of our people – united, honourable, credible, reclaiming again the higher ground, and not to be silenced. If this were to happen I believe that our fledgling government would be better informed and all the stronger, but also called to account by the people for delivering on their better health.

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Efficacy of cervical intrarepithelial neoplasia (CIN) treatment by cold coagulation

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SUMMARY

Our objective was to evaluate the efficacy of cold coagulation in the treatment of cervical intraepithelial neoplasia. The study design consisted of a retrospective review of case records of all women treated with cold coagulation from the colposcopy clinics inception in 1980 to 1994. A total of 725 women received treatment with cold coagulation. All grades of CIN were treated. 632 (87.1%) had long term negative follow up. 93(12.6%) of patients had abnormal cytological follow up, but only 45(6.2%) required re-treatment. Within the first year after treatment 52(7.1%) patients presented with persistent cytological abnormalities, 32(4.4%) required repeated treatment for persistent dyskaryosis. 41(5.6%) of patients had recurrent cytological abnormalities, 13(1.8%) required repeated treatment. Recurrence developed between two and 12 years from initial treatment. One case of cervical carcinoma following treatment with cold coagulation was recorded. Our data suggest that cold coagulation appears to be safe, efficient treatment for cervical intraepithelial neoplasia.

INTRODUCTION

Cold coagulation is one of many ablative methods designed to destroy an abnormal transformation zone. It has been successfully used to treat non-invasive cervical conditions since 1966. This treatment method was introduced to clinical practice for the first time by Kurt Semm;[1] it became a popular method for the treatment of CIN. In the1980s it was the second most popular treatment modality, for CIN in the UK. It has, however, lost some of its popularity due to the introduction of the Large Loop Excision of the Transformation Zone (LLETZ) performed under local anaesthesia. The latter, being an excisional rnethod, secured the whole transformation zone for histopathological examination.

Cold coagulation is a suitable therapy for the out-patient clinic. It is a relatively painless procedure requiring minimal or no analgesia. It is also user and patient friendly having a short treatment time, and virtually no immediate complications. All grades of CIN may be treated with cold coagulation.

The purpose of this study is to evaluate the efficacy of cold coagulation in the relatively static population of women treated in Belfast City Hospital colposcopy clinic.

PATIENTS AND METHODS

We reviewed the notes of patients who had attended the BCH colposcopy clinic between its establishment in 1980 and 1994. Patients treated with cold coagulation were identified and their medical records and cytology results were analysed.

The cytological results were obtained from the BCH Cytology Laboratory computer and the Northern Ireland Cervical Screening Programme database. Information regarding women attending other hospitals after initial treatment with cold

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coagulation at BCH was traced. Microsoft Excel was used for data analysis.

Standard management at the clinic consisted of colposcopic examination with confirmatory biopsy. Visualisation of the complete squamo-columnar junction and exclusion of any suspicions of invasion were the criteria required for cold coagulation treatment. Verbal consent was routinely obtained prior to treatment.

When suitable, patients were offered treatment with cold coagulation under local anaesthesia. Treatment was preceded by punch biopsy. All grades of CIN were treated in the same way by application of the Semm coagulator (WISAP, Germany) to the cervix. The probe heated to 120°C was applied to each part of the cervix for 30-40 sec. ensuring that the whole transformation zone was destroyed beyond the limit of aceto-white epithelium. All patients were advised to apply Sultrin cream (Janssen-Cilag) vaginally, nightly for one week and to avoid intercourse and use of tampons for three weeks.

Initially treatment was performed during the second visit, but as experience developed a "see, biopsy and treat" policy was employed, with only less experienced or trainee colposcopists awaiting biopsy results before treatment.

The pattern of follow up changed over the years of study, but all patients were followed up by at least cytological assessment. This was initially performed at the 3-4 months follow-up visit. Since 1990 follow-up has been by a standard pattern of review and smear by the hospital at six months post treatment. If this smear is normal, the patient attends her GP for a further smear at six months post treatment. Thereafter yearly smears are advised.

Patients with positive cytological results were reviewed colposcopically and various regimens of management were instituted depending on colposcopy findings and individual practice.

Failure of treatment was classified into two groups for the purpose of this study; persistent disease was recognised when abnormalities were identified between 6-12 months following initial treatment, recurrent disease if abnormalities appeared after 12 months.

Further management of patients with abnormal follow up cytology included repeat cold coagulation, Large Loop Excision of the Transformation Zone, cold knife biopsy and hysterectomy.

RESULTS

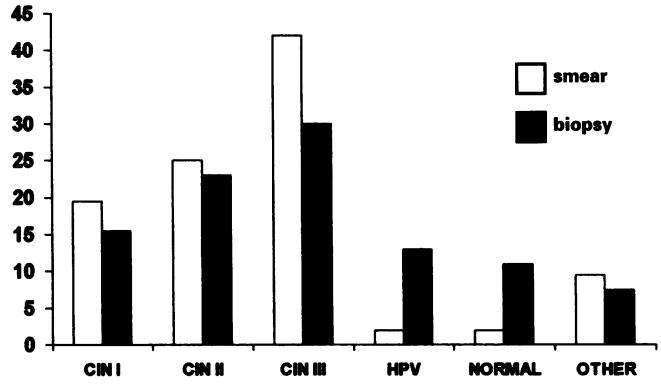
Out of 1329 patients attending the colposcopy clinic 725 (54.5%) patients received treatment with cold coagulation.

The mean age of patients at presentation was 28 years and ranged from 17 to 52 years. 35% of patients were nulliparous, 18% had one child, 19% had two children, and 12% had three or more children.

Distribution of referral smear findings and initial biopsy results are shown in Figure. 632(87.2%) patients had dyskaryotic abnormalities eradicated by initial cold coagulation treatment and their long term cytological follow up was negative. 93(12.8%) patients developed abnormal smear at some stage after treatment. 52 patients(7.1%) presented with persistent cytological abnormalities within the first year of treatment and 41(5.6%) with recurrent abnormal smears.

FIGURE

Distribution of referral smears and biopsies results, 95% of treated patients had biopsy taken prior to treatment.



Of the 52 patients with persistent abnormal cytological results 27(52%) presented with CIN III on referral smear, 12(23%) with CIN II and 6(12%) with CIN I, 3(6%) patients had unclassified CIN.

Of these 52 patients showing persistent cytological abnormalities 31(4.3% of all treated with cold coagulation) had further treatment, 20 on the basis of positive biopsy and 10 on colposcopic appearance (Table I).

21 patients were given no further treatment and were considered to have transient cytological

TABLE I

Management of patients with persistent cytological abnormalities

Smear results	*No*	*Biopsy results*	*No*	*Treatment*	*Recent smear No*		*No*
HPV	13	No biopsy	8	No treatment	8	N/a-TAH (hist.neg)	1
						Negative	7
		HPV	5	Cold coagulation	5	Negative	5
CIN	39	Dysplasia	16	Various treatment **(table 3)**			
		No biopsy	4	Cold coagulation	4	Negative	3
						BNA	1
		No biopsy	6	LLETZ (hist.neg)	6	Negative	5
						N/a-TAH (hist.neg)	1
		Biopsy negative	2	No treatment	2	Negative	2
		Biopsy positive	1	No treatment	1	Negative	1
		No biopsy	10	No treatment	10	Negative	5
						N/a-TAH (hist.neg)	1
						Defaulted	3
						Recurrence	1

HPV-human papillomavirus infection, CIN-cervical intraepithelial neoplasia, n/a-not applicable, TAH-total abdominal hysterectomy, hist.neg – histopathology results negative, LLETZ – large loop excision of the transformation zone.

abnormalities. 17 patients of this untreated group had negative follow up. Three of these patients have been lost to long term follow up, one patient had negative screening for five years and presented at sixth year with recurrent low grade disease. The treatment modalities of those who received subsequent treatment are summarised in Table II.

Hysterectomy was usually offered as a treatment option when other gynaecological problems were present. Of 9 hysterectomies performed seven uterine specimens showed no evidence of residual CIN.

Overall, 40% of patients with persistent cytological abnormalities at 4-6 months following treatment required no further treatment as abnormalities reverted to normal, suggesting that the rate of residual disease was less that 7, 1% already stated.

Recurrent disease was defined as abnormalities developing more than a year after treatment. 41(5.6%) patients treated with cold coagulation developed recurrent abnormal smears. These patients presented between two and 13 years from initial treatment.

26(3.5%) of them developed abnormal smears within first 5 years from treatment, a further 12 patients(1.6%) between year 6 and 10, three patients(0.4%) had recurrence more then 10 years following treatment (Table III).

Of those with recurrent abnormalities 18(44%) presented with CIN III on referral smear, 8 patients (19%) with CIN II, 6(15%) with CIN I, 5(12%) with unclassified CIN, 3 (7%) borderlines and 1 (2.4%) with normal cytology.

Out of 41 recurrent cytological abnormalities the majority (26 cases) were low grade abnormalities: 8 borderline nuclear abnormalities, 8 viral infections and 10 CIN I. Overall, recurrent abnormalities included 25 patients with dyskaryotic smears, 8 with recent borderline smears and 8 with transient viral changes.

TABLE II

Management of 16 patients with persistent cytological abnormalities confirmed by biopsy.

Referral smear	*No*	*Second treatment*	*No*	*Recent smear*	*No*
CIN 1	1	TAH	1	N/a	1
CIN 11	2	TAH	1	N/a	
		Cone biopsy	1	Lost from follow up	1
CIN Ill	12	Cone biopsy	12	Negative	5
				N/a-TAH	4
				-rad.hyst	1
				-died	1
				Lost from follow up	1
Not recorded	1	Cone biopsy	1	negative	1

N/a- not applicable, TAH-total abdominal hysterectomy, cone biopsy-any excisional surgery, rad.hyst.-radical hysterectomy

TABLE III

Management of patients with recurrent cytological abnormalities

Recurrent smear	*No*	*Management*	*No*	*Recent smear*	*No*
HPV	8	No treatment	8	negative	8
BNA	8	Awaiting further assessment	8		
CIN I	10	Cone biopsy	3	Negative	3
		Cold coagulation	1	Negative	1
		No treatment	3	Negative	2
				Lost	1
		Awaiting assessment	3		
CIN II	6	Cone biopsy	2	Negative	2
		Cold coagulation	1	Lost	1
		Cautery	1	Negative	1
		No treatment	2	Negative	2
CIN Ill	6	Cone biopsy	4	N/a-TAH	3
				Lost	1
No treatment	2	Negative	2		
CIN unclassified	3	Cone biopsy	1	Negative	1
		No treatment	2	Negative	2

N/a -not applicable, TAH – total abdominal hysterectomy, cone biopsy – any excisional surgery

6 patients had recurrent severe dyskaryotic smears. All of them presented with initial, referral CIN III and recurred within 5 years of initial treatment. 13(1.8%) patients received treatment for recurrent dyskaryosis, 10 of them were treated with excisional surgery, 3 with ablative methods. 28 patients did not receive treatment, 11 of them had low grade, transient abnormalities, 11 had recent positive cytology (8 borderline and 3 CIN I) and have been awaiting further assessment, and 6 had transient dyskaryotic smears which reverted to normal and remain so.

8 patients (1.1%) had complications recorded in their notes: 2 vaso-vagal faints, 5 cervical bleeding related to the biopsy site, and 1 secondary haemorrhage due to infection.

The only case of invasive disease following treatment with cold coagulation occurred in 1987. This patient was referred to the clinic in 1984, at the age of 23 following conisation of cervix for CIN III in another hospital. Colposcopy showed widespread dysplastic changes; smear CIN II and biopsy CIN II. She was treated with cold coagulation under general anaesthesia. Follow up smears were persistently abnormal. This patient underwent five further treatments to the cervix with different modalities for persistent dyskaryotic abnormalities. The last excision revealed invasive squamous carcinoma of cervix. She was treated successfully with radical hysterectomy and has been in regular follow up.

Out of 725 patients treated with cold coagulation 699(96, 4%) had at least a first follow-up smear and 587 (80.9%) have up to date negative follow-up smear. 106(14.6%) are lost from follow up: 42 emigrated, 64 can't be traced or refuse to have a smear, 2 died of other causes, 19(2.6%) patients had hysterectomy performed. 11(1.5%) patients have recent positive smears: 8 borderline and 3 mild dyskaryosis. Default rate at first follow up was 12%(87 patients). These patients failed to have first follow-up smear after treatment. However, 56 of them have an up to date smear, 19 emigrated, 2 had TAH and only 7(0.9%) of all treated patients) of them are truly lost to follow up.

Overall of 725 patients treated with cold coagulation 44 patients (6%) received repeated treatment for persistent or recurrent disease. 10 (1.3%) patients with recent abnormal smear have been awaiting further assessment. The success rate of treatment with cold coagulation in long term follow up at our colposcopy clinic was 92.7%.

DISCUSSION

A computerised call/re-call system for cervical screening was established in Northern Ireland in 1989. The results of all smears are held on a single data bank. There are 460,000 women aged 20 to 65 eligible for cervical screening in Northern Ireland. The recommended normal recall interval is 5 years and women are called to attend for cervical smear from the age 20. The response rate is still low at 67%.[2]

Every year 80 new cases of cervical carcinoma (including microinvasion) are detected in Northern Ireland, giving the prevalence of 9.6 per 100,000 women.[2] Of these cases 50% of women were unscreened, 7% screened more than 5 years before the occurrence, 26% had negative smear 5 years before and 16% had previous abnormal smear. The latter group consists of patients treated, who defaulted or who refused treatment. There was no incidence of invasive cervical carcinoma among teenagers in Northern Ireland.

In our setting, cold coagulation has been shown to be a safe and efficient treatment with a very low morbidity rate. This is in keeping with earlier work by Duncan[3, 4, 5] Cold coagulation was shown to be well accepted by both patients and colposcopists. However, it requires a competent colposcopist and compliance with strict selection of patients suitable for treatment with cold coagulation as established by Gordon and Duncan. Obviously a suspicion of invasion or unsatisfactory colposcopic assessment excludes any ablative method of treatment. Gordon and Duncan[3] claimed 95% primary success rate for CIN III and success rate of 96.5% with single treatment and 99% following one or more treatments with cold coagulation for patients with CIN I and CIN.[4] Our results are comparable with these studies. Despite these satisfactory results it has still been questioned whether or not cold coagulation can efficiently treat CIN lesions. The long term follow-up with persistent negative cytology illustrated by this study and those of Duncan and co-workers confirm the effectiveness of this treatment. Results of our study indicated a very low rate(7.1%) of persistent disease, much lower than reported by Semple.[6] He reported 14.8% rate of persistent abnormalities following CIN treatment with all modalities used by 19

colposcopy clinics in North West. The recurrence rate following treatment with cold coagulation is very low, 5.6% in our study, with mainly low grade abnormalities being found at follow-up. Not surprisingly we found the highest level of treatment failure among CIN III lesions which accounted for 42% of referred cases. It is our opinion that previous treatment to the cervix, as a factor changing its anatomy is a contraindication for cold coagulation treatment. The only case of invasive cancer of cervix following treatment with cold coagulation occurred in a woman who had previously had treatment to her cervix, which distorted the anatomy preventing the full lesion from being amenable to cold coagulation, although it should be noted that several attempts had been made to excise persistent abnormalities before she developed invasive disease. During the study period there were 10 cases of carcinoma of cervix diagnosed on histopathology as a result of excisional biopsies, which had not been colposcopically detected. All of these patients had unsatisfactory colposcopy, therefore had been considered unsuitable for treatment with cold coagulation and were treated by excislonal techniques.

We have not encountered unexpected histopathology results of microinvasive or invasive carcinoma from biopsies taken prior to the cold coagulation treatment.

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The prognostic value of FISH as an adjunct to conventional cytogenetics for the detection of cryptic gene rearrangements on chromosome 16. A retrospective investigation of 13 patients from Northern Ireland diagnosed with M4Eo acute myeloid leukaemia

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SUMMARY

M4Eo acute myeloid leukaemia (AML) patients with the typical chromosome 16 abnormalities have a favourable prognosis. These subtle 16q22 gene rearrangements can be difficult to detect by conventional cytogenetic methods and if missed could lead to the incorrect assignment of prognostic group and hence subsequent treatment strategies. We retrospectively studied 13 patients diagnosed with M4Eo AML for such chromosome 16 abnormalities comparing conventional cytogenetic (G-banding) and molecular (FISH) methods. G-banded analysis detected only 2 patients with definite chromosome 16 abnormalities whereas FISH detected 4 patients, one with the typical inversion and three with the typical chromosome 16 translocation. FISH analysis also confirmed a false +ve G-banded result in one patient and a false -ve G-banded result in another patient. Finally, FISH confirmed a deletion of one chromosome 16 homologue in another patient indicating a poor prognosis. The overall survival of patients with the typical 16q22 rearrangements (n=4) was also significantly better (P=0.007) than patients with normal chromosome 16 homologues or having other numerical and/or structural abnormalities (n=9). This set of data shows that FISH is a more accurate method for the detection of cryptic 16q22 gene rearrangements and because of the prognostic implications has become a mandatory test along with conventional cytogenetics for all newly diagnosed M4Eo AML patients in Northern Ireland.

INTRODUCTION

Reports have shown that karyotyping a leukaemic cell population using conventional cytogenetic methods is one of the most important prognostic determinants in acute myeloid leukaemia (AML).[1,2,3] Both conventional cytogenetic and molecular methods have led to the definition of three prognostic groups *(poor, intermediate & favourable)* in AML. Results from the Medical Research Council (MRC) AML 10 trial and other international groups have clearly demonstrated that AML patients with chromosome abnormalities such as inv(16)/t(16;16), t(15;17) and t(8;21) have a favourable prognosis.[4] Patients with an *intermediate* prognosis are those who have a cytogenetically normal karyotype or other chromosome abnormalities not associated with a good or poor prognosis. Patients with a *poor* prognosis are those with complex chromosome abnormalities (i.e. numerical and structural) or abnormalities such as abnormalities of chromosomes 5 or 7.

The typical chromosome 16 rearrangements consisting of either an inversion, inv(16)(p13q22), or a translocation, t(16;16)(p13;q22), are most closely associated with a distinct subtype of acute myelomonocytic leukaemia characterised by bone marrow eosinophilia. This subtype has been assigned the FAB-type M4Eo AML[5] and although the eosinophilia can be variable it has been shown to be part of the leukaemia cell population.

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Molecular studies have shown that these chromosome 16 abnormalities generate a fusion protein (CBFß-MYH11) between the core binding factor (CBFß) gene at 16q22 and the smooth muscle myosin heavy chain (MYH11) gene at 16p13 which plays a vital role in myeloid cell transformation leading to leukaemia. Despite such a transformation, it is still highly desirable to detect those M4Eo AML patients who possess such favourable chromosome 16 abnormalities.

Conventional cytogenetic methods consisting of cell synchronisation and Giemsa banding (G-banding) are currently used to detect chromosome 16 abnormalities but visualisation can often be difficult especially if metaphase preparations are of a poor quality. It is therefore likely that the frequency of these abnormalities is higher than reported [6] and individual patients unknowingly assigned to the wrong prognostic group and subsequent treatment strategy. The need for a more sensitive detection method as an adjunct to conventional cytogenetics at diagnosis is important for the correct stratification of such AML patients.

In this retrospective study we have assessed a molecular technique known as fluorescence *in situ* hybridisation (FISH) using a dual colour CBFß DNA probe for the detection of chromosome 16 abnormalities and compared the results with our own conventional cytogenetic (G-banded) method and published data.

MATERIALS AND METHODS

Patients

Thirteen patients were diagnosed with M4Eo AML in Northern Ireland at the Belfast City and Royal Victoria Hospitals during a five year period (January 1995 to December 1999). The diagnosis and classification of patients were based on standard morphologic, cytochemical and immunophenotypic studies of leukaemic cells according to criteria proposed by the FAB and the MIC cooperative study groups.

Conventional cytogenetics (G-banding)

Chromosomes were prepared and analysed from bone marrow aspirates using conventional techniques. Routine cytogenetic analysis was performed on all patients using a trypsin-giemsa banding technique. Metaphase cells were examined from short-term (24 hour) unstimulated bone marrow cultures and chromosome abnormalities were described according to ISCN (1995).[7] The number of metaphase cells analysed fully varied from 10 to 20 depending upon the quality of individual cell preparations.

