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The Ulster Medical Journal, Volume 71, No. 2,pp 96-97 November 2002.

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The Ulster Medical Journal, Volume 71, No. 2, pp. 98-100, November 2002.

Editorial

The changing face of research ethics

The oriental curse "may you live in interesting times" can surely apply to the medical profession, who have had over the last decade to absorb myriad changes in their professional lives. The changing circumstances of research ethics are no different and over the next 18 months there will be a transition from the voluntary self-regulation that has characterised medical research in the United Kingdom (UK) to regulation by statute. The new regulatory processes are a consequence of several forces;

- A new protocol on Biomedical Research, that has evolved from the ideals and aspirations of the European Convention on Human Rights, is to be incorporated into United Kingdom law by May 2004. Protection of the rights, safety and well being of research participants is the basis of this directive with participant autonomy being a dominant theme.

- Societal change in the UK also supports the paramount right of self-determination (autonomy) of patients and other research participants. The argument that patients, as beneficiaries of previous research, should have a responsibility to participate in research, holds little sway today.

- The establishments of Trusts as legal entities in the early 1990's imposed responsibilities on Chief Executives for the well-being of their patients and this included responsibility for research participants.

- The medical profession has been subjected to increased regulation in the form of revalidation and other aspects of clinical governance. A logical extension of these processes is "Research Governance" which is already in place in England, Scotland and Wales and will be introduced into Northern Ireland within 18 months.

- The Human Organs Enquiry highlighted a lack of regulations or guidelines concerning the use of post-mortem materials and waste human tissues (including blood) for research purposes.

A brief overview of the research ethics process in Northern Ireland may help to put these future changes into context. The Research Ethics Committee (REC) at Queen's University Belfast is an independent committee of the Faculty of Medicine and Health Sciences and has been in existence from 1971. My understanding is that this REC was one of the first to be established within the United Kingdom. The purpose of a Research Ethics Committee in reviewing a proposed study is to protect the dignity, rights, safety and well-being of research participants. However RECs also take into account the interests, needs and safety of researchers who are trying to undertake good research. Furthermore, RECs do not regulate research.

The medical profession, with little interest or financial support from the Department of Health established RECs throughout the UK. Despite this disinterest, for almost three decades RECs throughout the UK, have applied national and international ethical criteria as appropriate (The Nuremburg Code, the Declarations of Helsinki of the World Medical Association, the Royal College of Physicians, the Association of the British Pharmaceutical Industry, the Royal College of Psychiatrists, the Medical Research Council).

The process of formalising the role of RECs started in 1991 with the issuing of guidance (HSG [9]15) – the 'Red Book' - by the Department of Health but there was still no legal requirement for a researcher to submit a proposal to any REC and no support, either administrative or financial, for the functioning of RECs. In the last two years the Department of Health has established a Central Office for Research Ethics (COREC) that is co-ordinating the changes required to comply with

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the European Protocol on Biomedical Research. The changes will be profound and include;

- Research Ethics Committees will become legal entities but remain independent within the Department of Health.
- Common guidelines have been developed by COREC to regulate the composition and functions of all RECs. The remit of RECs has been significantly expanded to include all research involving human participants within the NHS whether they are patients, relatives of patients or NHS staff, research on the recently dead, human tissues or research using NHS premises or data. All research involving the above categories must be submitted to a recognised REC for approval. All research taking place within the NHS additionally requires the approval of the host NHS organisation – these are absolute requirements. To proceed without these will constitute research misconduct.
- A Standardised NHS application form, for all RECs and researchers, is to be introduced in October 2002 with full compliance in its use required by May 2003. This form is comprised of four parts; Parts A & B deal with the details of the research application and ethical issues. Part C deals with "Locality" issues pertaining to Multi-Centre approved trials and Part D addresses research management issues relating to approval, support and indemnity from host NHS trusts.
- A National Register of research studies and researchers is to be developed.
- The Department of Health will be required to fully resource the REC's to allow them to fully comply with the new stringent guidelines.