Fluorescence *in situ* hybridisation (FISH)

FISH was carried out using a commerically available dual colour LSI CBFß 16q22 probe mixture (Vysis, UK) containing a red coloured 5'CBFß probe (R) positioned centromeric to the 16q22 breakpoint and a green coloured 3'CBFß

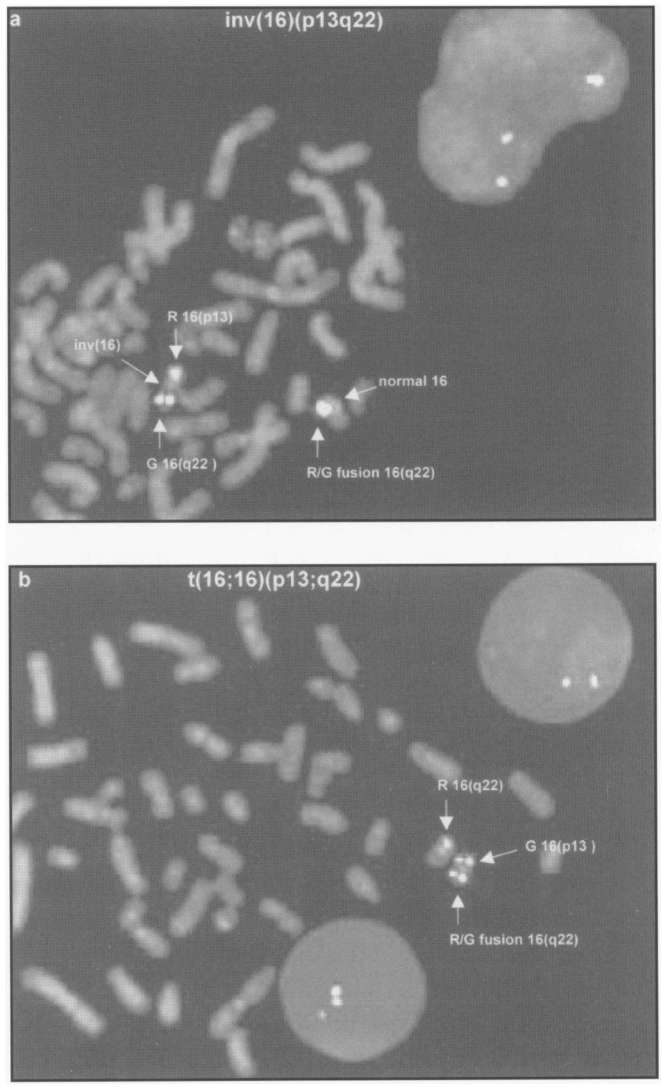

Fig 1. Representative fluorescence in situ hybridisation (FISH) analysis on metaphase spreads using the LSI dual colour CBFß (16q22) probe mixture (Vysis, UK). (A) Characteristic inversion 16 split signal pattern consisting of a Red signal (R) at 16p13 and a Green signal (G) at 16q22 on the inverted chromosome 16. (B) Characteristic chromosome 16 translocation split signal pattern consisting of a fused Red/Green signal (R/G) at 16q22 and a Green signal (G) at 16p13 on one chromosome 16 with a Red signal (R) at 16q22 on the other chromosome 16. (Published by permission of Vysis UK).

probe (G) positioned telomeric to the 16q22 breakpoint. Hybridisation to a normal chromosome 16 homologue should therefore show a fused red/green signal (R/G) at the 16q22 region (Fig la). Likewise, hybridisation to a chromosome 16 homologue containing an inv(16)(p13q22) will cause this fused R/G signal to split with the individual red (R) and green (G) signals appearing on opposite arms of the inv(16) chromosome homologue (Fig 1a). Hybridisation to chromosome 16 homologues involved in a t(l6;16) translocation preparation will result in a fused red/green signal (R/G) on the q arm at 16q22 on one chromosome 16 homologue and a green signal (G) on the p arm at 16p13 while the second chromosome 16 homologue will only contain the red signal (R) on the q arm at 16q22 (Fig 1b).

Statistical analysis

The outcome and survival of individual patients from the time of diagnosis was assessed in August 2001. Survival curves were estimated by the Kaplan-Meier method and compared M4Eo AML patients that were +ve by FISH for the typical 16q22 gene rearrangements (n=4) and the remaining M4Eo AML patients that were – ve by FISH for the typical 16q22 gene rearrangements (n=9) using the log-rank test. A P value <0.05 was considered statistically significant. All statistical computations were performed using SPSS for Windows (version 10).

RESULTS

Patient and cytogenetic/FISH data for the thirteen M4Eo AMI, patients are presented in Table 1.

TABLE

Clinical data, cytogenetic findings, FISH data and clinical outcime of 13 patients diagnosed with M4Eo AML in Northern Ireland.

Patient	*Age (yrs)*	*WCC[a] (x10⁹/l)*	*Conventional Cytogeneties*	*FISH*	*Outcome* (months)*
			definite 16q22 rearrangement		
1	21	179	46,XX,inv(16)(p13q22)[18a]/46,XX[2]	+[i]	Alive 32
2	43	ND	46,XY,inv(16)(p13q22)[71/46,XX[13]	+[t]	Alive 80
			suspected 16q22 rearrangement		
3	81	144	46,XX,?inv(16)(p13q22)[4]/46,XX[16]	–	Dead; <1
4	22	20	46,XX,?add(16)(?q12)[151/46,XX[5]	+[t]	Alive 28
			46,XY,del(16)(q22)[16a]/46,XY[4]		
			or		
5	50	ND	46,XY,t(16;16)(p13;q22)[16]/46,XY[4]	+[d]	Dead; <1
			apparently normal cytogenetics		
6	40	3	46,XX[10][q]	–	Alive 50
7	52	170	46,XX[12][q]	–	Dead; <1
8	59	120	46,XX[10][q]	–	Dead; 9
9	47	145	46,XY[20]	–	Dead; 4
			other numerical/structural abnormalities		
10	72	31	48,XY,+8,+22[cpl4]	+[t]	Alive 38
11	42	15	47,XY,+8[3]/46,XY[27]	–	Dead; 7
12	77	100	47,XY,+8,t(12;21)(p13.3;q11)18]/46, XY[2]	–	Dead; <1
13	71	100	46,XY,del(18)(q21)[12]	–	Dead; 7

[a]White cell count; [q]qualified result (i.e. <20 cells analysed); [i]inv(16)(p13q22), [t]t(16;16)(p13;q22); [d]del(16)(q22); *Outcome in months from date of diagnosis; ND not determined.

Their median age at diagnosis was 50 years (range 21-81 years) with a median white cell count (WCC) of 100 x 10^9/1 (range 3 to 179 x 10^9/1).

Conventional cytogenetic and FISH studies

Conventional cytogenetic and FISH data for all thirteen M4Eo AML patients are presented in Table 1. Patients were grouped into 4 categories according to conventional cytogenetic findings.

'Definite' 16q22 rearrangement

Conventional cytogenetics revealed *'definite'* 16q22 rearrangements in two patients (patients 1 & 2) both of which were confirmed by FISH. Furthermore, FISH was also able to further characterise these abnormalities as the typical chromosome 16 inversion in patient 1 and the typical chromosome 16 translocation in patient 2.

'Suspected' 16q22 rearrangement

Conventional cytogenetics indicated *'suspected'* 16q22 rearrangements in three patients (patients 3- 5). However, FISH analysis excluded a 16q22 rearrangement in patient 3 (i.e. a false +ve G-banded result) and confirmed the typical chromosome 16 translocation in patient 4. FISH also confirmed a deletion of one chromosome homologue at 16q22 in patient 5 due to the loss of the green telomeric CBFß probe signal, the prognostic significance of which will be discussed later.

'Apparently normal' cytogenetics

Conventional cytogenetics was apparently normal for all autosomal chromosomes in 4 patients (patients 6-9). However, a 'qualified' normal result (i.e. <20 cells analysed) could only be obtained in 3 of these patients (patients 6, 7, 8) due to the overall yield and poor quality of metaphase preparations. FISH, however, was able to exclude any 16q22 gene rearrangement in all four patients.

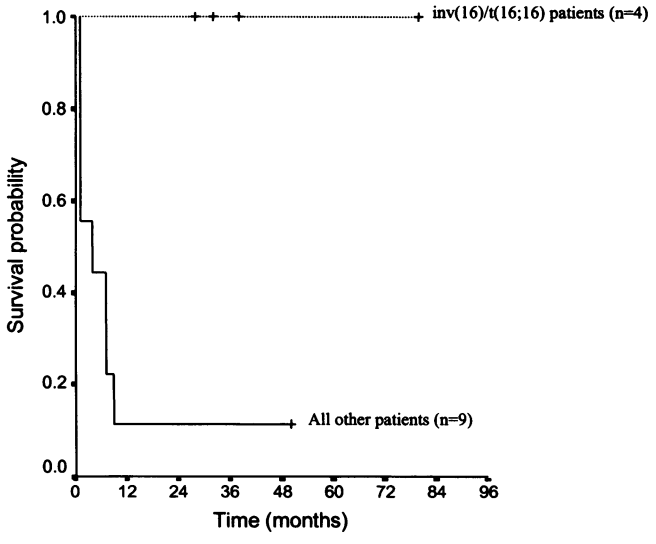

Fig 2. Kaplan-Meier survival curves for patients with chromosome 16 rearrangements (n=4) *vs* patients with either normal chromosome 16s or other Chromosome abnormalities (n=9). Log-rank test P=0.007.

'Other numerical and/or structural' abnormalities

Conventional cytogenetics detected other numerical and/or structural chromosome abnormalities in four patients with 'apparently normal' chromosome 16s (patients 10-13). FISH excluded 16q22 rearrangements in three of these patients (patients 11-13). FISH detected the typical chromosome 16 translocation in patient 10 (i.e. a false -ve G-banded result) who was reported to have only a trisomy for chromosomes 8 and 22 by conventional cytogenetics, the significance of which will be discussed later.

Survival of M4Eo AML patients

We compared the survival of M4Eo AML patients with the typical chromosome 16 abnormalities (n=4) and those patients with either normal chromosome 16s or other chromosome abnormalities (n=9) as illustrated in Figure 2. This Kaplan-Meier survival curve clearly demonstrated a significant longer survival and hence better prognosis for M4Eo AML patients with the typical chromosome 16 abnormalities (log rank test χ^2 =7.27; P=0.007).

DISCUSSION

This small retrospective investigation of 13 patients with M4Eo AML has highlighted the prognostic importance of FISH not only to detect but also to confirm and/or exclude 16q22 rearrangements that have previously been analysed using conventional cytogenetic techniques.

Conventional G-banded analysis detected 'definite' chromosome 16 abnormalities in only two (i.e. 15.4 %) of the 13 patients, both of which were confirmed by FISH. Because these 16q22 rearrangements can be difficult to detect, their frequencies are likely to be higher than reported [6] so it is of little surprise that FISH was able to detect a further two patients with the typical chromosome 16 abnormalities in our group of patients. FISH not only highlighted a false +ve G-banded result in one patient who only survived one month but also highlighted a false -ve G-

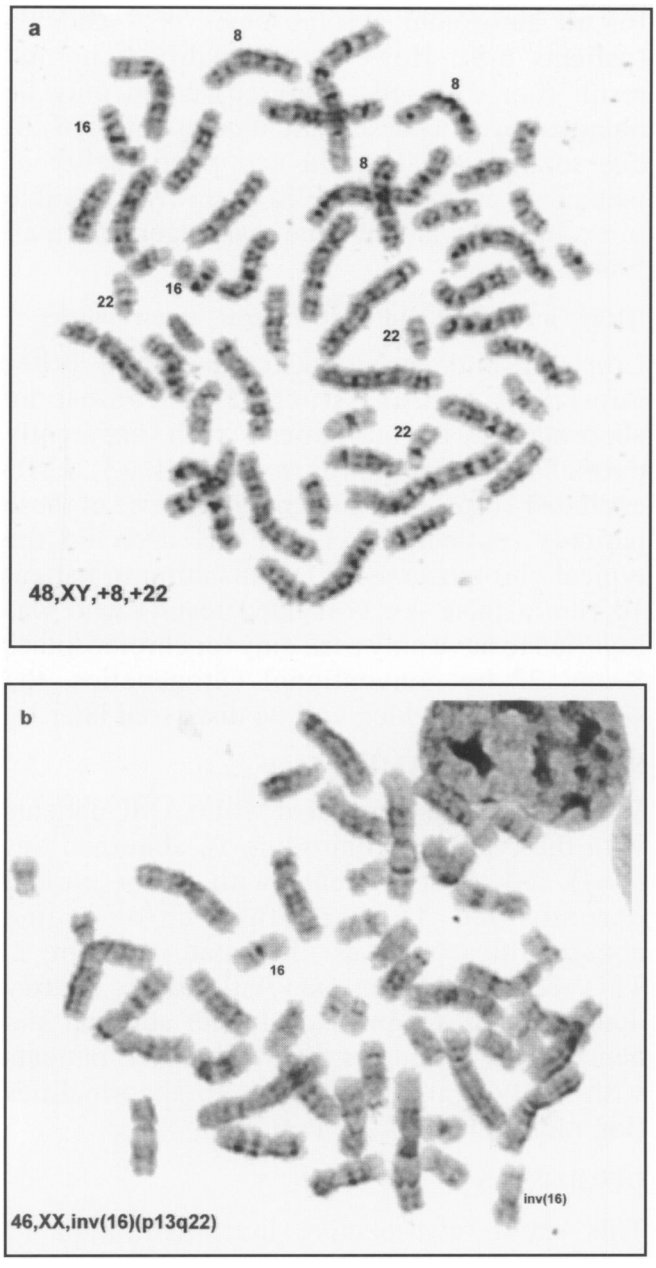

Fig 3. G-banded metaphase spreads in individual M4Eo AML patients. (a) Metaphase spread giving a false -ve G-banded result (patient 10) with 'apparently normal' chromosome 16s but trisomies for chromosome 8 and 22. (B) Metaphase spread for a patient diagnosed in May 2002 clearly showing the typical chromosome 16 inversion [inv(16)].

banded result in another patient who was thought to be carrying only trisomies for chromosomes 8 and 22 (Fig. 3a). FISH clearly unmasked the typical chromosome 16 translocation abnormality in this patient who is still alive after 38 months. Although trisomy 22 itself is rare in AML, it is a common secondary chromosome abnormality in patients with 16q22 rearrangements, as are deletions of the long arm of chromosome 7 and trisomy 8.[5,8] Interestingly, other groups have also unmasked cryptic chromosome 16 abnormalities upon reexamination of several AMLs that initially had been classified as having trisomy 8 or trisomy 22 as the only cytogenetic abnormality.[9] The detection of false G-banded results, both +ve and -ve, using the FISH technique clearly demonstrates that, without FISH, patients can be assigned to the wrong prognostic groups and hence treatment stratification.

FISH confirmed a deletion with a breakpoint at 16q22 in a patient 'suspected' of having a 16q22 rearrangement by conventional cytogenetics. It has been shown that patients with such a deletion have a poorer prognostic outcome than patients with the typical 16q22 rearrangements.[10] At the molecular level, these patients are also more than likely to have different consequences, since without the involvement of the smooth muscle myosin heavy chain gene located at 16p13, the generation of the typical chimeric CBFß-MYH11 fusion gene is not expected. It has also been suggested that patients with the deleted chromosome 16 abnormality should be excluded from the current treatment recommendations reserved for patients with the typical 16q22 rearrangment.[10] The survival of our patient with the 16q22 deletion (i.e. < 1 month) is concordant with the survival and poorer outcome reported for similar patients in other studies.[10-12]

Overall, the four patients with typical 16q22 rearrangements have had a better prognostic outcome compared to the other nine patients. Only one of these nine patients was still alive at the time of assessment, the other eight having already died with a median survival of 2.5 months (range 1-9 months).

Two newly diagnosed M4Eo AML patients have been referred for cytogenetic investigations since the introduction of mandatory FISH screening for 16q22 rearrangements. The first patient, diagnosed in December 2001, showed the typical inversion by conventional cytogenetics and which was confirmed by FISH. The second patient, diagnosed in May 2002 also showed the typical inversion by conventional cytogenetics. The bone marrow sample for this second patient yielded metaphase spreads of extremely good quality and therefore the inversion was easily confirmed by conventional cytogenetics (Fig. 3b). FISH analysis, however, was still carried out and confirmed the conventional cytogenetic findings.

Although this series of patients is small it was notable that 50% of the chromosome 16 abnormalities detected showed the chromosome 16 translocation. This is in contrast to some previous studies that showed a higher incidence of chromosome 16 inversions.[12] Whether this is a mere chance finding, a feature of the local population or reflects failure of other laboratories to characterise the chromosome 16 translocations is unclear.

In conclusion, FISH has proved to be a more sensitive technique compared to conventional cytogenetics for the detection of 16q22 rearrangements. Because of the simplicity of this technique and the availability of the commercially available CBFß probe, FISH has now become a mandatory diagnostic test along side conventional cytogenetics for detection of 16q22 rearrangements in newly diagnosed M4Eo AML patients in Northern Ireland.

ACKNOWLEDGEMENTS

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Missed injuries in the acutely traumatised hand

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SUMMARY

A prospective study of 500 consecutive patients referred from accident and emergency departments in Northern Ireland with acute hand injuries was performed to assess the incidence of missed injuries. An injury was 'missed' if a patient was receiving inappropriate treatment or returned due to persistent symptoms despite being examined, treated and discharged. There were 16 (3.2%) missed injuries. Seven involved tendon only, four were isolated nerve injuries and four were mixed tendon and nerve injuries. The remaining case was a ruptured ulnar collateral ligament of the thumb metacarpophalangeal joint. Thirteen injuries were open, with a glass laceration being the most common mechanism of injury. The time to detection of a missed injury was on average 11 days (range 1-62 days). Missed hand injuries in Northern Ireland are uncommon but do occur. A thorough clinical examination and accurate injury documentation remain fundamental in their prevention.

INTRODUCTION

Acute hand injuries account for 6.6% of all new attendances at Accident and Emergency Departments in Northern Ireland.[1] It is recognised that despite best efforts, hand injuries may be missed.[2, 3, 4, 5] Missed hand injuries may lead to a prolonged period of disability, further surgical intervention and a sub-optimal outcome.

The purpose of this study was to assess the incidence of missed injuries being referred to the Regional Plastic Surgical Unit and to identify any common contributing factors.

PATIENTS AND METHODS

A prospective study of 500 consecutive patients with acute hand injuries referred to the Regional Plastic Surgical Unit in Northern Ireland, was performed over a six month period. The Unit accepts all hand and wrist injuries, except for bony and/or ligamentous injuries to the carpus and distal forearm.

On admission, patients were assessed and the following data recorded; age, gender, hand dominance, the injured hand(s), whether the injury was open or closed, the diagnosis and if the injury was missed. The introduction of a hand injury chart (Figure) provided an objective method of recording a patient's injuries.

An injury was defined as 'missed' if a patient was receiving inappropriate treatment or returned to the Accident and Emergency department due to persistent symptoms despite being examined, treated and discharged.

The Accident and Emergency records of patients with missed injuries were subsequently retrieved. From these notes we recorded; the date of injury, the grade of the initial examining medical officer, the mechanism of injury, the clinical diagnosis and any documented difficulties in patient assessment.