As already stated, RECs do not regulate research; they give an opinion on research proposals brought to the committee. Furthermore RECs at present are not required to monitor the research process, merely advise. Research Governance is concerned with standard setting (ethical, scientific quality), defining mechanisms of delivery of such standards, describing monitoring and assessment arrangements. While we still await the completed Additional Protocol on Biomedical Research from the European Union, the most recent draft does not deal with post mortem material and this is an interesting oversight. However one must recognise that the various international guidelines have assumed that human research participants were alive! Furthermore "ownership" of postmortem material is confounded by the status of the deceased in that once deceased, a person no longer legally exists and therefore (the deceased or family) cannot have property rights over post mortem material.

Following concerns raised by the Human Organs Inquiry, COREC have specifically included research using human tissues (e.g. blood, bone, skin, organs) of past or present patients and the recently dead, within the remit of Research Ethics Committees. While it is entirely appropriate that this category should be submitted to the Research Ethics Committee it will cause great difficulties for many laboratories who use surplus tissues, following diagnostic testing, for standard setting and the development of new analytical tests. A generic consent form, that will allow patients to donate surplus tissues, is urgently required.

What should researchers, who wish to continue their studies, do?

- Applications must be submitted by established Principle Investigators (PI). From October 2002, PIs should apply to the Research Ethics Committee, QUB using the Standard NHS application form (Parts A & B) that can be obtained from the COREC website. As an electronic format is unavailable at present submissions should be made in paper format.
- In parallel to the ethical submission PIs will be required to submit their proposals to the research management process within their employing Trust. Each Trust that wishes to support research is required to have established a research management process that deals with host indemnity, approval and support. (COREC advises that, to minimise delays, ethical review and the research management process should proceed in parallel.)
- It is the Principal Investigator's responsibility to ensure that the design, conduct and reporting of the study conforms to the new standards.

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In conclusion, the research ethics process is in a period of rapid transition from voluntary self-regulation to regulation through legislation. It is hoped that the new regulations will improve research quality and safeguards for the public. The significant increase in bureaucracy will necessitate the development of several fully resourced RECs in Northern Ireland that will apply the new regulations while minimising administrative delays. For RECs, researchers and trust research management offices the next 18 months will indeed be "interesting times"

Dr Terry McMurray, MD, MA(Ethics & Law), MEd, Chairman, Research Ethics Committee, Queen's University Belfast.

Useful links:

Central Office for Research Ethics
http://www.corec.org.uk

Convention on Human Rights and Biomedicine.
http://conventions.coe.int.Treaty/en/Html/l 64.htm

Use of human organs and tissues.
http://www.doh.gov.uk/orgretentionadvice/index.htm

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Anti-tumour necrosis factor therapy for severe inflammatory arthritis:

Two years of experience in Northern Ireland

A P Cairns, A J Taggart

Accepted 26 June 2002

SUMMARY

Etanercept and infliximab are novel biological agents targeted against tumour necrosis factor alpha (TNFα), a key cytokine in the pathogenesis of rheumatoid arthritis (RA). We report the results of their use over a two year period in 94 patients with severe inflammatory arthritis. Eighty-eight adults with active inflammatory arthritis (82 with RA), unresponsive to all conventional treatment, received biological therapy in one of five specialist centres in Northern Ireland. 69 adult patients (78%) had a good response to treatment, four a partial response, and seven no response. The results of treatment could not be assessed in eight patients because they had only recently commenced therapy. Four patients had a mild allergic reaction to treatment but one patient developed fulminant lung fibrosis which may have been due to drug therapy and eventually proved fatal. There were four cases of major infection requiring hospitalisation. Two patients responded to treatment, but one succumbed to bacterial pneumonia, and another to bacterial meningitis. Six children with juvenile idiopathic arthritis (JIA) received etanercept. Four achieved a good response, one a partial response, and one no response to treatment. This study shows that the impressive response to anti-TNF therapies extends beyond the realm of clinical trials to everyday clinical practice. These agents represent a major advance in the treatment of severe inflammatory arthritis but they should be used with caution, particularly in the elderly and in patients who are predisposed to infection.