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FIGURE

NORTHERN IRELAND PLASTIC AND MAXILLOFACIAL SERVICE

HAND INJURY CHART

Name:

Occupation:

Date of birth:

Hand Dominance: Right / Left / Neither

M / F:

Injured hand: Right / Left / Both
(If both - complete separate chart for each hand)

HISTORY:

Date/ Time/ Place of injury:

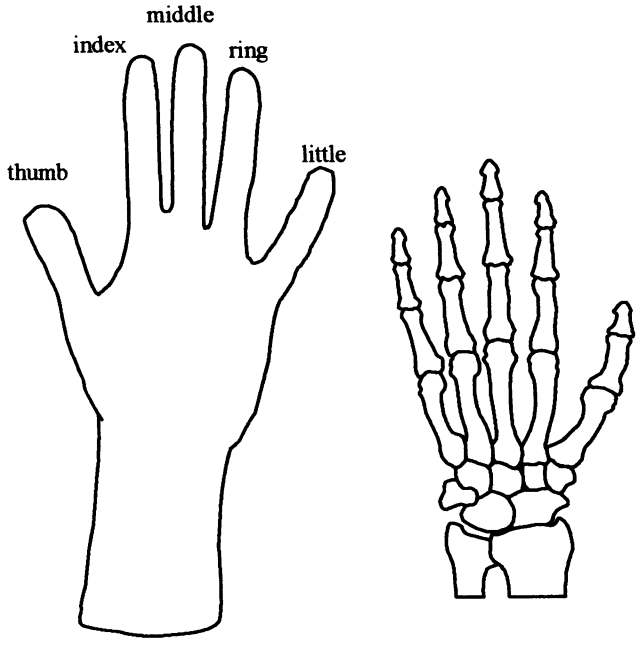
Mechanism of injury:

EXAMINATION:

Indicate on diagrams; lacerations, skin loss, burns, infection, amputations, sensory loss, bone injuries, retained foreign body.

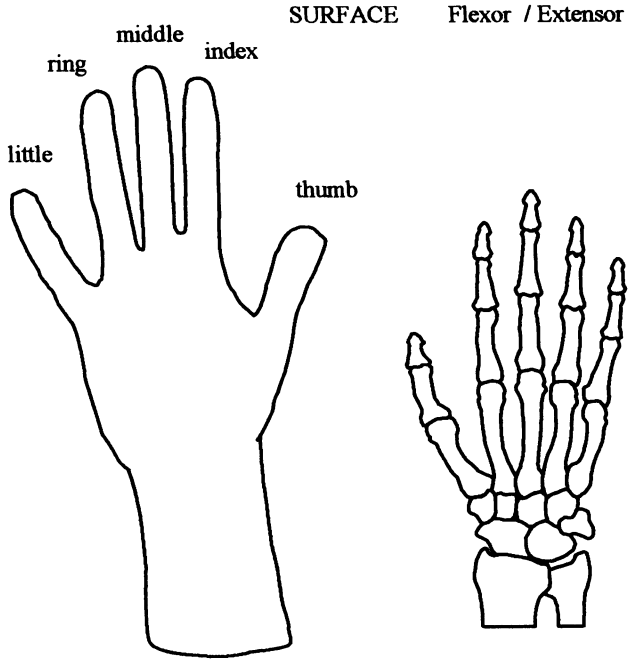
HAND Right / Left

SURFACE Flexor / Extensor



HAND Right / Left

SURFACE Flexor / Extensor



Tendon injury:
(circle those divided)

Thumb	APL/EPB	FPL	EPL
Index	FDS	FDP	EDC/EI
Middle	FDS	FDP	EDC
Ring	FDS	FDP	EDC
Little	FDS	FDP	EDC/EDM

Nerve injury:
(circle those divided)

median
ulnar
radial
digital common
radial / ulnar

Ligament injury:
(especially thumb)

radial collateral
ulnar collateral

Circulation:

Normal yes/no
Details

X-RAY: (hand +/- amputated part) Yes / No

PHOTOGRAPH: Yes / No

DIAGNOSIS:

EXAMINED BY:
(Print Name and Grade)

RESULTS

There were 16 (3.2%) missed injuries in the 500 consecutive patient referrals. The average age of patients was 29 years (range 19-53 years) with a male to female ratio of 3:1. In seven cases the dominant hand was involved.

Thirteen injuries were open. Of these, five involved tendon only, four were isolated nerve injuries and four were combined tendon and nerve injuries. Three injuries were closed. There were two isolated tendon injuries and one ruptured ulnar collateral ligament of the thumb metacarpophalangeal joint (Table I). In all of the patients with a missed injury, it was a Senior House Officer who performed the initial assessment.

A glass laceration was the most common mechanism of injury, accounting for 6 cases (Table II). Difficulty in performing a clinical examination was recorded in one patient who was uncooperative due to alcohol intoxication. The average delay to detecting a missed injury was 11 days (range 1-62 days).

TABLE I

Missed hand injuries in 500 patient referrals

	Missed injury	*No. patients*
Open		
Tendon only	Extensor digitorum	2
	Flexor digitorum profundus	3
Nerve only	Median nerve	2
	Ulnar digital nerve	1
	Radial digital nerve	1
Combined	Median nerve and flexor digitorum superficialis	1
	Ulnar nerve and flexor carpi ulnaris	1
	Flexor digitorum profunds and radial digital nerve	1
	Radial digital nerve and extensor digitorum	1
Closed		
	Flexor digitorum profundus	2
	Ulnar collateral ligament thumb metacarpophalangeal joint	1
	Total	16

TABLE II

Mechanism of missed injuries

	Mechanism of injury	*No. patients*
Open	Glass	6
	Knife	4
	Metal	1
	Fall	1
	Crush	1
Closed	Assault	1
	Sports injury	2

DISCUSSION

This study confirms that missed hand injuries do occur, but it is reassuring to note that they represent only a small percentage (3.2%) of the total referrals. Our findings suggest that missed injuries are more common in patients with hand or wrist trauma caused by glass and in patients examined by junior medical staff.

A previous study by Hill *et al*[1] described the characteristics, causes and disposal, of all isolated injuries to the hand and wrist in Accident and Emergency Departments in Northern Ireland. Using this data we can estimate that over 7,000 hand injuries will have passed through feeder departments over the six month period in which this study was performed. Patterns of disposal after initial attendance, also show that 87.3% of lacerations to the hand and wrist, including tendon and nerve injuries, will have been referred to our service.

The extent of underlying damage is often underestimated with glass lacerations. Blunt objects may cause little damage to deep structures, whereas thin slivers of glass which produce an unimpressive skin wound commonly divide tendons and major nerves.[6] Although they account for only 5.1% of hand injuries in Northern Ireland [1] glass was involved in almost 40% of the missed injuries we detected.

It is well recognised that peripheral nerve injuries can be difficult to assess in the immediate post injury period. Some patients often appear to have function in a nerve which is subsequently shown to be divided. Lynch and Quinlan[7] confirmed that a nerve impulse can jump a transection gap for up to 72 hours, until Wallerian degeneration occurs. This has clear implications for early nerve assessment by Casualty Officers. If a divided nerve remains in anatomical contact it may continue to transmit impulses and early assessment is therefore incomplete. If immediate exploration is not being carried out, patients with

suspected nerve injuries should be reassessed approximately 72 hours later. At this stage Wallerian degeneration will have removed the possibility of jump transmission and the correct diagnosis can be established.

Failure to perform a comprehensive clinical examination is the most likely reason that missed hand injuries occur. This is often due to inexperience on the part of the junior doctor, compounded by a lack of knowledge of the complex anatonnical and functional features of the hand. Consulting a more senior member of the team or referral to a hand injury review clinic are important options that should be available. Finlayson *et al* [3] highlighted the benefits of a next day review clinic for patients attending casualty with acute hand or wrist injuries. Detection of unsuspected significant injuries, avoiding inappropriate treatment and teaching junior medical staff are clear advantages of this clinical setting.

Examination of the hand requires patient co-operation. Injuries can be missed when trying to assess patients who are uncooperative due to alcohol intoxication or drug abuse. The patient's response to the clinical examination may also be confused by emotional distress or the presence of pain. It is therefore important either to reassess the patient when they are more co-operative or ensure that they are reviewed the following day.

No previous study has attempted to quantify the problem of missed hand injuries or identify contributing factors. It is hoped that our findings, with an emphasis on a thorough history, clinical examination and accurate injury documentation using a hand injury chart, will help to reduce their occurrence.

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Do the COL1A1 and *Taq 1* Vitamin D receptor polymorphisms have a role in identifying individuals at risk of developing osteoporosis?

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SUMMARY

The distribution of the *Taq 1* polymorphism in the vitamin D receptor (VDR) gene and the *MSc 1* polymorphism in the collagen 1 alpha 1 (COL 1AI) gene were studied in 266 female and 55 male patients attending an osteoporosis clinic. Allele frequency in control (T- or Z-score >-1.0) and osteoporotic (T- or Z-scores <-2.5) groups were compared using Chi squared tests. No differences were found between the 2 groups with either of the polymorphisms. When allele frequency was compared in patients with and without history of fracture, no differences were found in the frequency of the COL1A1 alleles. However there were significantly more fracture patients, who had been previously treated with corticosteroids for other conditions, carrying the T allele of the VDR polymorphism ($X^2 = 5.65$, $p>0.01<0.02$). In conclusion, neither of these polymorphisms aid in the prediction of osteoporosis but the VDR T allele may carry an increased fracture risk in patients who require corticosteroid treatment.

INTRODUCTION

Bone mineral density (BMD) is regulated by a complex interaction of genetic and environmental factors. Polymorphisms in the vitamin D receptor (VDR) and regulatory region of the type I collagen gene (COL1A1) have been associated with decreased bone mass and increased risk of osteoporotic fractures. Morrison[1] described a *Taq 1* polymorphism in codon 352 of exon 9 of the VDR gene resulting from a C→T transition. Grant[2] described a novel G→T polymorphism in the regulatory region of the COL1A1 gene which was found to be strongly associated with low BMD and increased risk of osteoporotic fracture.

We have studied the distribution of these two polymorphisms in a group of people referred to the osteoporosis clinic in Northern Ireland to assess if there is any association between either of these genotypes and low bone mineral density (BMD) or the risk of osteoporotic fracture in our local population.

METHODS

Patients

Patients attending the osteoporosis clinic for bone scans were studied. These patients had been referred to the clinic for a variety of different reasons e.g. family history, early menopause and long term treatment with corticosteroids. The bone density was measured by dual energy X-ray absorptiometry (DXA) using a Hologic4500A bone densitometer. Lumbar spine (L1-L4) and total hip BMD were measured and T-scores and Z-scores obtained. The local ethical committee approved the study and patients gave informed written consent. Blood was collected from 266 females (aged 28-83, median 64 years) and 55 males (aged 22-75, median 51 years). All subjects were Caucasian and 62 of the females (23%) and 10 of the males (18%) had a family history of osteoporosis. The BMD result from the subject's first visit was recorded and a blood sample sent for gene studies. At the end of the study (after the

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genotyping had been carried out) the patients were classified as to whether or not they had been treated with corticosteroids, for other medical conditions, and whether or not they had suffered a low trauma fracture. Steroid treatment was defined as ≥7.5mg for ≥6months and the classification of a low trauma fracture was a subjective assessment made by the doctor after discussion with the patient.

DNA Isolation

Ten millilitres of blood was collected from each patient into tubes containing EDTA. The plasma was removed and the DNA was extracted from the white cells using the method of Jean Pierre.[3] The DNA was dissolved in Tris-EDTA buffer (10mM) to give a concentration of approximately 250μg/mL and stored at –70°C until analysis. Before analysis the samples were diluted to 25μg/mL with double distilled, sterile water.

COL1A1 Genotyping

The primers used were those described by Grant,[2] namely a forward primer of 5'-TAACTTCTGGACTATTTGCGGACTTTTTGG-3' and a reverse primer of 5'-GTCCAGCCCTCATCCTGGCC-3'. The primers were purchased from Gibco BRL, Life Technologies, UK. Polymerase chain reaction (PCR) was carried out using Taq DNA polymerase (Boehringer Mannheim) under standard conditions on a Perkin Elmer 2400 Thermal Cycler. The thermal cycling protocol consisted of 35 cycles of 94°C for 30 seconds, 63°C for 30 seconds and 72°C for 30 seconds with an initial denaturing step of 94°C for 3 minutes before the first cycle and a final extension step of 72°C for 7 minutes. The PCR product was incubated at 37°C with *Msc 1* overnight (17 hours) and the digests electrophoresed on a 1% agarose (Gibco BRL, UK) plus 2.5% Nusieve (KMC Products, UK) gel and stained with ethidium bromide. Wild type DNA (G/G) has a single band at 255bp, heterozygotes for the G→T polymorphism have two bands at 237bp and 255bp, and homozygotes for T/T have one band at 237bp. These correspond to the SS, Ss and ss genotypes respectively.

Vitamin D Receptor Genotyping

The primers used were those described by Morrison[1] namely a forward primer of 5'-CAGAGCATGGACAGGGAGCAA-3' and a reverse primer of 5'-GCAACTCCTCATGGCTGAGGTCTC-3'. The primers were purchased from Gibco BRL, Life Technologies, UK. PCR was carried out using Taq DNA polymerase (Gibco BRL) using standard conditions on a Perkin Elmer 2400 Thermal Cycler. The protocol was 35 cycles of 94°C for 30 seconds, 63°C for 20 seconds and 72°C for 20 seconds with an initial denaturing step of 94°C for 3 minutes and a final extension step of 72°C for 7 minutes. The PCR product was digested with *TaqI* for 2 hours at 65°C, the digests electrophoresed on a 2% agarose gel and stained with ethidium bromide. Homozygotes for the T nucleotide (TT) have two bands at 495bp and 245bp, heterozygotes with C→T (Tt) have four bands at 495bp, 245bp, 290bp and 205bp and homozygotes for the C (tt) nucleotide have three bands at 290bp, 245bp and 205bp.

Statistics

The WHO criteria for defining patients with ostoeporosis classifies those with T-score of >-1.0 as "normal", <-1.0->-2.5 as osteopenic and < -2.5 as osteoporotic. The T-score compares the BMD with that of the mean for a young adult population. Since our population spanned such a

TABLE I

Summary of genotypes

	No. of Patients	*sstt* *f*	*ssTt* *f*	*ssTT* *f*	*Sstt* *f*	*SsTt* *f*	*SsTT* *f*	*SStt* *f*	*SSTt* *f*	*SSTT* *f*
Total population	314	0.6	1.6	0.3	4.8	14.3	9.2	8.6	33.1	27.4
All Females	261	0.8	1.9	0.4	5.0	14.9	8.4	9.2	32.6	26.8
All Males	53	0.0	0.0	0.0	3.8	11.3	13.2	5.7	35.8	30.2

f = frequency (%)

TABLE II

Demographic details of patients, who have had no steroid treatment, when classified by lumbar and hip T- and Z-scores

	Females			*Males*		
	Osteoporotic	*Osteopenic*	*Control*	*Osteoporotic*	*Osteopenic*	*Control*
Lumbar T-score						
Number	125	48	29	12	9	4
Age Range (years)	35-83	28-76	34-78	29-65	28-75	41-70
Median age (years)	63	64	58	46	41	66
Lumbar Z-score						
Number	36	87	79	8	13	4
Age Range (years)	35-78	28-83	37-78	29-65	28-75	41-70
Median age (years)	64	63	64	52	44	66
Hip T-score						
Number	61	91	48	2	13	10
Age Range (years)	35-83	28-81	34-75	39-59	29-75	28-70
Median age (years)	67	64	58	49	46	45
Hip Z-score						
Number	11	72	117	1	11	13
Age Range (years)	35-76	28-83	34-81	39	29-75	28-70
Median age (years)	65	63	64	39	46	49

wide age group (28-83 years) we also classified patients according to their Z-scores which compares their BMD with age-matched controls. In order to be as comprehensive as possible we used both the T-score and Z-score at both the lumbar and hip sites to classify patients as those with normal bone density, those who were osteopenic, and those with osteoporosis. The numbers in each group varied according the site and scoring system used (Tables II and III). Those with T or Z scores >-1.0 were regarded as having normal bone density and were classified as our "Control" group. The normal (or control), osteopenic and osteoporotic groups were sorted according to whether or not they had received steroid therapy and whether or not they had sustained a low trauma fracture. The Chi-squared test was used to compare the frequency of the S with s and T with t alleles in patients who were classified as "controls" (T- or Z- score >-1.0) with those who were classified as "osteoporotic" (T- or Z- score <-2.5) using both the lumbar and hip BMO scans. Chi-squared was also used to compare the frequency of the S, s, T and t alleles in patients who had sustained a low trauma fracture with those who had no history of fracture.

Results

Fifty females and 22 males had received steroid therapy (≥7.5mg for ≥6 months minimum). Thirteen females and seven males were uncertain as to whether or not they had received a significant course of steroids. These 20 patients were included in the calculation of the overall genotype frequency in the population (Table I) but were not included when the patients were divided into steroid and no steroid groups. There were no hip scores for five female patients and, due to technical difficulties with the assays, we were unable to obtain COL1A1 genotypes on five patient samples (4 females and 1 male) and VDR genotypes on two patient samples (1 female and 1 male).

The numbers of patients classified as controls, osteopenic and osteoporotic differed according to whether they were classified according to their T-score or Z-score or according to their lumbar or hip scores (Tables II and III).

The genotype frequency in our total population for the collagen *Spl* site ploymorphism was 69% SS, 28% Ss and 3% ss, which conforms to Hardy-Weinberg equilibrium. Females had the same distribution but none of the males in our study

TABLE III

Demographic details of steroid treated patients when classified by lumbar and hip T- and Z- scores

	Females			*Males*		
	Osteoporotic	*Osteopenic*	*Control*	*Osteoporotic*	*Osteopenic*	*Control*
Lumbar T-score						
Number	29	16	5	12	9	1
Age Range (years)	35-81	35-83	36-60	28-68	22-73	41
Median age (years)	65	67	44	47	54	41
Lumbar Z-score						
Number	7	17	26	10	9	3
Age Range (years)	50-61	35-74	36-83	28-66	22-73	41-61
Median age(years)	60	58	68	49	54	49
Hip T-score						
Number	14	20	13	4	15	3
Age Range (years)	50-81	39-83	35-76	38-64	22-73	41-61
Median age (years)	63	66	60	52	51	52
Hip Z-score						
Number	2	16	29	2	14	6
Age Range (years)	73-81	39-75	35-83	38-41	22-69	41-73
Median age (years)	77	59	68	40	53	53

had the ss genotype, with 72% being SS and 28% being Ss. The genotype frequency of the *Taq 1* polymorphism in our population is 37% TT, 49% Tt and 14% tt, which conforms to Hardy-Weinberg equilibrium. The frequency in the female population was 36% TT, 49% Tt and 15% tt and in the male population it was 43% TT, 47% Tt and 10% tt. Due to the small numbers in some of the genotypes (especially the ss genotype) it was not possible to apply statistical methods to the individual or combined genotypes. When Chi squared tests were applied to the numbers of patients bearing the S or s and the T or t allele in the control groups and osteoporotic groups there was no significant difference between them, whether they were classified by lumbar or hip T- or Z- score. One hundred females and 26 males had a history of fracture. The T allele was more prevalent in patients with a history of fracture (χ^2=5.05, p>0.02<0.05). This trend was evident in the steroid treated group (χ^2=5.65, p>0.01 <0.02), but not in the no steroid group (Figs. 1 & 2). There was no difference in the frequency of the S or s allele in patients with a history of fracture.