INTRODUCTION

RA is a common disease (prevalence 0.5-1%),[1] with a tendency for ongoing inflammation, which may lead to progressive joint destruction, functional impairment and handicap. Spontaneous remissions are rare and it is now known that significant joint damage can occur within the first two years of disease onset.[2,3] Modern management strategies stress the importance of early diagnosis and treatment with disease modifying anti-rheumatic drugs (DMARDs), particularly methotrexate, which is now the "gold standard" by which other therapies are judged.[4] Despite this, a significant number of patients (around 10%) fail to respond to conventional DMARDs, either alone or in combination. Their disease follows a relentless downhill course with persistent joint inflammation and damage. RA of this severity carries a significant mortality[5] which is compounded by the need for regular corticosteroid therapy in order to achieve some quality of life.

The cytokine, TNFα, is produced by activated macrophages, and has a central role in the pathogenesis of RA with elevated TNFα levels found in affected Joints.[6] It is also implicated in a number of other inflammatory diseases including

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ankylosing spondylitis, psoriatic arthritis, juvenile idiopathic arthritis, Behcet's and Crohn's disease. Infliximab and etanercept are the first of a new class of targeted modifiers of biological response to TNFα which have been licensed for use against intractable rheumatoid arthritis. Infliximab (*Remicade*) is a chimeric monoclonal antibody whilst Etanercept (*Enbrel*) is a soluble TNF receptor antagonist. Both drugs act to reduce the effective levels of intra-articular TNFα. Infliximab is administered by intravenous infusion every 6-8 weeks and is given concurrently with methotrexate (or azathioprine) to reduce the risk of allergic reaction to the chimeric protein. Etanercept is self-administered subcutaneously twice a week. Both drugs have been shown to be extremely effective in controlling active rheumatoid disease and retarding the progression of joint damage when compared with methotrexate,[7-9] and etanercept has also been shown to be effective in treating resistant JIA.[10]

The British Society for Rheumatology (BSR) has produced guidelines for the administration of these drugs in the UK.[11] To be considered for these therapies patients must have active RA as defined by the Disease Assessment Score (DAS) [12] – a validated composite score consisting of weighted swollen and tender joint counts, ESR, and patient functional visual analogue scale. They must also have failed on at least two conventional DMARDS (including full doses of methotrexate if tolerated). Contraindications to treatment include active infection, malignancy within the past 10 years, multiple sclerosis, severe heart failure, an indwelling catheter and chronic leg ulcers. There has been a trend towards the earlier use of these drugs, particularly in the USA, and increasing evidence suggests that they are effective in other inflammatory arthritides such as ankylosing spondylitis and psoriatic arthritis.[13, 14]

METHODS

Detailed records were kept of all patients receiving anti-TNF therapy (infliximab or etanercept) for inflammatory arthritis in Northern Ireland between November 1999 and October 2001. Response to treatment was assessed after three months as defined by BSR Guidelines for patients with peripheral joint disease (DAS score improved by > 1.2, or total DAS reduced to <3.2). Response in ankylosing spondylitis patients was assessed using ESR, CRP and BASDAI (Bath Ankylosing Spondylitis Disease Activity Index).[15] Patients were monitored at regular intervals throughout the study period for signs of adverse drug reaction or intercurrent illness.

RESULTS

88 adults (mean age 51 years, range 23-78; 65 female, 23 male) with inflammatory arthritis received treatment in five specialist centres. All had established, severe, active disease, unresponsive to multiple conventional therapies. 66 patients were treated in Musgrave Park Hospital, nine in Altnagelvin Area Hospital, five in Craigavon Area Hospital, five in Antrim Area Hospital, and three in the Ulster Hospital, Dundonald (fig. 1). 82 patients had RA, four ankylosing spondylitis, one psoriatic arthritis, and one persistent juvenile arthritis. 52 patients

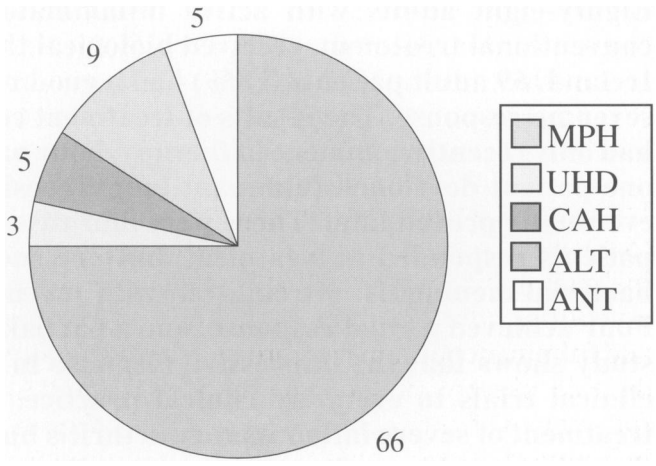

Fig 1. Adult treatment numbers by location (n=88; MPH=Musgrave Park Hospital, UHD=Ulster Hospital Dundonald, CAH=Craigavon Area Hospital, ALT=Altnagelvin Area Hospital, ANT=Antrim Area Hospital).

received infliximab (59%), and 36 etanercept (41%). 47 of the patients (53%) were taking concomitant oral corticosteroids. Six children (mean age 14, range 8-18, three male, three female) with JIA received etanercept, all in Musgrave Park Hospital.

63 of 82 (76%) patients with RA achieved a good response to treatment. Four (5%) had a partial response (i.e. met DAS response criteria but required intermittent intramuscular or intravenous steroid therapy) and seven (9%) did not respond. Eight patients (10%) had not been on treatment long enough (3 months) to be assessed (fig. 2). Both patients with psoriatic arthritis and persistent juvenile arthritis achieved a good response

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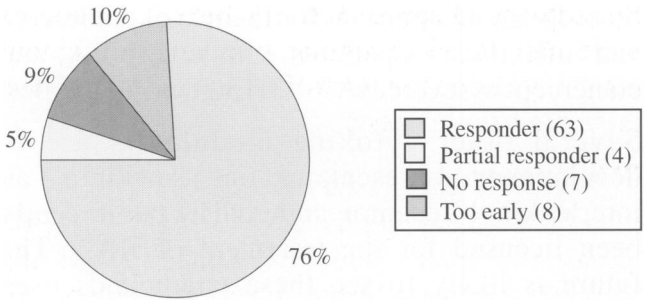

Fig 2. Response to anti-TNF therapies in adults with rheumatoid arthritis (n=82).

according to DAS scores and all patients with ankylosing spondylitis achieved a good response according to ESR, CRP and BASDAI scores. Overall, 78% of adults achieved a good response, 5% a partial response and 8% no response. 9% of patients could not be assessed because they had only recently commenced treatment. There was a trend towards higher response rates for infliximab and methotrexate (n=52, 42 (80%) responders) compared with etanercept monotherapy (n=36, 27 (75%) responders) in all adults.

In the adult group, four minor allergic reactions (5%) were reported. A fifth patient, receiving infliximab (with methotrexate), developed acute alveolitis, adult respiratory distress syndrome and fulminant pulmonary fibrosis. She eventually died despite treatment in an intensive care unit for seven weeks. There were four cases of major infection (5%), requiring hospital admission. One patient, on infliximab (with azathioprine, not on oral steroids), developed miliary tuberculosis. This was isolated from sputum and urine after 12 weeks of treatment.

Pre-treatment chest X-Ray had been normal, and there was no prior history or family history of tuberculosis. A second, on etanercept, developed probable septic arthritis in three joints, although an organism was not isolated as antibiotics had been given prior to joint aspiration. Both patients responded to appropriate antibiotic therapy. A third patient, on etanercept, developed a middle ear infection, which rapidly progressed to pneumococcal meningitis with brain abscess, and died after a protracted illness. A fourth patient, also on etanercept, developed a severe lobar pneumonia and died after a short illness. The mean age of patients with major infections was 65 years (range 53-76). 18 (20%) minor infections were recorded, during which biological treatment was temporarily discontinued.

Treatment was withdrawn in 18 of 88 adult patients (22%). The reasons for withdrawal were adverse events (nine patients), non-response (five patients), other (unrelated) illness (two patients), and other reasons (two patients) – one attempting to conceive, one concerned about potential adverse effects.

Six children with JIA received etanercept. Four achieved a good response to treatment, one a partial response and one no response. Treatment was temporarily withdrawn in the partial responder because of an episode of gastroenteritis.