DISCUSSION

Osteoporosis is the most common metabolic disease. It is a disease in which the density or mass of the bone is reduced, leading to an increased risk of fracture. The ability to predict and prevent osteoporotic-related fractures would be of major benefit to both patient and NHS. Thus finding a biochemical or genetic marker which could predict those at greatest risk of developing osteoporosis is an attractive proposition. To date none of the biochemical markers have proved of any value in diagnosing osteoporosis, although they have their uses in monitoring the effects of treatment. The early reports on the COL1A1 Spl[2] and vitamin D receptor *Taq 1*[1] polymorphisms appeared hopeful of being able to correlate genotype with bone density and risk of fracture. However subsequent studies with both these polymorphisms have brought conflicting reports. In contrast to many previous studies [2, 4-7] we found no significant difference in the distribution of genotypes for the COL1A1 genotypes in the osteoporosis and control groups or any association between genotype and fracture. Other studies [8-11] report similar results to ourselves with no

Fig 1 VDR genotype in patients who had not been previously treated with corticosterolds

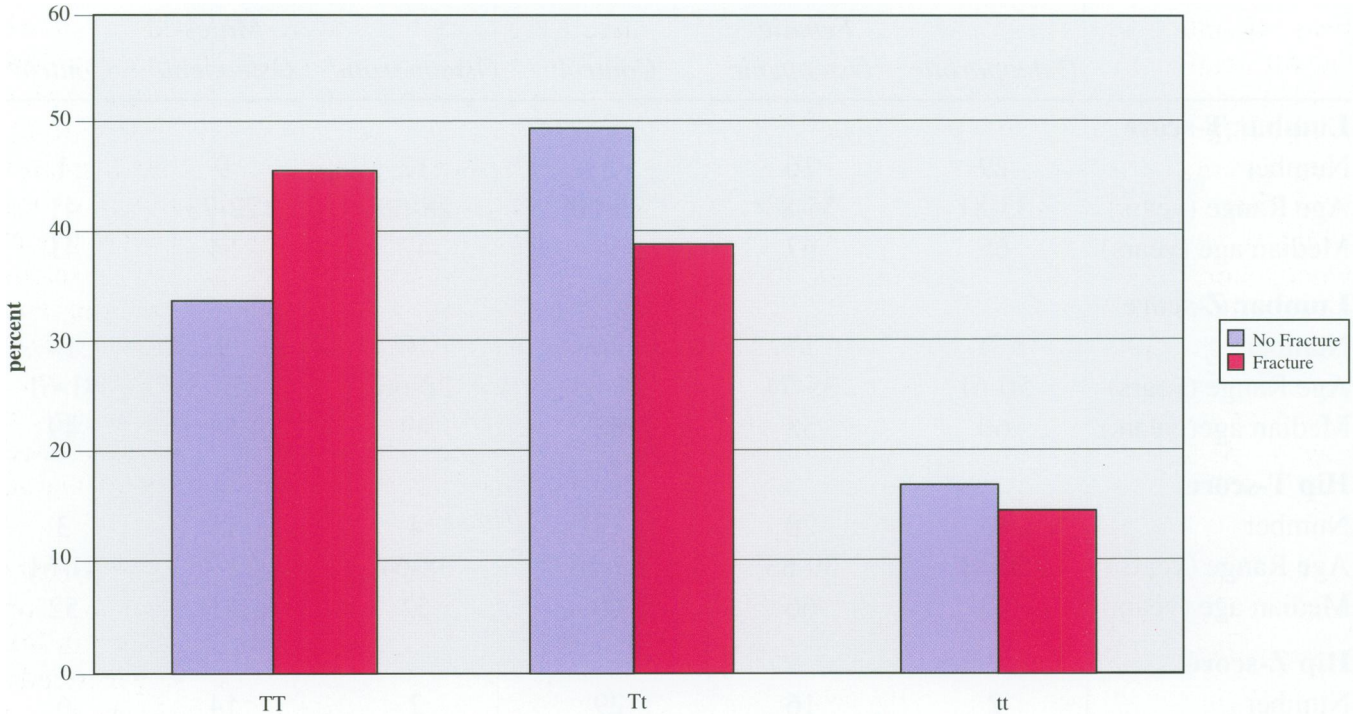
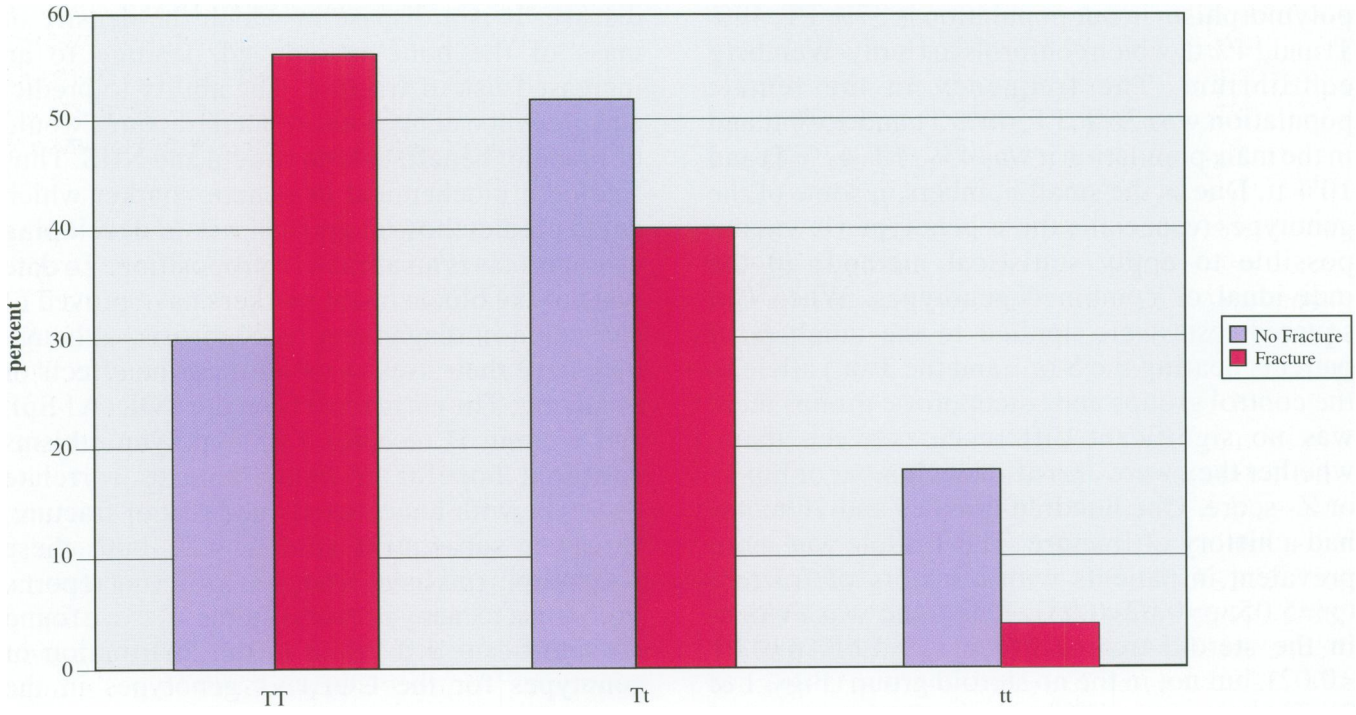


Fig 2 VDR genotype in patients treated with corticosteroids for other diseases



association between COL1A1 genotype and either BMD or fracture. Beaven[12] has reported ethnic differences in the prevalence of the s allele, being lower in an African and Asian population than in European countries and Han *et al*[13] have found the Spl polymorphism to be absent in a Korean population. However, all the studies mentioned above which found a positive association between the polymorphism and BMD or fracture risk were carried out with Caucasian European or American subjects, so racial differences are unlikely to be the reason for the disparity in the findings. In most cases the distribution of the genotypes was similar to ours in the non-osteoporotic population; it was in the osteoporotic group that the distribution of the genotypes differed in the studies which had positive findings. The criteria used to choose the patient group may be the key to the differences in the findings of the various studies. Utterlinden[14] whose overall distribution was very similar to ours, only found genotype related differences in the bone mineral density in women in the 75-80 year old age group, younger groups showed no difference between the genotypes. Since our study spanned a wide age range any differences in the oldest patients may have been diluted by the younger patients. (We did not pursue this possibility since, if genotyping is to be of any use in a clinical situation it would be very important that the risk of osteoporosis could be identified in young patients, before clinical osteoporosis is evident.) A recent study by Brown[15] found the association between COL1A1 polymorphism and the rate of lumbar spine bone loss to be dependent on dietary calcium. Carriers of the "s" allele lost more bone in the low calcium intake group but the carriers of the "S" allele lost more bone in those with a high calcium intake. Since our patients were chosen at random from patients attending the Osteoporosis Clinic it is likely that they spanned a range from low to high calcium intake.

We found no association between the *Taq 1* polymorphism genotype and BMD as assessed by both T-score and Z-score which again contrasts with some of the earlier studies" [1-6] but confirms other studies.[17-19] A meta- analysis of 16 published papers[20] showed great disparity between studies, with some finding an association between the TT genotype and lower BMD, some finding an association between the tt genotype and lower BMD and others finding no association. Marked racial difference in the distribution of the genotypes have been reported.[17, 21, 22] We found no over-representation of any genotype in either our steroid or no steroid groups with osteoporosis. However the TT genotype was over-represented in patients who had been treated with corticosteroids and who had sustained a low trauma fracture (56% in the fracture population compared to 30% in the control population). Most studies have excluded corticosteroid treated patients from their study population but one Australian study[23] which looked specifically at patients who were on corticosteroids for various diseases, like ourselves, failed to find any association between BMD and VDR genotypes at any site. A preliminary study by Chamberlain,[24] in a UK population, found an over-representation of the TT genotype in corticosteroid treated patients who had very low BMD or evidence of vertebral fracture.

Osteoporosis is a major side-effect of steroid therapy but some individuals do not develop osteoporosis. It is possible that the susceptibility to steroid induced osteoporsois is genetically modified. Glucocorticoids influence the regulation of calcium and phosphate metabolism and inhibit vitamin D_3-mediated induction of genes in osteoblasts [25] so polymorphisms or mutations in the vitamin D receptor may be one of the factors involved in how individuals handle their treatment. Our study suggests that the TT genotype may be a risk factor for fractures in patients treated with glucocorticoids. However 40% of patients with a fracture history were Tt and 4% were tt so further studies on large numbers of patients with steroid-induced osteoporosis are required.

Due to the small number of people with the ss genotype it was not feasible to compare people with the two "high risk" genotypes (ie ss and TT) with the seemingly "low risk" genotypes (ie SS and tt). One female had the ssTT genotype. Her lumbar and hip T-scores were –3.47 and –1.78 and Z-scores were –1.42 and –0.11 respectively, she had no familyhistory of osteoporosis but had had a low trauma fracture. The most frequent genotype in our population was SSTt (Table I) and this was consistent in all the groups of patients except the steroid treated patients with a history of fracture, in which SSTT was the most common genotype. This probably reflects our findings with the VDR receptor genotypes rather than a synergistic or additive effect of the two types of polymorphism. The number with the SsTt

genotype was considerably less in patients with fractures than those without fractures but the numbers were too small to draw any definite conclusions. Further investigation with larger numbers of patients may reveal more significant differences between the genotypes but for a genetic test to be of value in diagnosis or risk stratification one or two genotypes would have to stand out in the patient group, even in small numbers of patients.

In conclusion, we have been unable to present any evidence that either COL1A1 or VDR genotyping, singly or together, have a role in predicting either risk of osteoporosis or risk of fracture.

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How reliable is a radiological report in osteoporosis in diagnosing low bone density?

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SUMMARY

Patients are often referred to osteoporosis clinics with a radiological diagnosis of osteoporosis. Previous studies attempting to ascertain risk of osteoporosis from radiographs have been conflicting. The aim of our study was to determine how reliable spinal radiographs were at detecting low bone density compared with Dual Energy X ray Absorptiometry (DXA). We retrospectively measured the Bone Mineral Density (BMD) at the spine in 130 patients with a radiological diagnosis of osteopenia or osteoporosis in the absence of vertebral fractures. They were compared with a group of 119 age and sex matched patients with one or more low trauma vertebral fractures. There was a statistically significant difference in the mean BMD between these two groups. 12.7%, of the x-ray group with osteopenia reported, had a normal bone density, 49.2% had osteopenia (T-score -1 to -2.5) and 38.1% had osteoporosis (T-score <-2.5). Of those with a radiological report of osteoporosis, 12.8% had a normal bone density, 44.7% had osteopenia and 42.6% had osteoporosis. We conclude that a radiological report of low bone density is a strong predictor of osteopenia or osteoporosis by BMD measurement.

INTRODUCTION

It has been a generally held view that bone loss of less than 30% cannot be detected radiologically.[1,2] However, these conclusions were drawn from in vitro experiments carried out over 40 years ago.

Previous studies have attempted to ascertain the reliability of X-rays in estimating low bone density, although the results have been conflicting. Some were underpowered,[3-5] and one of these used the femoral condyle and ankle as the preferred region.

The aim of our study was to determine how reliable spinal radiographs are at detecting low BMD compared with DXA at the spine.

METHODS

Patients

We retrospectively studied the BMD of 130 patients (118 female, 12 male) who had been consecutively referred to the Osteoporosis Clinic at the Belfast City Hospital by their General Practitioner or other specialist from hospitals throughout Northern Ireland. These patients had x-rays of dorsal or lumbar spine, or both, which commented on the presence of osteopenia or osteoporosis in the absence of any vertebral fracture. We included a subgroup of patients in whom an additional report of degenerative osteoarthritic changes had been made.

Results were compared with a group of 119 age and sex matched patients (108 female, 11 male), attending our osteoporosis clinics with one or more low trauma vertebral fractures (defined as a loss in vertebral height of 20% or more). The X-rays were reported by a radiologist in the referring

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hospital and as this was an observational study of clinical practice, no attempt was made to standardize radiographs. They used the classification of either osteopenia or osteoporosis. The latter is regarded as demonstrating more bone loss but there is no objective way of making this distinction.

MEASUREMENT OF BONE MINERAL DENSITY

BMD was measured by DXA using the Hologic 4500 A bone densitometer. Measurements were made in the Ll-L4 region and the results expressed as gm/cm2. Osteoporosis was defined as a value for BMD that is 2.5 standard deviations (SD's) or more below the young adult mean value (T-Score less than -2.5). Osteopenia denotes a T- score that lies between -1 and -2.5 and normal was taken as a T- score >-1, according to the WHO criteria.[6]

Data Analysis

Data were analyzed using SPSS. Descriptive statistics are reported and an independent samples 't' test was used to compare BMD levels between x-ray patients and fracture patients.

RESULTS

Tables 1 and 2 show the characteristics of the study groups. The two groups were well matched for age (mean 63.8 yrs in the x-ray group and 63.9 in the fracture group).There was a statistically significant difference in the mean BMD between the two groups (0.8gm/cm^2 vs 0.68gm/cm^2, $p<0.0001$) 84% of patients in the fracture group were classified as having osteoporosis, 13.4% osteopenia and 2.5% had normal bone density. 49.2% of patients with a radiological diagnosis of osteopenia had this confirmed by DXA while 38.1% had osteoporosis and 12.7%, a normal BMD. 42.6% of patients with a radiological diagnosis of osteoporosis had this confirmed by DXA. However a higher proportion actually had osteopenia, (44.7%) and 12.8% had a normal BMD.

DISCUSSION

A large proportion of patients in the fracture group had evidence of osteoporosis. These were people in whom there was evidence of low trauma vertebral fracture, which is an important risk factor for osteoporosis. BMD is not a perfect measurement to diagnose osteoporosis particularly in older patients when the lumbar spine is employed. For example, spinal osteoarthritis may affect the measurement.[7]

Our study has shown that a radiological report of osteoporosis is very useful in diagnosing low bone density, but could not accurately differentiate between osteopenia and osteoporosis as measured quantitatively by DXA. Of the 110 patients referred with low bone density by radiology, 87.2% had this confirmed by DXA. This is in contrast to the study of Scane et al,[3] which showed that only 66.7% of women with apparent osteopenia on spine x-ray without vertebral deformation had a bone density below the normal range for young women. However, this was a very small study. In a review of 269 referrals for bone density measurements on the basis of an x-ray report of osteopenia by Ahmed et al,[8] the highest proportion of women in any one group (out of nine) referred for BMD measurement as having osteoporosis was in the radiographic osteopenia group (n=268; 24% at the spine, 11% at the femur and 29% at the spine, femur or both). This was despite the finding that the mean Z scores for BMD were lower in secondary amenorrhoea and premature menopause groups. Michael et al[7] reported on 80 individuals in whom radiographs and BMD, as measured by quantitative CT, were performed. They concluded that radiographs were reliable in detecting low bone density in osteoporotic individuals without fracture Masud et al,[9] who assessed osteopenia in spine radiographs and BMD as measured by DXA in a large sample of 818 patients concluded that 'high grade' osteopenia should be an indication for bone densitometry and that a 'normal' x-ray is unlikely to have a significantly low BMD.

This finding was supported by Garton et al,[10] who assessed the BMD and spinal radiographs of patients randomly selected from the community. Their sample comprised more men than women (107 vs 93), which does not correspond to the true referral patterns for osteoporosis. However, if the diagnosis of osteoporosis depended on radiological features alone, then 38.1% of patients with osteoporosis would have been missed. Conversely, 44.7% of the patients with a radiological diagnosis of osteoporosis would have possibly received treatment for osteoporosis when they had osteopenia or a normal bone density.

The interpretation of radiographs depends on film penetration, patient positioning and inter/intra observer variability. In the study of Epstein et al,[11] the authors concluded that there was poor agreement between radiologists and within the

TABLE I

Patient Characteristics

	X-Ray Patients N(%)	*Fracture Patients N(%)*
Total No. of	130	119
Patients (n)	(M=12, F=118)	(M=11, F=108)
Age Range (y)	28-88	25-81
Mean Age (y0	63.8	63.9
Mean BMD (gm/cm^2)	0.80	0.68

TABLE II

Radiological Diagnosis vs Bone Mineral Density

	Osteopenia	*Osteoporosis*	*Low Bone Density and Degenerative changes*	*Fracture Patients*
	N=63	*N=47*	*N=20*	*N=119*
T-Score>-1.0 Normal	12.7%	12.8%	20%	2.5%
T-Score –1 to –2.5 Osteopenia	49.2%	44.7%	35%	13.4%
T Score <-2.5 Osteoporosis	38.1%	42.6%	45%	84%

same radiologist on reviewing the same film at a different time. However, only 15 pairs of films were reviewed, chest radiographs were employed and DXA was not used to measure BMD, as the design of the study was primarily to establish concordance and reproducibility of observations. This is in contrast to the study by Jergas et al,[12] in which a larger sample of 100 patients was used. DXA was used for quantitative assessment of BMD. There was considerable agreement between the observers but only when a substantial amount of bone was lost.

Garton et al[10] concluded that in an assessment of 200 patients that interobserver agreement was fair to moderate and intraobserver agreement was moderate to good. They also concluded that although the overlap between the different gradings of osteopenia was considerable, BMD was significantly related to visually estimated osteopenia. Epseland et al[13] showed fair to excellent overall interobserver and intraobserver agreement.

These studies support our conclusion that a spinal radiograph is very useful in the diagnosis of low bone density. The usual indication for spinal x-ray is to establish a cause for back pain. If there is no evidence of fracture, low bone density is reported by the radiologist, then the patient should be referred for a DXA scan. Radiologists should be encouraged to report any loss of vertebral height more than 20% as a vertebral fracture in these patients should be treated. Our study would suggest that there is no value in attempting to differentiate between osteopenia and osteoporosis on x-ray. A radiological report of low bone density on thoraco-lumbar x-ray is a strong predictor of osteopenia and osteoporosis by bone mineral density measurement.

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Air raids and the 'Wee' Hospital

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Many members of the public are unaware that the Ulster Hospital existed before opening on its present site at Dundonald. Its history before then has been documented (Marshall 1959,[1] Logan 1987 [2]) and the reasons for moving from the centre of Belfast in 1891 to Roundhiil House, Templemore Avenue, in the east of the city. After a period in Roundhill House it was demolished and a new purpose built hospital was constructed which opened in 1912. (fig. 1) This was subsequently extended in 1937 just before the war. It was affectionately known locally as the "Wee Hospital".

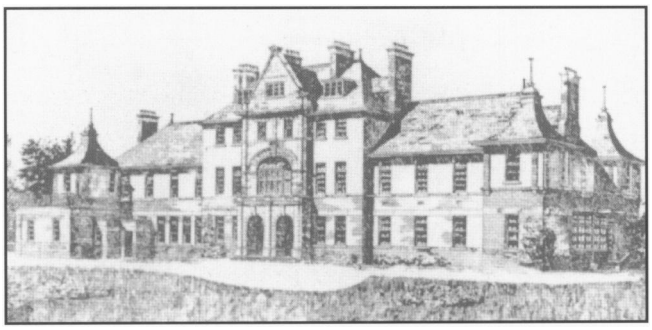

Fig 1. The Ulster Hospital for Children and Women, Templemore Avenue in 1912.

As far as is known there is only one account of the destruction of the hospital in 1941. The little booklet titled "Air Raids. A Belfast Hospital's Trinity" was published anonymously to raise money for the construction of a new hospital. However, the author was known to be Mr R J McConnell (fig. 2), a surgeon on the staff of the hospital. I am only aware of one copy of this document, which was given to me by a retired doctor who practised on the Beersbridge Road.

While relating in some detail the events of one night's bombing (April 15th-16th 1941) in a satirical and entertaining manner the book vividly describes what it was like to be in the centre of a target area of enemy bombing, and names many of the people present and how they behaved. As

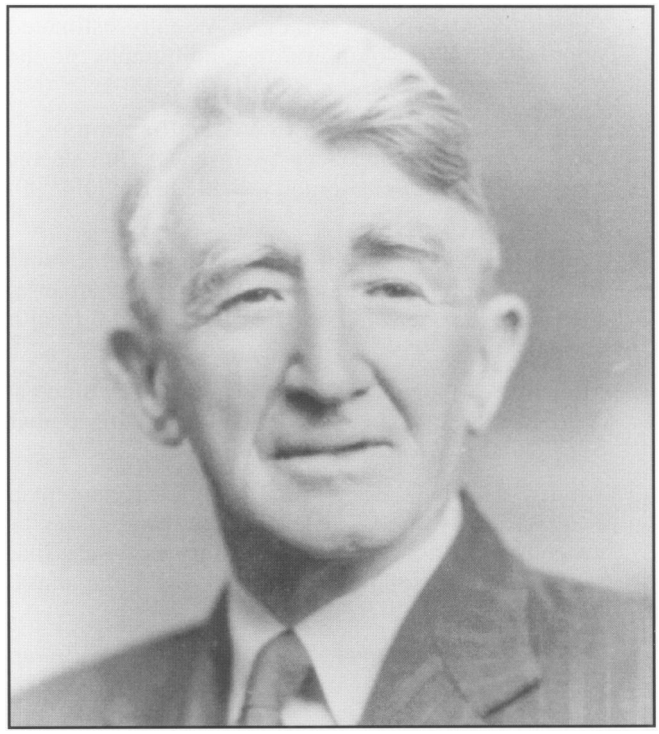

Fig 2. Mr R J McConnell

the book is twenty-six pages in length only extracts can be recorded here. (printed in italics

The evening started by Mr McConnell and four colleagues setting off from the University area by car which, near Shaftesbury Square, showed *"ominous protests from the engine [which] suggested trouble in the respiratory system, or possibly in the alimentary, just in fact, night starvation"*. After some mechanical adjustments under the light of flares and tracer bullets they were able to proceed to the hospital where, apart from those too ill to move, the patients were in the air raid shelter. It is recorded that thirty to forty children, some dangerously ill, were there together with an unrecorded number of gynaecological

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patients. (It must be remembered that most of the children less acutely ill had already been moved to Saintfield House, the home of Reverend Canon Blackwood-Price). The fire-watchers were on the roof and among these were two medical students called Neely and Kennedy. They had been at the Royal Victoria Hospital where the former told me they could get free food if they were fire-watching, but as they were resident in the Ulster Hospital they thought they should return there. They boarded a tram, the driver of which ignored traffic lights, proceeding at "forty" through the centre of the city *"with Neely's persuasive presence on the driving platform and Kennedy helping the sturdy conductor to appease the other passengers, the tram finally landed them in Mountpottinger, somewhere near the Hospital"*.

Throughout the night the extern was manned as it had been classified as an "inner casualty receiving hospital, Class 1". Soon the casualties began to arrive. *"One, a boy of about eighteen had gone out to see the shooting and suddenly a crack on the back like the kick of a horse knocked him on his mouth and nose."* He had a piece of metal buried in the muscle of his back which later in the night on its removal was found to be a German machine gun bullet. Another patient had been blown off a roof and fractured his femur which was placed in a Thomas splint after treatment for shock. Shock was common in the casualties and was treated by *"a simple routine of heat rest, sedatives and fluids... and gave excellent results. Apart from this masterly inactivity the most difficult of all forms of treatment. and the most thankless is undoubtedly indicated in the vast majority of cases."*

A man and a woman were admitted with a series of parallel cuts of varying lengths and depths. Both were filthy with their clothes torn and covered in blood. These injuries could not be explained until at operation a piece of glass was found in the bottom of each wound. It is interesting that patients were operated upon during the course of the raid. This showed the tremendous courage of the staff, most of whom stayed at their posts for the whole night. Miss Isobel Dixon, the radiographer, refused to retire after a heavy piece of concrete fell on her and she was diagnosed as having fractured ribs. It is also worth recording that many of the senior honorary staff turned up to help, leaving their homes in much safer areas of the city. While the doctors behaved bravely there were others who were prepared to exploit the raids, even in such dreadful circumstances, to make political gain from the situation as explained in the following extract. *"About this time the Mountpottinger area was being heavily bombed. We didn't like it, but it provided a glorious opportunity for those who knew all about German intentions. They told us how the raiders deliberately bombed hospitals and churches, but not Roman Catholic chapels. Hospitals with a hope of spreading epidemics: bacteriological laboratories, they said, were a special target. So authoritative were their statements that we almost felt the Aga Agar with its countless deadly billions pouring down on us. Roman Catholic chapels were spared lest Mr de Valera should be annoyed or the Roman Catholic vote in America antagonised. It was useless for us to point out that if the aim of the Luftwaffe even approached the accuracy alleged, there wouldn't be a ship-building yard in the country capable of producing a decent sized 'Robina',"*

Apart from time spent operating on and examining casualties Mr McConnell seems to have moved around the hospital. He describes at one point what this must have been like: *"On the stairs we heard the, now all too familiar, drone of Heinkels, and just as we reached the landing beside the big stained-glass window, we recognised, amid the general din of anti-aircraft guns, the initial swish of a released bomb . . . we took the remaining steps to the hall three at a time, and hurriedly crouched against the inner wall of the old telephone room. But long before we could assume a position of any comfort, the bomb struck with a thud and the crash which followed rattled, not only the Hospital, but our teeth. The explosion seemed to be quite near, indeed for a moment or two we thought it had got the extern."* It seems extraordinary that when he entered the women's ward *"a kind of singsong was in progress, and a response to the clarion call of "now then girls, altogether" would surely have softened even the rigid auricles of John Knox"*. Sister King and her nurses certainly knew how to maintain the patients' morale.

But still the casualties arrived. One amusing if sad case deserves description in the author's own words: *"One of them, a stoutish lady in the*

Mr M R Neely subsequently became a consultant obstetrician and gynaecologist in the hospital and the present gynaecological ward is named Neely in his honour

'roaring forties', was more concerned about a fur coat she had lost than about her injuries, though these were by no means trivial. Her home, along with most others in the street, had been completely wrecked, yet she begged, bullied and badgered us for permission to go back and look for her lost treasure. Lest we should be over-persuaded by this determined woman, we hurried her off to the ward. Our victory was short-lived. Half-an-hour later her bed was empty, and she had to be posted 'missing' believed treasure hunting! Shortly afterwards, she was hustled back to the Hospital by two extremely harassed looking wardens. They had, they told us, to descend almost to the level of the Gestapo to prevent her clearing the ropes which surrounded the area in which her home had once stood. Again she was comfortably bedded; again, and with all the wiliness of a fox, she silently disappeared. This time she was posted "'missing' believed untameable."

A few days later we heard that, with three friends, she had been admitted to the Royal Victoria Hospital, all four of them suffering seriously from coal gas poisoning – she was the only survivor! Eventually she came back to the 'Ulster' to have her wounds dressed and to show us the root of her persistence, and our anxiety – the fur coat! This garment may have been mink, skunk or sable, we do not know; it may have been Bond Street or North Street, we are no judges, and she did not enlighten us, but when she displayed a secret pocket cunningly hidden underneath the lining and filled with a wad of notes, we readily understood its lure. How she eluded the vigilance of the police, the wardens and the soldiers in order to search the dangerous wreckage which had once been her home, we cannot tell, but our heartfelt sympathy goes out to the unfortunate guardians of public safety who, without doubt, performed deeds of the greatest valour in their unsuccessful efforts to repress her."

The bombs continued to fall and the effects produced are recorded.

"We were in the air raid shelter when a huge bomb – audible all the way – almost completely wrecked, as we were to learn later, Westbourne Street and Tower Street. The blast from the explosion forced open the particular door of the shelter which led into Glenmore Street. Instantly, and in tones of touching hospitality, we heard Sister Wilson calmly exclaim, 'Come right in Mr Murphy, I thought I knew your knock.' To really appreciate the revival value of such a remark made at such a time, one must be able, not only to thole a split infinitive, but to have swithered in an air raid shelter swaying and rattling from its foundations, in which debris was flying about all over the place and a hurricane lamp performing extraordinary and alarming antics and from which the vivid splutterings of incendiaries on the cobbles of Glenmore Street, and the crackling roar of nearby flames could be seen and heard. Nor must we omit the preliminary five or six seconds of dread suspense already described. Few, we think, will deny the right of Sister Wilson's remark to permanent record in the annals of the Hospital."

Later there was a more serious explosion when the hospital received a direct hit which destroyed the gynaecological theatre so recently completed. *"Shaking and shuddering, crunched and cracking the whole Hospital, in fearsome chunks, thundered down on top of us, or so it seemed to everybody in the anaesthetic room."* While neither staff nor patients were injured flames were seen to rise from the region of the boiler house which was reported to be in ruins. The flames were not from the boiler house but from an ignited burst gas main in the street outside.

". . . the boiler house was in ruins and in an atmosphere of escaping gas with its threatening odour Water pouring through the ceiling sizzled as it fell on the still glowing furnaces. Great twisted pipes and heavy slabs of masonry suspended in mid air by the flimsiest looking, we know not what, made a crazy frame-work through which we could see the burning gas, and beyond it right into the intimacies of the houses on the far side of Glenmore Street."

Many casualties were expected from this street but only one came *". . . an old man, more confused than hurt. He was under the stairs, he told us, with his wee dog, when the bomb 'went off'. After that he didn't know what happened until he was pulled out of his house and brought to the Hospital. "Right enough," said the old man, "they hauled me out of me house and pushed and pulled me to the Hospital, but" and he yammered it in endless reiteration, "they have went and lost me wee dog on me. He was sitting on a chair, bent forward and clutching his head between his hands, with an elbow on each knee. Suddenly, as we talked, he stiffened, gazed fixedly*

at his feet for a moment or two and wailed, "Och doctor dear, look at what yiz have done, look at what yiz have done, yiz have stitched me feet on the wrong legs, what wull a do, what wull a do?" This tragedy was easily fixed when his boots were removed and put on the right feet. The "wee dog" was also found by a student and the old man regained his equanimity.

Whilst there were no serious injuries amongst the hospital staff there was one very lucky escape. When the hospital was struck by the bomb *". . . Dr Brennan was resting on the bed in the small ward beside the Gynae theatre, fortunately he heard it coming, and shrewdly guessing its objective, was under the bed when it arrived, not more than ten yards from where he lay. Needless to say, the structural alterations caused by the explosion were noisy, sudden and extensive, and Dr Brennan quickly recovering his wits, and with the bed still on top of him, realised that he was sliding head first into Glenmore Street, about twenty feet below"* where his shoes and stethoscope were found next day. Fortunately Dr Brennan is alive and well at the time of writing.

This however was not the final bomb of the night as it was soon realised that an incendiary had struck the roof. Attempts were made to control this with a stirrup pump as a temporary measure while awaiting professional assistance. The pump was incapable of reaching the flames and the Matron, Miss Aicken, organised a chain of people to pass buckets of water from the baths which had been filled in anticipation of such an event. While this was going on an oil bomb struck the roof and the fire became uncontrollable and evacuation of the hospital became essential. (fig. 4)

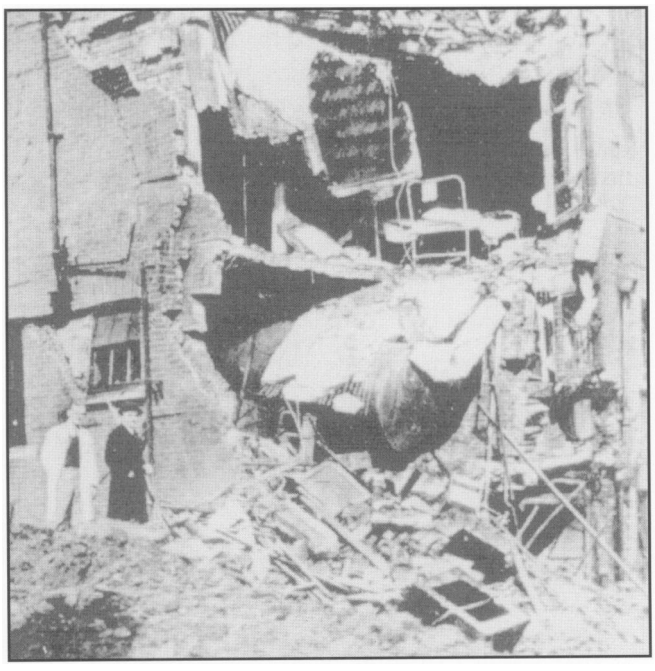

Fig 3. Dr G A Donaldson and Dr R Marshall survey the damage to the hospital. Dr Brennan's bed can be seen on the first floor.

The members of staff were then collected in groups and were taken in cars by some of the medical staff to safer areas, despite the appearance from the hospital of fires in all directions. The younger medicals remained around the hospital

Fig 4. The Hospital after the Blitz.

and while in great danger they tried to salvage as much of the valuable equipment as possible. The more senior members retreated to the Royal Victoria Hospital presumably to help deal with the casualties there.

Despite the flippant and humorous way in which this account was written the extreme bravery of all those present throughout the night cannot be underestimated. Today with films on television of bombings taking place in various parts of the world we can appreciate, from the safety of our armchairs, the danger of such action. What must it have been like for those brave members of the hospital staff to have been present on that fateful night?

The account given by McConnell in the little book records the events taking place on one night. However, Marshall (1959) chronicles some of the events as taking place on different nights. For the sake of historical accuracy an extract of his paper is included:

"During the first raid on 7-8 April 1941, the Hospital was sprayed with incendiary bombs, quickly dealt with by gallant hands. The second attack was 15-16 April, when a large bomb was dropped immediately outside the wall of the new

wing, completely destroying it . . . The Hospital, thus mutilated, maintained its function as a casualty clearing station, and members of the honorary staff continued in turn to sleep in the draughty premises at night. On 4-5 May the Germans returned, and this time dropped an oil bomb on the roof, setting fire to the Hospital and virtually destroying it. Mr R J McConnell, Mr Ian McClure, Dr Hilton Stewart, and Miss Isabel Dixon, our radiographer, were on duty on that occasion . . . It was a source of great gratification to all of us that Mr McConnell, Miss Aicken and Miss Dixon received official commendation from His Majesty for their gallantry, and, as well as these, the Committee and Medical Staff very warmly commended Dr Hilton Stewart, Mr Ian McClure and indeed all those who had been on duty during this, the most dreadful of the air-raids."

Another account of the blitz was sent to me in 1987 by a nurse then called McBryde who worked in the hospital from 1938 to 1941. (Trimble, M)[3] It is worth quoting in full. *"And then the blitz came. Every time the German planes came the hospital was hit so the children were evacuated to Saintfield and patients were kept to a minimum. The ward staff were on the alert on the night of the Big Fire. I had no patients in the hospital, the theatre and the maternity wards had been bombed on a previous night – I had no patients on the district – they had been evacuated to safer areas. I was asked to stay with half a dozen gynae patients in the basement shelter. During that long night only Mr McConnell and Mr McClure came to see us and later commented in their little book that no one envied Sister McBryde her job that night. When the mighty land mine fell near us one expected something to fall down but instead the ground gave a mighty heave and seemed to rise up. No lives were lost but a lot of the staff lost entire possessions, myself included and the dream of a lovely wardrobe of clothes hasn't even been realised."*

The hospital was obviously not in a state to continue in Templemore Avenue. A disused school at Haypark off the Ormeau Road was purchased and adapted for the gynaecological patients. The children were transferred to Saintfieid House. Ultimately the "wee hospital" was partially rebuilt and used for seeing outpatients. Later it became a general practitioner maternity unit and then a health centre.

When a city was bombed heavily during the war it was customary for a member of the Royal Family to pay a visit. In May 1941 Her Royal Highness the Duchess of Gloucester paid a visit to Belfast and the Ulster. She asked if she could become a patron of the hospital and has maintained an interest in it since. She celebrated her one hundredth birthday at Christmas 2001.

The major outcome of the bombing was the realisation of the ambitions of the Medical Staff. Hitherto the hospital had been for children and women. It was hoped that after the war the hospital would also cater for men – they wanted a general hospital. The little booklet was written to raise funds and ultimately £100,000, a huge amount then, was handed over to the Northern Ireland Hospital Authority and the Ulster Hospital was built and reopened at Dundonald.

Perhaps it puts the plight of the Ulster Hospital into perspective to relate some of the statistics of the German blitz on Belfast. The first raid on 7th-8th April 1941 was small, only six bombers being involved. It was strategically important in that the four and a half acre Harland and Wolff fuselage factory was reduced to ashes and there was also damage to the docks. On the second night (15th-16th April) nearly two hundred bombers were involved. They dropped two hundred and three metric tonnes of blast bombs and eight hundred fire bomb canisters. More than seven hundred people died and over fifteen hundred were injured. There were sixteen hundred homes destroyed and twenty-eight thousand damaged. The raid on 4th-5th May killed one hundred and fifty people and injured a similar number. The raids severely damaged fifty-six thousand houses and damaged three thousand two hundred rendering fifteen thousand citizens homeless. It was said that ten thousand people slept in the fields and ditches for several weeks (Bardon, 1982).[4]

ACKNOWLEDGEMENTS

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Trust

Annual Oration: Royal Victoria Hospital, Belfast, 3rd October 2002

D P Byrnes

Not so very long ago a solitary skier was making his rapid way down a lonely mountain when he miscalculated and launched himself over a precipice. He was falling to what he thought was certain death when he managed to grab the proverbial small bush projecting from the cliff face. He hung in abject terror for some moments and then began to call out for help. "Is anyone out there?" he cried. This he repeated several times when to his great relief a deep and authoritative voice seemed to boom from a great distance. "My son if you have trust in me, let go of the branch". There was silence for a few moments upon which the skier, in a more plaintive voice croaked "Is there anyone else out there?"

Trust in the sense of belief or reliance on others is, I submit, a complex and perhaps fragile commodity which we doctors may sometimes take for granted in our patients and their families. It is relatively easy to define in the dictionary sense but not, I believe, in the context of the doctor/patient relationship. We speak of belief in another, sincerity, compassion, honesty, competence. We also consider trust as a group of persons administering a fund or a property for the benefit of others, such as the Royal Group of Hospitals Trust. More of that later.

Human beings are naturally inclined to trust others. On frequent occasions however we have little choice in the matter. As we sit in seat 11D on an Airbus 321 about to take off, our imposed trust in the pilot is mixed with a degree of hope. We certainly have no say as to how many degrees of flap he deploys for the take-off or whether he has checked the engine exhaust gas temperatures. We cannot even see if the runway is clear. Is our patient's trust in us the childhood or the air passenger variety? Is it natural, ie. instinctive, or imposed, i.e. the patient has little choice?

Hippocrates who lived from approximately 460 to 377 BC in Greece was perhaps the first to consider and write about a doctor's duty. Essentially he wrote and presumably taught on how one should earn and maintain a patient's trust. It is interesting to speculate on why he felt it was necessary to write the eponymous oath. Could it be that he witnessed quacks and frauds in his travels around Greece and Asia Minor? He was alleged to have promulgated the simple phrase "Primum no nocere" – first do no harm. This phrase of course is in Latin and may more properly be attributed to Galen who lived in the second century AD, some five hundred years after Hippocrates. He was also born in Greece but emigrated to Ancient Rome where he entered the court of the Emperor Marcus Aurelius. His influence was far reaching right up through the Middle Ages to the Renaissance.

Galen was an interesting man. It is said that he was arrogant and unpleasant. He is reputed to have said "whoever seeks fame need only become familiar with all that I have achieved."

To make a name for himself he gave public demonstrations of his anatomical and surgical skills. One of these involved dissecting the nerves of the neck of a live pig. As these were severed, one by one the pig continued to squeal until he cut one of the laryngeal nerves when to the awe of the crowd the squealing naturally stopped. Little did they know that, with his snip Galen was disproving the Aristotelian belief that bodily control resided in the heart.

As modern medicine has evolved it has moved towards a balance – sometimes precarious – of paternalism and autonomy. Doctors can perhaps do more but patients – probably rightly – wish greater control. If a bus driver presents with a skull base meningioma I have the training, responsibility, presumably the expertise, and indeed the professional incentive to, tell him with a degree of paternalism, what I believe he needs.

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He of course has the autonomy to decline treatment or even ask for another opinion. If he accepts my management I hope and indeed expect that he will trust me to do what is best for him. "What is best for him?" There is a phrase on which we could spend a few moments. Plainly one of a doctor's duties, possibly the principle one is to endeavour to do what is best for their patient. What is that? And perhaps more importantly, who decides? If curing an illness or condition is the definition, how often is that achieved? We do not cure diabetes or a fracture, or measles. Is it prolonging life as long as possible? The celebrated man on the upper deck of the Clapham omnibus or the idealistic young medical student might say "certainly". But consider the confused, distressed, eighty-nine year old in pain with disseminated carcinoma and acute pneumonia. We could prolong life briefly perhaps with antibiotics. Is that in her best interest? Is it to control pain and distress. Veterinary surgeons have the ultimate option in that regard but not us.

Christiaan Barnard, the pioneering cardiac transplant surgeon stated "the prime goal is to alleviate suffering, not to prolong life and if your treatment does not alleviate suffering but only prolongs life, the treatment should be stopped."

That outlook does not diminish our regard for life as sacred, not just in the theological sense but in the moral, born perhaps out of self-interest. We do not want anyone to take our life, but I submit we want it to end with compassion on the part of our carers and with dignity when it becomes inevitable.

Deciding what is best for a patient is however on a day to day basis relatively straightforward. If a patient has a brain abscess, I will attempt to drain or excise it by operation and prescribe the appropriate antibiotics. If I suspect cardiac failure I will enlist the help of a physician or cardiologist to advise me or often, if the truth be told, get the Senior House Officer to sort it out. There is comfort and satisfaction out of being successful. There is even, dare I say it, a danger of certain smugness in those with experience. Of course those emotions can transmit the wrong message and even interfere with trust.

However, life – God – is a great leveller, some would say referee. Time and again one has a run of, in my case, apparent surgical success to the point where one is tempted to feel that the clinical problem has been, at last overcome only to be brought crashing down to earth with chagrin and humility by a series of setbacks whereby one can even doubt one's own ability and competence. It is then with relief the pendulum swings back again. I am convinced there are few areas of human endeavour where this happens with such intensity as in the specialty of neurosurgery, perhaps I am being a little biased.

How do we earn the trust of our patients? Do we earn it at all? In the main our patients seem to rely on what we say. This reliance is becoming less however and I assume that this change is due to a number of factors. Previous generations were aware of illness and death around them. The average young person in our society now has probably never seen a dead body let alone a dead child. In former years death was a fact of life, as it were and it seems people had a certain fatalistic outlook. It strikes me as somewhat ironic however that in days past when the doctors could do relatively little, their word probably had a greater impact and acceptance. People nowadays seem to find it difficult to accept death or chronic illness especially in the young as it is, in relative terms, rare.

The second point it seems to me is that people are more educated. They know cancer, coronary heart disease and meningitis to some extent and, more significantly, that the doctor's pronouncement is in the form of an opinion. There may be other opinions i.e. the one being offered may be wrong.

Thirdly, the public feel that they have been let down by the medical profession in recent times. One thinks of the infamous Dr Shipman, retained organs in Alder Hay Hospital in Liverpool, even in our own Province recently a general practitioner was publicly censured for his behaviour by the General Medical Council. Our patients are more likely to question our opinions and plans but not necessarily in the spirit of distrust, although sometimes that aspect if not so far away. Luckily, perhaps reasonably, because of increasing education and public awareness, they do not blame us, the NHS doctors individually, for the occasionally threadbare service although it often causes embarrassing strain between doctor and patient because a treatment even promised cannot be delivered. If I had a pound for every time a patient or relative said "we know it is not your fault doctor" I would be doing well. Perhaps on reflection I probably do have a pound for each time. On that note I quote one of my surgical

colleagues, "I used to come in each morning wondering what I was going to do for my patients, now I wonder what I am going to say to my patients!"

All in all however, we do have I believe the trust of our patients. Why is this? Are we inherently more trustworthy than people in other professions or jobs? Is this why we follow a medical career? Alternatively are we "just as other men" but constantly and consistently trying to live up to a higher standard but not always succeeding?

Would you trust a used car salesman? Many would not. Is this fair? Have you ever been cheated in a transaction? If such a person tries to sell you a car, he or increasingly nowadays, she will naturally praise its good points and gloss over the bad. If you are trading in a car do you not do exactly the same? You may not, for instance trust members of the Inland Revenue Service. I would suggest that they have very much more reason not to trust us and I include doctors in this. Others, of course, are having similar difficulties in professional life in terms of public confidence. The lawyers, I understand, especially in the United States, are having a particularly rough ride. I have heard it said that if you are a lawyer's wife or, of course a lawyer yourself as the case may be, in the state of Nebraska you had better not become pregnant as you may have difficulty finding an obstetrician.

Perhaps society itself is less trusting generally, perhaps with good reason. In former days certainly in rural areas, one could leave one's door open and one's car unlocked safe, in the knowledge that nothing would happen. Child abuse or paedophilia did not seem to occur but perhaps for "did not happen" could one use the phrase "was not reported". Even though there seems to be more crime, more abuse, more greed, it is hard to see how human nature could have changed that much in the space of fifty years. Indeed I wonder whether there is less hypocrisy than there used to be, if so then that is no bad thing.

Part of this apparent problem of lack of trust may simply be that society is more questioning. Again that is not necessarily a bad situation. I well remember in my younger days, consultant surgeons really were a law onto themselves. They answered to no one and were not questioned even by their peers. Such a man, and it always was a man in those far-off times, could and often did continue, for example, performing an operation when the procedure was plainly obsolete. That hopefully is not likely to occur now what with audit, clinical governance and the new fangled appraisal system. Having said that I secretly suspect that my younger neurosurgical colleagues worry a bit about my version of cervical discectomy!

However, the pendulum must not be allowed to swing too far whereby we as consultants lose our clinical freedom and independent decision making because I believe that they are some of the great strengths of medicine as we practice it in general and in the NHS in particular. "Political correctness" is a cruel unreasonable and sometimes sadistic task master. Witness, the rules, regulations and hoops we must jump through as members of a selection panels. Interviews nowadays, I believe, are so constricting and constrained as to be sometimes almost meaningless. We are not permitted the latitude in our questions to draw out a candidate and allow him or her to show their strengths or ability to think on their feet. That is surely not good for quality of medical practice in the future.

Most would believe trust lies in communication with the patient. This is a cliché but it is nevertheless valid. The majority of doctors know this from both happy and bitter experience. I have had patients and families who I could see did not trust me and often looking back must admit I could have done more in terms of time and explanation. I could have been less rushed. By the same token the most expensive piece of cut glass in my home is a present from the widow of a patient with malignant brain tumour for whom I could do little beyond biopsy. He died a few months later under my care. Presumably that lady trusted me as having done the best I could and that must have come from my explanations.

Recently this degree of trust for the doctor/patient relationship has taken something of a battering in this country. I have mentioned Shipman and Alder Hay. There was also the unfortunate saga of the Bristol paediatric cardiac surgery cases. I feel that the event was handled extremely badly by the medical profession.

We have long guarded our right as doctors to regulate ourselves through the General Medical Council. (GMC) Along with that right, there is of course the responsibility of performing it – the self regulation – properly. Have we in the form of the GMC done so? Speaking personally I have

always regarded the GMC as a monolithic objective impartial not to say wise body in its dealings with the medical profession the public at large and especially with the apparently dysfunctional doctor. I have been comfortable in the knowledge that should I, so to speak get in trouble, then I would have nothing to fear so long as I performed in a reasonable manner. I must say I no longer feel so secure for reasons that are not yet clear in my own mind. In the Bristol heart case one has visions of that body being intimidated by distressed, emotional relatives on the doorstep of the Council in Hallam street with small black boxes and white crosses representing the tragic childhood deaths and rumours of government instructions that there was to be no wrist slapping on this occasion. One wonders if the GMC is out of its depth overwhelmed by the number of cases being reported to it and that the flames are being fuelled by the tabloid press. Perhaps the chalice of self-regulation is a poisoned one or to mix the metaphor this treasure of self-regulation clasped close to our bosom is in fact an asp. Perhaps the time has come to share the burden.

There is nowadays a movement towards accountability and transparency. If that means that we doctors should be clear and willing to explain why and how we do things, then fair enough. If it means that every step we take can be questioned by those who will not take the trouble to learn the problems or, dare I say it, those who cannot come to terms with their own or their family's illness then no.

It has become commonplace to have lay people on medical committees as happens in the GMC. There is even the suggestion that lay people should be present, for example, in the committees of the Medical Royal Colleges. Along with our efforts to convince the public both of our honesty and difficulties, what better way than working with a group of non-medical people to help us deliberate. On the other hand, there is little point I suggest in having a greengrocer on a committee who decides on surgical SHO rotations. However, such a person might be very helpful as we struggle with European Directive on Working Hours for example. We must not be afraid to open our windows but at the same time be willing to counter, with some vigour, spurious ill-informed and sometimes spiteful criticism and accusation. Those of you who have had dealings with the Legal Department of this hospital may know that a situation pertains which I feel is ridiculous. A letter is not infrequently received from a solicitor on behalf of an ex patient alleging substandard care or even negligence. In it there are no specific complaints but the clinician involved is obliged to write a report detailing his management and refute allegations of which he is ignorant. I feel that this is an unacceptable form of pandering and should cease. Why is it that when complaints or claims come to nought do we carry on as if nothing has happened? I am reminded of a retired orthopaedic colleague addressing the Northern Ireland Medicolegal Society as President. He stated, from experience that a doctor who has ever faced a lawsuit even if successfully defended, never quite recovers from the experience. I also with experience, agree. What nonsense is it that we have to spend anxious hours retracing our steps and our charts to answer charges which are often at best the result of disgruntlement or unrealistic expectations? Of course we must be brought to task if our efforts do not reach the proper standard of "due care and attention" and it is right that our patients have a system of seeking and gaining redress if they genuinely feel that they have not received proper care. I am merely appealing for reasonable balance. Ironically the more time we must spend in these exercises of self-justification, the less time we have and the more distracted we are from helping our current patients. What is more I believe the vast majority of the public would have sympathy with this position.

How can we as doctors in as much as we have lost the trust of our patients and public, regain it? I suppose that just as the days of leaving our back doors unlocked and the keys in our cars, safe in the knowledge that nothing will happen, are gone perhaps this is a new age and our efforts to return what some would say is the age of innocence has also gone and cannot be retrieved.

I believe we can regain at least some of the lost ground if we can consistently and constructively show our patients that we are not only doing our best but also admit that we do not know everything. If we can be honest without pretence or arrogance and are willing to spend the extra five minutes explaining the situation. In all humility I must admit that on many occasions I have not practised what I preach here.

In spite of all the problems and trials – in all senses – which we as doctors must contend they shrink into insignificance compared with the

difficulties our patients and their families have to endure.

The profession we pursue is I believe hugely rewarding and fulfilling. What could possibly impart more job satisfaction than to remove completely the brain tumour of a young mother and return her intact to her anxious family?

Now let us turn to a trust of a different type. The Royal Group of Hospitals Trust. On the 1st April 1993, just under ten years ago, the Royal Group of Hospitals became a Trust. What has it meant for our beloved institution? A Trust is the holding of a property or administering a fund for the benefit of others. In a sense the Royal has been a Trust since the day it opened its doors. In the document of application for Trust status in 1991, it was stated and I quote; "we believe that the Trust status will further assist us, The Board of Clinical Directors and Senior Management, in securing the fundamental purpose of the Royal Group of Hospitals, which is to provide the highest quality, cost effective health care as an outstanding teaching centre through exceptional service to our patients, staff and community in an environment of education, training and research" I further quote from the application "we believe that the new powers and freedoms available to Trusts to manage their own affairs will achieve better and faster decision making and allow us to deliver high quality service to our patients". Another part of the application "the senior doctors, nurses and professional staff will through representation on the Trust governing body have a direct say". Trust status was granted on the 1st April 1993 almost ten years ago. Has it been a success? How is success measured? We certainly have a magnificent new building. However from my own perspective I cannot say that the hospital is in better order now than it was in 1982. Maybe had we had not been granted Trust status the situation would now be worse. Who can be sure? How do we measure this?

I am obliged to say, admittedly as a clinician, not charged with administrative responsibility or fiscal prudence that I believe there are inherent flaws in the present system. We have clinical directors of the different specialties who have been placed in the invidious position of having responsibility without adequate resources.

This system, not of course the responsibility of the Royal Trust itself or even the Northern Ireland Department of Health, is I believe politically dishonest. How can a clinical director who has to cancel operating sessions every month watch waiting lists grow longer and skilled nurses resigning, be expected to provide a clinical service appropriate to the 21st century.? I believe that this hospital is trying to do too much. It cannot I maintain be all things to all people any more than a doctor can be an expert in every specialty. I am convinced that it should play to its strengths, it should decide in some responsible representative way what jewels are in the crown and polish them at the expense of other endeavours. I concede that these thoughts emanate from a specialist who perhaps cannot see the big picture of health care provision but one can see that we are not succeeding now. We cannot be a local hospital, a district hospital, a referral hospital and the premier university hospital all at the same time. It is a wasteful morale sapping endeavour. I realise and readily admit that we doctors do not have a monopoly of regard and fondness for this great institution and in many respects the pressure on our non-medical colleagues administering it is may be even greater on occasion. I realise too that we can always trot out the phrase "clinical need" which must be galling for non-clinicians to repeatedly hear. I know that this hospital will weather these storms as it has weathered others. In spite of all the doom and pessimism this is a great, dare I say it, magnificent institution and to be part of it is a tremendous privilege. Speaking in broader terms, and this is directed to young medical students to whom the oration is traditionally addressed, there is no occupation where job satisfaction is greater in terms of emotional and intellectual reward than being a doctor, doing what you believe.

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Case Report

Hyperglycaemia, glycosuria and ketonuria may not be diabetes

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Diabetic ketoacidosis is a well recognised, important, but rare differential diagnosis of acute abdominal pain in children. We report a case highlighting the need for complete assessment of any child presenting with new-onset glycosuria, ketonuria and hyperglycaemia. Causes other than diabetes may rarely produce these findings.

CASE REPORT A girl aged three years and ten months with a six-hour history of abdominal pain and vomiting was referred to the surgical team by a general practitioner. Past medical history included a diagnosis of non-specific abdominal pain at three years old. There was no significant family history nor recent illness in the family circle.

On examination she was restless and thirsty, but apyrexic. There was no foetor or rash. She had grunting respiration with tachypnoea, but the lungs were clear on auscultation. Her abdomen was soft with mild generalised tenderness and no localised guarding or rebound in any quadrant. Urine dipstick analysis showed three pluses of ketones and three pluses of glucose. Blood glucose was 16 mmol/L on ward testing.

Further history suggested thirst earlier in the day and possibly some recent weight loss. With this history, and initial findings a paediatric medical opinion was sought regarding a diagnosis of diabetes mellitus. Laboratory blood glucose was 16.3mmol/L. Acid base balance was normal with a blood gas pH of 7.38, and base excess of -1.Blood count, electrolytes, abdominal and chest radiographs were all normal. CRP was elevated at 88.9mg/L.

On the basis of these results repeat abdominal examination was undertaken three hours after admission. At this time her temperature was 37.6C, again she had generalised abdominal tenderness, maximal in the lower abdomen now with associated guarding and rebound.

A presumptive diagnosis of acute appendicitis was made and an exploratory laparotomy undertaken through a lower mid line incision. A perforated appendix was found along with pus in the peritoneal cavity. Appendicectomy and peritoneal lavage were performed.

Postoperative recovery was uneventful, and she was discharged home on the third postoperative day. Subsequent random blood glucose was normal at 4.6mmol/L. Her HbAlc was normal while islet cell antibodies were negative. At review she was well, with no complaints or complications.

DISCUSSION

Rarely diabetic ketoacidosis may present with acute abdominal pain.[1] As this is an important diagnosis it is listed in most surgical and medical textbooks.

The absence of any acid-base disturbance, ruled out the diagnosis of diabetic ketoacidosis in this little girl. No active infection could be identified in her ears, throat, respiratory or urinary tracts, but an elevated CRP indicated the presence of an acute inflammatory process. "Active observation", an important concept in patients with abdominal pain, identified the emerging peritonism requiring surgery.[3]

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The systemic stress response is well recognised, particularly in critical care medicine. Trauma, burns or unresolved infection are all causes. This hypermetabolic state is associated with enhanced peripheral glucose uptake and utilization, increased gluconeogenesis, depressed glycogenesis, glucose intolerance and insulin resistance. Hormones such as glucagon, cortisol and epinephrine, as well as cytokines all play a role. These changes may be viewed as maintaining glucose to the wound and immune tissues.[4]

The absence of islet autoantibodies makes an immediate or future diagnosis of type 1 diabetes unlikely.[5] In the absence of any incipient diabetes, the metabolic disturbance of this child was presumably a stress response that settled rapidly when the underlying cause was treated. Hyperglycaemia to such a high level (>16.7) as a stress response, is unusual. In a study of children with burns to >60% body surface area, such high blood glucose levels occurred in less than 7% of children.[6] In the absence of any acid-base disturbance we presume our patient's ketonuria was due to starvation ketones which occur after a period of fasting.

No surgical or paediatric textbook we consulted discusses this stress response as a differential diagnosis for hyperglycaemia and glycosuria in children.[7,8] The learning point is that a child can rarely present with the triad of hyperglycaemia, glycosuria and ketonuria without a diagnosis of diabetes or diabetic ketoacidosis. Two mechanisms, are at work, namely a stress response and starvation ketones. The key factor is the absence of metabolic acidosis. In such cases the underlying cause inducing the metabolic stress response must be identified and treated.

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Case Report

Langerhans cell histiocytosis of the perianal region

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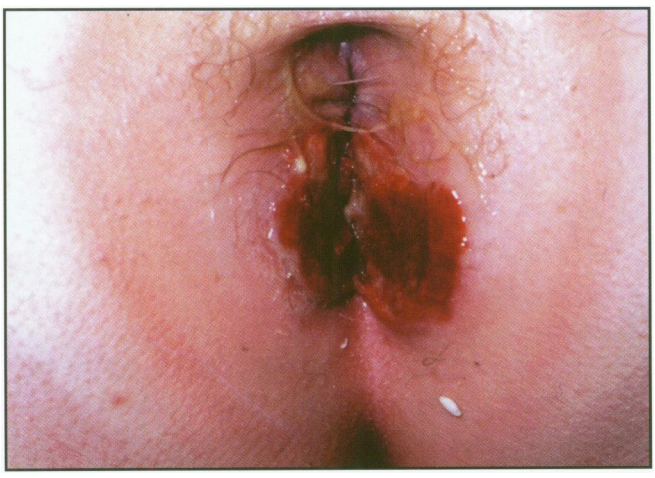
A 19 year-old male presented to the surgical outpatients with a two year history of a perianal lesion which had recently increased in size. He reported that it was only occasionally painful but his main problem was that of surface bleeding. He gave no history of trauma. However, he did report that he had had a neurosurgical procedure many years previously.

Examination showed two flat sessile lesions on each buttock in the perianal region which were granulomatous in appearance. There was evidence of surface bleeding. (figure) These findings were highly suspicious of squamous cell carcinoma of the anus. He was boarded for biopsy, which was performed without complication.

The histopathology showed ulceration of the epidermis and underlying sheets of histiocytic cells, appearances in keeping with Langerhan's cell histiocytosis or Histiocytosis X. There was no evidence of malignancy.

The lesions were subsequently excised and the wound was allowed to heal by secondary intention and did not require grafting.



Figure

When he was informed of the diagnosis, he reported that his previous neurosurgical procedure had been performed for this condition.

Examination of the archived charts confirmed this. Indeed, 11 years prior to this incident he had attended a neurosurgical unit with a two-year history of proptosis affecting the right eye. Routine neurological examination was normal except that his right eye was displaced downwards and forwards. A CT scan showed destruction of the bone in the right anterior frontal region with a soft tissue mass extending into the anterior cranial fossa, in keeping with an extra-dural mass. A right frontal craniotomy had been performed and the lesion was removed in a piecemeal fashion. It was felt at the time of the procedure that not all the lesion had been excised; however, the bony defect was repaired with titanium gauze. Two months later he underwent a course of chemotherapy, consisting of prednisolone, vincristine followed by mercaptopurine. One year later he developed diabetes insipidus. However a repeat CT scan had shown no pituitary involvement. He responded well to nasal desmopressin. A repeat CT scan six months later showed no evidence of further disease and he subsequently underwent a titanium cranioplasty to cover the bony defect. He was kept under review with no evidence of recurrence and a MRI four years later showed no evidence of recurrence of disease.

He remained well with no symptoms until his attendance at the surgical outpatients five years

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later. Since then an isotope bone scan and CT abdomen and pelvis have been normal. He remains under review.

DISCUSSION

Langerhan's cell histiocytosis (previously known as histiocytosis X) is a rare condition that generally affects children. It comprises a group of disorders that demonstrate proliferation of the Langerhan's cell derived from bone marrow.

The clinical spectrum is wide but can be generally classified according to three distinct clinical entities;

1. Sib-Letterer-Siwe disease. An acute progressive disseminated disease, which presents with fever, anaemia, organomegaly and thrombocytopenia. Death may occur due to infections or progressive anaemia.
2. Hand-Schuller-Christian disease. An intermediate clinical form *aka* multifocal eosinophilic granuloma. This often presents with the classical triad of diabetes, proptosis and bony lesions. This syndrome would indeed be attributable to the case in question.
3. Hasimoto-Pritzker disease. A congenital form of the disease that is often self-limiting.

The underlying cause is still as yet unknown. Various hypotheses have been cited as to the cause ranging from reactive processes to neoplastic processes.

The annual incidence is in the range of 5per million per year with a male: female ratio of 2:1.

The classical multifocal form, which has occurred in this patient only rarely, presents with all three of the triad of proptosis, diabetes insipidus and bony defects.

When a patient is diagnosed with Langerhan's Cell Histiocytosis, a standardised evaluation is usually undertaken; this has been developed by the Histiocyte Society. Routine blood tests should include full blood count, liver function tests and coagulation studies. Due to the possibility of diabetes insipidus a urine osmolality is mandatory, as is a chest radiograph.

More specific tests are required depending on the site of the suspected lesion.

Treatment of the condition is dependent upon the extent of the disease and upon the involved organs. Cessation of smoking is essential. Glucocorticoids have been used either topically for skin lesions or systemically for more invasive disease. Chemotherapeutic agents are indicated for multisystem disease. Trials have shown combinations of vinblastine, etoposide and prednisolone for a period of six weeks to be effective, followed by mercaptopurine, vinblastine and prednisolone for one year.

Prognosis is variable upon the type of disease encountered. Unifocal LCH generally has an excellent prognosis whereas multifocal disease has a much poorer prognosis. Letterer-Siwe disease has an even poorer prognosis and mortality can reach 50%.

Relapse is not uncommon and can occur up to 10 years after the disappearance of the original disease.

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Case Report

Thrombotic thrombocytopenic purpura associated with cerebral SLE

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A case of thrombotic thrombocytopenic purpura in a patient with a recent flare of cerebral lupus is presented. The patient presented with neurologic symptoms, pyrexia, thrombocytopenia and leucocytosis. Following initial investigation, imaging of brain and negative microbiology, a diagnosis of cerebral lupus was made and appropriately treated. After a stable period of two weeks, deterioration in clinical status, haematology and renal indices, a diagnosis of thrombotic thrombocytopenic purpura (TTP) was made and treated. The two diagnoses presenting together are briefly discussed.

CASE REPORT: A 74-year-old Caucasian lady presented with a 3-day history of headache, drowsiness, vomiting and generalised aches and pains. She had a 2-year history of systemic lupus erythematosus (SLE). Her disease was controlled on prednisolone 5mg daily, and hydroxychloroquine 200mg daily. On this regimen she had been stable for two years. She had recently been diagnosed with hypertension, and was on bendrofluazide 2.5mg daily, and atenolol 50mg daily.

On initial examination she was alert and orientated, with a temperature of 38.2°C. The blood pressure was 160/78 mmHg with no postural drop. There was no neck stiffness, photophobia, or focal signs of infection. There was no evidence of cutaneous vasculitis, mouth ulceration, or synovitis.

Investigations revealed: Hb-11.7g/dl (11.5-16.5g/dl), platelets 115x 10^9/l (150-400), WCC-19.2x10^9/l (neut-16.38), total protein-69g/L (60-80g/L), serum electrolytes and urea and creatinine were normal. The erythrocyte sedimentation rate (ESR) was 44mm/hr, C reactive protein (CRP) 87mg/l (<l5mg/L), C3 0.77g/L (0.88-2.01g/L) and C4 0.10g/L (0.16-0.47g/L). MSSU was negative. Blood cultures were negative including fungal, acid fast and viral cultures. Anticardiolipin and lupus coagulant were within normal limits. Chest X-ray was normal.

A CT scan of brain was normal, lumbar puncture revealed an elevated WCC 196/mm^3 (50% lymphocytes and 50% neutrophils), with an elevated protein count 0.99g/L (0.2-0.4g/L), glucose 1.4mmol/L (2.4-4.4mmol/L). Serum glucose was 4.9mmol/L. CSF culture was negative including acid fast fungal and viral cultures. PCR and antigen levels for meningococcus were negative.

The patient developed an absence seizure with transient right-sided weakness followed by a focal seizure progressing to a generalised tonic-clonic seizure. Glasgow Coma Scale (GCS) post seizure was 9/15. Her GCS improved; however the patient remained confused and cognitively impaired, with brisk reflexes and an extensor left plantar reflex.

Magnetic resonance imaging (MRI) of brain revealed mild to moderate degree of cerebral parenchymal loss. Wide scattered ill-defined high signal intensity was noted in the white matter, which was thought to represent gliotic ischaemic changes.

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A clinical diagnosis of cerebral lupus was made. The patient was given intravenous methylprednisolone, 1g for 3 consecutive days, then commenced on oral prednisolone daily and she received pulse cyclophosphamide 500mg intravenously weekly. There was an improvement in her cognitive impairment and clinical condition. After a stable period of two weeks, her clinical condition declined with deterioration in cognitive function. Her platelet count fell to 41 x 10^9/l and Hb to 7.4g/dl, (normal MCV and MCH). On 24 hour urine collection she had 1.13g proteinuria. Total bilirubin and lactate dehydrogenase were mildly elevated. Direct Coombs test was negative. Reticulocyte count was 3.5%. Prothrombin time and fibrinogen were normal. Blood film revealed fragmented red blood cells. Bone marrow aspirate did not detect a monoclonal T-cell or B-cell population. There were some megakaryocytes present but they were not particularly plentiful. Some histiocytes were also present. On peripheral blood analysis there was no evidence of platelet associated immunoglobulin detected by flow cytometry.

In view of the fragmented red cells, clinical deterioration and renal involvement a diagnosis of thrombotic thrombocytopenic purpura (TTP) was made. Plasmapheresis was instituted. The patient responded rapidly after three therapies with an increase in platelet count, improvement in renal function and cognition.

DISCUSSION

Systemic lupus erythematosus is a chronic often life-long, autoimmune disorder associated with multi-organ involvement. CNS lupus is one of the four most common causes of death in SLE (7-13%,[1] the other three being infection, cardiac involvement and lupus nephritis. The diagnosis of cerebral lupus can be very difficult. In the setting of a lupus patient with pyrexia, a raised white cell count, and immunosuppressed, it is vital to exclude infection. Fever occurs in 90% of patients with active SLE. Cerebral lupus can present with either diffuse or focal signs. In diffuse disease symptoms and/or signs such as intractable headaches, seizures, aseptic meningitis, psychiatric disease and coma may occur. In focal disease, manifestations include focal seizures, stroke syndromes, and movement disorders and transverse myelitis. There may be signs of active lupus disease elsewhere such as alopecia, vasculitic rash, mouth ulceration or arthritis. When the disease is active there can be immunologic abnormalities: marked inflammatory response; low levels of serum complement; and elevation of anti-nuclear antibodies. Risk factors for the development of CNS disease in a lupus patient are not clearly defined. One study by Karassa *et al*[1] tried to define these risks. In the study the most frequent neuropsychiatric SLE (NPSLE) syndromes were cerebrovascular disease (28%), seizures (25%), acute confusional states (19%), and psychosis (9%). 3-8% of patients presented with a combination of two or more symptoms. It was suggested that vasculitis, thrombocytopenia and anti-phospholipid syndrome features correlated with CNS involvement. It was negatively associated with articular features and discoid rash. Normal levels of dsDNA were also seen in active CNS disease, but anti La antibodies as well as low level of complements especially C4 were seemingly strongly associated with NPSLE. TTP has rarely been seen in association with SLE, but is recognised in the literature and the two disease processes were first described together in 1939. The ability to diagnose TTP as a separate process, in the setting of SLE is challenging, as TTP has no specific diagnostic test and also because TTP shares, in common with SLE, clinical signs and features such as fever, renal abnormalities, neurological deficit, thrombocytopenia, and haemolytic anaemia.

The pathogenesis of the two disease processes is different. Microangiopathic haemolytic anaemia is rarely seen in SLE, and only if the disease is very active, with severe vasculitis. On the other hand, the serological abnormalities seen in SLE are not seen in TTP.[2] Thrombocytopenia and haemolytic anaemia in TTP is therefore usually due to a microangiopathic process, whereas in SLE it is usually due to an immune mediated process.[3]

TTP has been associated with SLE in three distinct populations.[4] These are TTP presenting subsequent (group 1), preceding (group 2), or concomitantly (group 3) to SLE. The most common presentation with SLE is with group 1 and the least common with group 3. TTP can also be associated with SLE whether it is active or inactive.[4]

The incidence of TTP and SLE remains unknown. In 1994 it was reported by Bray *et al* to be as low as 0.5 %.[5] Caramaschi *et al* in 1998[3] quoted a

frequency of 2-3%. The large autopsy report by Petz *et al* in 1977 reported a 5% incidence of TTP in SLE patients.

The development of TTP associated with SLE suggests that the two processes have features in common. In both diseases, direct endothelial injury by autoantibodies, platelet abnormalities, and disorders of fibrinolysis can occur. Yet the fact that TTP can develop in quiescent or active SLE suggests that the two are separate processes.

Treatment strategies for TTP were dramatically improved with the introduction of plasma exchange. Indeed it has been suggested that survival of the patient correlates with the rapidity of diagnosis, and the use of plasma exchange rather than actual disease activity.[2,4] Since plasma exchange is considered the treatment of choice for TTP and is thought to be of some benefit in vasculitis, delay in its usage until a definitive diagnosis is reached may increase morbidity and mortality.[5] This case highlights the difficulty in treating SLE patients. It emphasises the importance of early diagnosis of TTP in a SLE patient in order to combine plasma exchange and immunosuppressant therapy, which undoubtedly improves outcome.

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Case Report

Multiple primary neoplasms developing in a case of prostate cancer

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Carcinoma of prostate is the second most common cause of cancer death in men in the UK. It is known that patients with carcinoma of prostate are at significant risk of developing a second primary neoplasm.[1] These second primary are mainly colorectal, stomach or urinary bladder. The histopathology of gastrointestinal tumours is usually adenocarcinoma. We report a case of prostate cancer that developed an unusual combination of atrial myxoma, small bowel carcinoid, basal cell cancer on shoulder skin, rectosigmoid adenocarcinoma and caecal adenoma over a period of five years.

CASE REPORT A 73 years old man presented with significant bladder outlet obstruction in 1996. On clinical examination he had a smooth enlarged prostate. The postate specific antigen (PSA) was elevated at 38.5ng/1. Transurethral resection of prostate was performed; 21gm of this was resected. The histopathology report was adenocarcinoma of prostate (Gleason score 3, in 90% of resected tissue). The staging CT scan was normal, and bone scan revealed a suspicious area of increased uptake near the right femoral metaphysis. The patient was started on hormonal treatment in the form of Goserelin injections. The serum PSA level returned to normal within 1 year and has remained within the normal range for 5 years. A bone scan repeated after 3 years was also normal.

In June 2000 the patient underwent an emergency left brachial embolectomy. Histology showed only blood clot. Subsequent 2D echocardiography confirmed the presence of a lesion with features of atrial myxoma almost filling the entire right atrium. After discussion with the patient, conservative treatment of the myxoma was decided upon and anticoagulation therapy was started.

In March 2001 the patient presented with vomiting and abdominal distension. X-ray showed features consistent with small bowel obstruction. An exploratory laprotomy was carried out. A small bowel tumour was identified with extensive mesenteric lymphadenopathy and was resected. Histopathology confirmed small bowel carcinoid. All the mesenteric lymph nodes were negative for metastases.

In July 2001 the patient presented with bleeding per rectum. Colonoscopy showed a rectosigmoid pedunculated polyp more than 2 centimetres and moderate divericular disease of the sigmoid colon. The rectosigmoid polyp was snared and excised and was confirmed to be an adenoma with a focus of adenocarcinoma.

In 2001 a 1cm lesion on the left shoulder was biopsied and found to be a basal cell cancer. It was treated with flurouracil cream and colistin sulphate and polymyxin B sulphate cream.

On routine follow-up colonoscopy in November 2001, a flat growth in the rectum was found along with a large polypoid lesion in the caccum and a small polyp in the transverse colon. The histopathology confirmed the presence of a rectal adenocarcinoma and a tubulovillous adenoma of the caecurn with no dysplasia.

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The patient was also on medications for hypertension and gout.

DISCUSSION

This patient developed multiple primary neoplasms of prostate, small bowel, heart, rectum, caecum and skin. The pathology was as varied as adenocarcinoma, myxoma, basal cell carcinoma and carcinoid.

The patient gave no family history of any disease or malignancy. His only risk factor was heavy smoking, which he had stopped 5-6 years before his first diagnosis. Apart from the lesion seen on bone scan (which was not apparent on subsequent bone scan) there was no other evidence of metastasis from any of the primary neoplasia.

The clinical picture in this case does not fit into any described multisystem genetic syndromes like Carney or Gorlin syndrome where more than one malignant tumour occurs.

The interval between the first two primary neoplasms detected was 4 years. The subsequent intervals were 2 years, 6 months, and 3 months. This is keeping with other reported cases. For reasons unknown, the mean interval between diagnosis of first two primaries is always greater than the subsequent neoplasms detected.[2]

Multiple primary neoplasms in a single individual is a known clinical entity. It is not yet fully understood but it is blamed on chromosomal instability, genetic predisposition, and environmental risk factors.

11q13 is a homogenously mutated gene in the majority of MEN 1 tumours, whereas BRCA1 and BRCA2 mutations might be associated with increased susceptibility for developing more than one neoplasm in cancer of breast or ovary. This suggests that a single mutation can bring about malignant change in more than one organ.[9, 10]

A patient with heritable cancer syndromes often develops multiple primary cancer (MPCs) suggesting hereditary predisposition.

Out of 50,000 cancer cases recorded at National Cancer Center Japan, 2000 had MPCs. This frequency is rising in Japan probably due to exposure to carcinogens.[3] Thus environmental factors, carcinogens, genetic predisposition, mutations, and even heredity and familial syndromes are thought to play a role in developing MPCs.

It has been noted that patients with carcinoma of prostate are at a significant risk of developing second malignancy (as high as 15.2% in a Japanese study).[2, 5] Stomach, urinary bladder, colon and lungs are the commonly involved organs.[8] It has also been reported (as seen in this case report) that overall survival of patients with prostate cancer was not significantly reduced by the association of MPCs,[2, 4] and chances of developing MPCs increase with the tumour grade,[5] and the fact that a patient already has a malignancy makes him prone for MPCs.[6]

CONCLUSION

Patients with cancer prostate are at high risk of developing multiple primary neoplasms. The mechanism however is not fully understood. The mean interval between detection of second primary neoplasm after carcinoma of prostate is usually longer than subsequent detection of neoplasms. Multiple primary cancers however do not seem to significantly affect the overall survival of patients with prostate cancer.

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Case Report

Richter's syndrome: a novel presentation

E F Smyth, R J V Bartlett, M L Shields, T J White, C Wengraf

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Chronic lymphocytic leukaemia with transformation into a large cell lymphoma (Richter's syndrome) is usually associated with the rapid demise of these already immunocompromised patients. There have been no previously recorded cases involving the nose. We report such a case and describe a successful treatment approach combining monoclonal antibody therapy with a mini-allogeneic bone marrow transplant.

CASE REPORT A 54-year-old man presented to the otolaryngology department with a swelling on the dorsum of the nose, which had been rapidly enlarging for one month. Two years prior to this he was diagnosed with chronic lymphocytic leukaemia (CLL) and was stabilised initially with six courses of Chlorambucil. He relapsed one year later and bone marrow assessment following further treatment with six courses of Fludarabine showed only a partial response. One year further on he presented with the nose swelling. He had no symptoms suggestive of systemic involvement. On examination there was a 2 x 2.5cm soft mass on the dorsum of the nose continuous with a blue swelling obstructing the left nostril. The remainder of his physical examination was unremarkable. An axial CT scan (fig. 1) of his paranasal sinuses demonstrated a soft tissue mass, closely related to the left side of the anterior nasal septum, 2cm in diameter. Bowing of the nasal septum, as seen in the coronal reconstructions (fig 2) suggested the mass had been present for some time while the co-existing opacification of the left frontal air cell is a feature of sinus outflow obstruction.

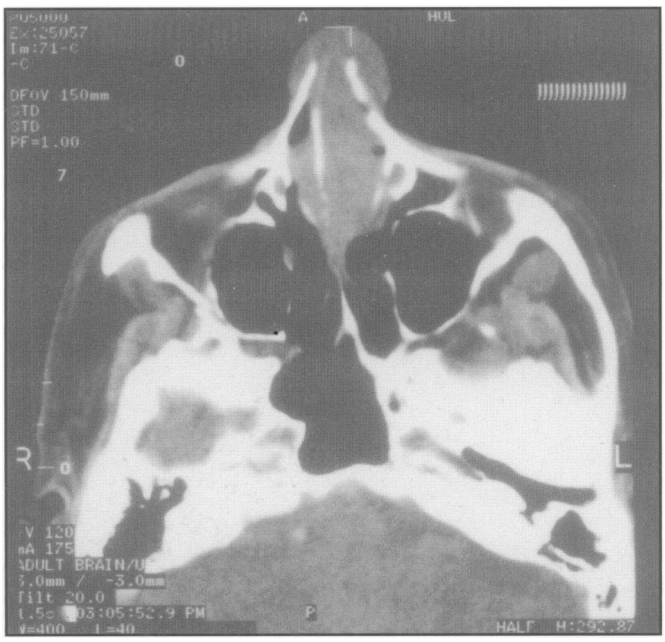

Fig. 1

An intranasal incisional biopsy confirmed a high-grade large cell transformation of the CLL - Richter's Syndrome.[1] He was treated with a six cycle chemotherapy regime of Cyclophosphamide, Hydroxorubicin, Vincristine and Prednisolone (CHOP) commencing two months after the swelling presented. It resolved and follow-up MRI scan at six months was normal.

The patient was subsequently treated with a further course of Fludarabine and the monoclonal antibody, CAMPATH-1H, before receiving a mini-allogeneic bone marrow transplant from his

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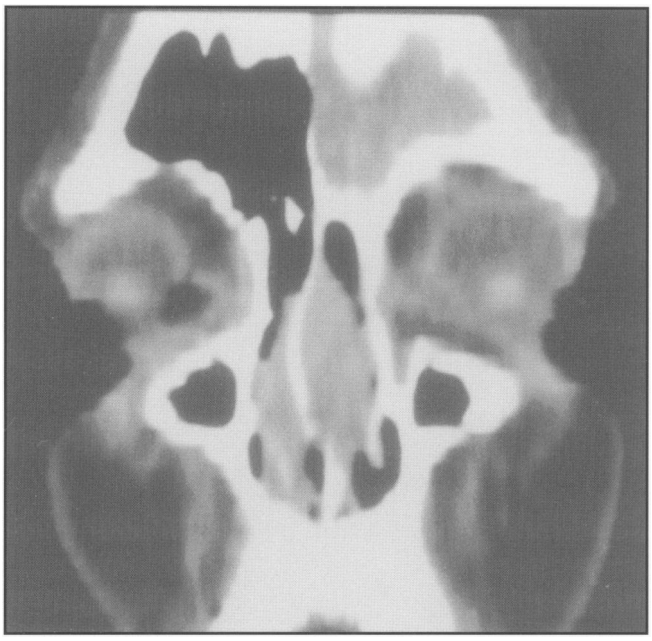

Fig. 2

brother one year from presentation. A PCR-based assay showed that complete haemotopoietic chimaerism was achieved after the transplant, however, he also had low-grade graft versus host disease.

Presently, three and half years from initial presentation, he has a normal quality of life in continuing complete remission from both the transformed disease and the CLL.

DISCUSSION

Richter's syndrome refers to the development of aggressive non-Hodgkins Lymphoma during the course of chronic lymphocytic leukaemia. Affecting 5% of these patients, it represents one of the possible anaplastic transformations of the leukaemia.[2] Disease onset is typically manifested by a sudden clinical deterioration of the patient and is characterised by rapid progression of lymphadenopathy, by extranodal disease and by constitutional symptoms. Histological examination is required to make the diagnosis of high-grade lymphoma. Immunophenotyping of the cells taken from the tissue biopsy and from a bone marrow aspirate expressed the same cell surface Kappa light chains suggesting clonal evolution rather than new disease.[3]

Robertson *et al* report a modest 5-month median survival despite multiagent therapy.[4] There is some evidence that patients may do quite well after high dose chemotherapy with stem cell support. Rodriguez *et al* have published data suggesting an improved prognosis in a series of patients receiving high dose chemotherapy followed by allogeneic bone marrow transplantation.[5]

Despite resolution of the nasal lesion following the CHOP regime the patient also underwent a bone marrow transplant and treatment with monoclonal antibody in order to provide him with the best chance of achieving complete remission. A high-dose conditioning regime is normally used prior to bone marrow transplantation. However, previous treatment with chemotherapy precluded mobilisation of autologous peripheral blood stem cells needed to compensate for the bone marrow suppression, which normally occurs following such a regime. He was therefore treated with a reduced dose of Fludarabine and CAMPATH-1H, a monoclonal antibody against CD52, an antigen expressed on greater than 95% of all normal human blood lymphocytes and most B and T cell lymphomas.[6;7] In the first report of the antibody, tumour regression was seen in two patients with advanced non-Hodgkin's lymphoma treated with CAMPATH-1H.[8] It is currently recommended for the treatment of patients with Fludarabine refractory CLL and preliminary data suggest it is effective as a first line agent in the treatment of B-cell CLL.[9;10] By activating various immune effector functions, including antibody-dependent cellular cytotoxicity, the antibody not only targets tumour cells, it temporarily destroys the recipient's T-cells. The resultant complete donor chimaerism may reduce the risk of transplant rejection and confer a survival advantage.[11] The "mini" from mini-allogeneic transplant refers to the reduced dose of chemotherapy used.

To the best of our knowledge there have been no previously reported cases affecting the nose to date. A handful of cases have been described with skin involvement, however, it is rarely limited to cutaneous locations.[12]

It is our aim to highlight not only this novel presentation but also the encouraging result obtained from new treatment techniques with monoclonal antibody and the reduced intensity conditioning chemotherapy regime.

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Case Report

Post-operative hyperkalaemic paralysis

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Tetraparesis is more often a clinical feature of profound hypokalaemia [1, 2] than hyperkalaemia. Neurological features of hyperkalaemia are rarely seen in clinical practice, as they are precluded by cardiotoxic complications such as arrhythmias. However, patients may develop flaccid paralysis of skeletal muscle with areflexia mimicking symptoms of acute inflammatory demyelinating polyneuropathy.[3] Severe hyperkalaemic paralysis has previously been reported secondary to nonsteroidal anti-inflammatory drugs [4] spironolactone,[5] and a combination of chronic renal failure and ACE inhibitors.[6] We report a case of post-operative secondary hyperkalaemic paralysis presenting with neurological symptoms 18 days after an anterior resection (with diverting loop ileostomy) for a rectosigmoid colonic adenocarcinoma.

CASE REPORT A 57-year-old man was referred to the colorectal clinic with symptoms of change in bowel habit, colicky central abdominal pain and weight loss. He had a history of maturity onset diabetes mellitus, hypertension and peripheral vascular disease having previously had a right femoral angioplasty. Medication consisted of metformin, gliclazide, amlodipine, atorvastatin, aspirin and lisinopril combined with a thiazide diuretic. A double contrast barium enema and flexible sigmoidoscopy revealed a polypoid lesion at the rectosigmoid junction. Histology of representative biopsies confirmed endoscopic suspicion of an adenocarcinoma. He underwent a technically difficult anterior resection with formation of a defunctioning loop ileostomy. Histopathology reported a Dukes' Cl (PT3 N1 Mx) rectal adenocarcinoma, which extended to within 1mm of the circumferential margin. Apart from poor post-operative glycaemic control necessitating an increased dose of metformin, he made a relatively uneventful recovery and was discharged home on the twelfth post-operative day, confident with ileostomy management. The electrolytes were normal at the time of discharge.

After 48 hours he developed increased ileostomy effluent output followed by symptoms of anorexia, nausea then vomiting. By the following day he was feeling generally tired and weak. He continued to deteriorate over the next 48 hours, and became bedbound. There were however no bulbar or respiratory symptoms.

On readmission clinical examination revealed that he was afebrile but markedly dehydrated and weak, hypotensive (75/50 mmHg) with a heart rate of 60 beats/min and respiratory rate of 14 breaths/min. Capillary blood glucose was 18 mmol/L. Abdominal and respiratory examination were unremarkable. Glasgow coma scale was 15/15, there was no facial asymmetry and other cranial nerves were unaffected. Neurological examination of the limbs revealed profound weakness of all four limbs, particularly distally (MRC grade 1-2/5). He was areflexic and generally flaccid. There was no sensory deficit and plantar responses were bilaterally flexor. The differential diagnosis was wide (Table).

Blood results at the time of admission revealed a serum potassium of 8.8mmol/L (confirmed on repeat sample), urea 45.8mmol/L, creatinine

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TABLE
Differential diagnosis

Acute inflammatory demyelinating polyneuropathy (AIDP)
Metabolic neuropathy/myopathy
Carcinomatous neuropathy/myopathy
Lambert-Eaton myasthenic asyndrome
Critical illness neuropathy/myopathy

644umol/L and a compensated metabolic acidosis (base excess -9.5). An electrocardiogram showed T wave 'tenting' consistent with hyperkalaemia. Calcium gluconate was administered intravenously with oral calcium resonium subsequently. Two consecutive infusions of 50% dextrose and insulin were administered with normal saline rehydration resulting in resolution of the acidosis and improvement in the electrolytes. Within hours of treatment neurological symptoms resolved and muscle power returned. Urea and creatinine fell to normal levels over course of one week. He was discharged 9 days after readmission and has remained well.

DISCUSSION

Hyperkalaemic paralysis can be primary or secondary. Patients with primary episodic or hereditary hyperkalaemic periodic paralysis have a genetically determined defect in the sodium channels of muscle fibre membranes (channelopathy).[7] Typically the clinical onset is in the first decade of life with attacks of flaccid paralysis lasting from a few minutes to several hours, at intervals of hours to days. Attacks are usually induced by the ingestion of potassium and by rest after exercise. Affected individuals may exhibit the ability to "walk off' an attack and can be successfully treated by thiazide diuretics, acetazolamide and salbutamol.

Secondary hyperkalaemic paralysis occurs later in life and is caused by a partial defect in the sodium channels of muscle fibre membranes, however the precise mechanism is unknown. The potassium may have either a direct effect on the muscle cell membrane or possibly disturb the peripheral nerves supplying the muscle.[7] It usually occurs in elderly patients with underlying chronic renal impairment, but can be precipitated by drugs[4,5,6] or trauma.[8] Flaccid paralysis with areflexia (initially affecting the legs and progressing to the arms) with preservation of sensation and cranial nerve function are signs common to both hyperkalaemic paralysis and acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome). Paralysis can be so severe and progressive as to involve respiratory muscles necessitating artificial ventilation.[9] This also has implications for the anaesthetist's choice of muscle relaxant prior to intubation. A depolarising agent such as suxamethonium may further increase serum potassium precipitating a fatal arrhythmia.

The largest cohort of cases of secondary hyperkalaemic paralysis in the literature suggests that the clinical presentation and subsequent clinical course in our patient is typical of this condition. Of the 18 cases described by Evers *et al*,[15] presented with tetraparesis/tetraplegia and three with paraparesis. Paralysis typically began distally with an ascending course and although significant sensory signs were not found, sensory symptoms were reported in five cases. The mean serum potassium concentration at presentation was 9.0 mmol/L, two-thirds of cases had chronic renal impairment and 10/18 cases were precipitated by potassium-sparing diuretics. The generally favourable prognosis of the condition is emphasised by 15/18 patients making a good recovery within hours to days, although the potentially serious consequences are also highlighted by the two deaths due to cardiac arrest.[10] Our patient had a major colorectal operation 18 days before becoming paralysed. An ACE inhibitor in combination with increased ileostomy output leading to dehydration caused progressive renal impairment, leading to hyperkalaemia and secondary paralysis. Progressive weakness and physical inability to drink exacerbated the dehydration.

The prognosis for secondary hyperkalaemic paralysis is good if recognised and treated. Clinicians should be aware of this possible complication in post-operative patients with electrolyte disturbance secondary to increased stoma effluent.

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Book Reviews

Menopause in Practice. Catrina Bain, Mary Ann Lumsden, Naveed Sattar, Ian A Greer. £14.95. ISBN 1-85315-516-0. Published November 2002. The Royal Society of Medicine Press Limited.

This is an attractively presented slim volume aimed at primary care. The information is detailed and adequately referenced, yet easy to read and well laid out.

Hormone replacement therapy has been the subject of adverse publicity in recent years and the publication puts much of this in perspective, dealing with the benefits of HRT and problems for the prescriber. The chapter dealing with preparations and routes of administration is especially helpful and it also deals with selective Oestrogen receptor medications and alternative therapies.

Apart from extolling the virtues of HRT in the prevention and treatment of osteoporosis, there are useful separate chapters dealing with the problems of HRT and various thrombo-embolism and cancer, giving practical advice throughout.

Overall this makes a useful, easily readable reference book for practitioner's regularly HRT and although it seems somewhat expensive at £14.95 I would recommend that every health centre should keep one available for quick answers to prescribing problems.

JOHN H PRICE

The Ulster at Dundonald. C. J. H. Logan. Available from The Ulster Hospital shop and Easons, Newtownards.

The Ulster Hospital dates back to 1872 and the history of its earlier period has been described in publications by Dr Robert Marshall and Miss K. N. M. Kelly. The building in Templemore Avenue was almost totally destroyed by German bombing in 1941. This volume therefore sets out to describe the hospital history on its new site when rebuilt after World War II.

The author Mr Hume Logan has worked for his entire consultant career at the Ulster Hospital (since 1962) and is therefore well placed to cover the modern period. However he has also researched as far as records allow the decisions regarding fund rising, site for rebuilding and scope of the hospital. Progress must have seemed interminable to those keenly interested for nothing had been decided by 1948, when the new Northern Ireland Hospital Authority was established. Then there was severe shortage of funds in its early years and the foundation stone was not laid until 1957.

The account of these preliminary years makes fascinating, if depressing, reading but the perseverance of the Management Committee chaired by Lady MacDermott, and the medical staff prevailed in the end. Analysis of the later developments is equally valuable, particularly the establishment of undergraduate teaching of obstetrics and gynaecology and postgraduate teaching. Then came gradual amalgamation with the Ards Hospital the opening of a laboratory, of an Intensive Care Unit and a Diabetic Unit. Altogether the author has been able to present a detailed but readable picture balancing the important medical develop such as the Laser' Clinic, with the interest of Rosemond Praeger's sculpture and visits by such figures as Diana, Princess of Wales, and Frank Carr.

It is clear that the Casualty (Accident and Emergency) Department was inadequate from the outset. Even before "the troubles" there were complaints of overcrowding and although expansion took place chronic underfunding (in relation to the expanding population of North Down) meant the it was always "too little and too late". The development of other services such as Coronary Care, Geriatrics and Plastic Surgery have, perhaps had fewer problems and the book presents a picture of a dedicated and hard-working staff battling to overcome the chronic bed shortages and inadequate building programme.

Altogether it is a valuable account of the post-war development of one of the teaching and specialist hospitals of Belfast but it is clear that the planners had never recognised its needs until forced to do so by a near crisis.

The book is attractively produced and illustrated but it must be said that its historical value would have been enhanced by an index.

R S J CLARKE

Medicine and Art. Alan E H Emery and Marcia L H Emery. The Royal Society of Medicine Press Limited. ISBN 1-85315-501-2. £40. Published November 2002. www.rsmpress.co.uk

This book is timely – the renaissance in the place of the arts and humanities in medicine over the last twenty years or so had been remarkable and has reminded us that there is more to healing than the tablet and the knife. Here we have a collection of fifty three plates reproducing paintings of medical scenes from the 13th century (Hippocrates Medicating a Patient, an illustration from De regime acutorum) to the 22nd (an embroidery by Louise Riley reproduced from the cover of the Lancet). Each is accompanied by an entertaining but scholarly miniessay describing the picture and the artist and relating both to the history and period of the picture.

As a start this book would be an invaluable introduction to the history of medicine for students. It reminds us that until the late 18th century the only accepted methods of clinical assessment were feeling the pulse (Physician Taking a Patient's Pulse in a Persian garden – 17th century – from the cover of Avicenna's Canon of Medicine) and examining the urine (The Village Doctor by David Teniers the Younger – c 1650). The text of the latter picture draws our attention to the discovery of Thomas Wills about this time that a sweet taste in the urine was pathognomonic of diabetes but also that many of the itinerant uroscopists were charlatans. This particular (and remarkably colourful) aspect of medicine is well represented by The Doctor Robert Macaire by Honoré Daumier (1836) and The Quack Doctor by Geritt Dou (1652). William Hogarth was particularly critical of the 18th century charlatans and his picture The Inspection, from the Marriage á la Mode series (1743) is described in entertaining detail. The birth of modern investigatory medicine in the 19th Century was accompanied by the invention of a number of diagnostic tools including the ophthalmoscope (Charles

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Altogether it is a valuable account of the post-war development of one of the teaching and specialist hospitals of Belfast but it is clear that the planners had never recognised its needs until forced to do so by a near crisis.

The book is attractively produced and illustrated but it must be said that its historical value would have been enhanced by an index.

R S J CLARKE

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This book is timely – the renaissance in the place of the arts and humanities in medicine over the last twenty years or so had been remarkable and has reminded us that there is more to healing than the tablet and the knife. Here we have a collection of fifty three plates reproducing paintings of medical scenes from the 13th century (Hippocrates Medicating a Patient, an illustration from De regime acutorum) to the 22nd (an embroidery by Louise Riley reproduced from the cover of the Lancet). Each is accompanied by an entertaining but scholarly miniessay describing the picture and the artist and relating both to the history and period of the picture.

As a start this book would be an invaluable introduction to the history of medicine for students. It reminds us that until the late 18th century the only accepted methods of clinical assessment were feeling the pulse (Physician Taking a Patient's Pulse in a Persian garden – 17th century – from the cover of Avicenna's Canon of Medicine) and examining the urine (The Village Doctor by David Teniers the Younger – c 1650). The text of the latter picture draws our attention to the discovery of Thomas Wills about this time that a sweet taste in the urine was pathognomonic of diabetes but also that many of the itinerant uroscopists were charlatans. This particular (and remarkably colourful) aspect of medicine is well represented by The Doctor Robert Macaire by Honoré Daumier (1836) and The Quack Doctor by Geritt Dou (1652). William Hogarth was particularly critical of the 18th century charlatans and his picture The Inspection, from the Marriage á la Mode series (1743) is described in entertaining detail. The birth of modern investigatory medicine in the 19th Century was accompanied by the invention of a number of diagnostic tools including the ophthalmoscope (Charles

The Ulster Medical Journal, Volume 72, No. 1, pp. 64-66, May 2003

Book Reviews

Menopause in Practice. Catrina Bain, Mary Ann Lumsden, Naveed Sattar, Ian A Greer. £14.95. ISBN 1-85315-516-0. Published November 2002. The Royal Society of Medicine Press Limited.

This is an attractively presented slim volume aimed at primary care. The information is detailed and adequately referenced, yet easy to read and well laid out.

Hormone replacement therapy has been the subject of adverse publicity in recent years and the publication puts much of this in perspective, dealing with the benefits of HRT and problems for the prescriber. The chapter dealing with preparations and routes of administration is especially helpful and it also deals with selective Oestrogen receptor medications and alternative therapies.

Apart from extolling the virtues of HRT in the prevention and treatment of osteoporosis, there are useful separate chapters dealing with the problems of HRT and various thrombo-embolism and cancer, giving practical advice throughout.

Overall this makes a useful, easily readable reference book for practitioner's regularly HRT and although it seems somewhat expensive at £14.95 I would recommend that every health centre should keep one available for quick answers to prescribing problems.

JOHN H PRICE

The Ulster at Dundonald. C. J. H. Logan. Available from The Ulster Hospital shop and Easons, Newtownards.

The Ulster Hospital dates back to 1872 and the history of its earlier period has been described in publications by Dr Robert Marshall and Miss K. N. M. Kelly. The building in Templemore Avenue was almost totally destroyed by German bombing in 1941. This volume therefore sets out to describe the hospital history on its new site when rebuilt after World War II.

The author Mr Hume Logan has worked for his entire consultant career at the Ulster Hospital (since 1962) and is therefore well placed to cover the modern period. However he has also researched as far as records allow the decisions regarding fund rising, site for rebuilding and scope of the hospital. Progress must have seemed interminable to those keenly interested for nothing had been decided by 1948, when the new Northern Ireland Hospital Authority was established. Then there was severe shortage of funds in its early years and the foundation stone was not laid until 1957.

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Reviews of medical literature are extremely useful to practising doctors, as they often contain large amounts of relevant information in a small space. An unfortunate premise of this book is that an expert's (non-systematic) review of his or her area of expertise is somehow unreliable or dangerous. As evidence based theory becomes widely accepted such mistrust is largely misplaced. Nonetheless, there is a place for structured, systematic reviews of medical literature to answer important clinical questions. This book is a helpful summary of how to judge someone else's review and how to conduct your own.

The authors, who are clearly enthusiastic about systematic reviews, take the uninitiated through the systematic review process in a step-by-step manner. The book is concise and illustrates the main points from published studies. They also cite important references, many of which are available for free from websites, or can be accessed electronically from local medical libraries.

Overall, the book is not easy to read, but it is intended as a how-to-do-it manual rather than information to remember and recall. A great weakness of evidence-based texts is their focus on therapeutic interventions, and the lack of detail on reviewing studies of diagnostic tests, prognosis or aetiology. The authors admit this weakness, and try to balance things out with an illustrated example on reviewing literature on diagnostic tests.

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