DISCUSSION

In this cohort of 94 patients, at least 78% of adults and 67% of children with inflammatory arthritis achieved a good response to anti-TNF therapy as defined by BSR response criteria. Although the scoring systems used in Europe (DAS score) and North America (American College of Rheumatology (ACR) response criteria) differ slightly, these results compare favourably with large scale published trials where 42% to 59% of established RA patients receiving infliximab (with methotrexate) achieved an ACR 20 response (20% improvement in disease activity), and 72% of early rheumatoid arthritis patients receiving etanercept achieved an ACR 20 response after 12 months of treatment.[7-9] This confirms that the efficacy of anti-TNF therapies extends beyond trial conditions to everyday clinical practice. This was further emphasised by the fact that many of our patients were able to reduce or stop their oral corticosteroids. These drugs therefore represent a major advance in the treatment of inflammatory arthritis.

Both drugs were generally well tolerated with 80% of adults and 75% of children remaining on treatment at the end of the study period. This compares favourably with conventional DMARD therapies. Infections were common, with minor infection seen in one fifth of patients receiving these drugs. Serious infections occurred in 5% of our patients. Although this group of patients is prone to infectious complications by nature of their inflammatory condition, and use of DMARDS and corticosteroids,[5] it remains to be seen whether this serious infection rate is higher than would be seen in a group with similar characteristics, but not receiving anti-TNF therapy. Data from trial conditions would suggest that serious infection rates are similar in established RA patients receiving methotrexate

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alone (8%), compared with those receiving methotrexate with infliximab (6%).[8] A major trial comparing etanercept alone with methotrexate alone in early RA found no difference in the rate of serious infections between the groups (both less than 3%).[9] The slightly lower serious infection rate in this study may be partly attributable to the fact that these patients had early, rather than established, rheumatoid disease. The BSR is compiling a registry on the use of anti-TNF drugs with control groups not receiving either drug, which should allow a more formal assessment of the relative risk of infectious disease attributable to anti-TNF therapy in clinical practice.[11]

In our study the average age of patients who developed serious infection was greater than in the cohort as a whole (65 versus 51 years) and this has led to even greater caution in the use of these drugs in older patients, particularly those with multiple co-morbidities. Serious infections occurred with both etanercept and infliximab, and seemed to progress rapidly. All patients receiving potent immunosuppressives should be educated about symptoms that might suggest infection and should be encouraged to report such symptoms to their doctor immediately and, in the case of etanercept, stop administering the drug until advice is received. All of our patients are instructed about the risks of sepsis before they start biological therapy and each is given an information card (similar to the well-known steroid card) to carry in the event of an emergency. This is particularly pertinent for patients self-administering etanercept, where we have noticed that a number of patients seem reluctant to stop temporarily their injections in the presence of minor infection, because of a worry about the loss of clinical effect.

The use of these drugs has significant resource implications. Each drug costs approximately £8000 per patient per year, and treatment must be continued long-term if it is to remain effective. The additional demands on medical and nursing staff must also be considered. Patient selection, drug administration and ongoing safety monitoring are all costly but essential parts of a biological treatment programme. Nevertheless, the benefits of these new therapies are such that these costs can be fully justified in terms of the potential prevention of long-term joint damage and disability. It is not surprising therefore, that the National Institute of Clinical Excellence has recently given approval for the use of etanercept and infliximab in patients with severe RA, and etanercept in severe JIA[16, 17] in England and Wales.

Several other cytokine modulators are in development at present, and one (Anakinra – an interleukin 1 receptor antagonist) has recently been licensed for the treatment of RA.[18] The future is likely to see these compounds used much earlier in the course of the disease and in various combinations. The ACR now recommends considering the use of biological agents if there is ongoing rheumatoid disease activity after three months of full dose methotrexate therapy.[19] Combinations of biological agents which work at different points in the inflammatory cascade may ultimately make the induction of disease remission a realistic prospect.

In conclusion, our experience in Northern Ireland over a two year period has confirmed that the anti-TNF therapies, etanercept and infliximab, represent a significant advance in the treatment of severe RA and JIA. They are also of benefit in other inflammatory arthritides such as psoriatic arthritis and ankylosing spondylitis. Adverse events in this cohort were not uncommon, and there were a number of serious infections in our patients (5%). These sometimes occurred rapidly and with little warning. We therefore recommend that these drugs be administered only in specialist centres to carefully selected patients. Our experience confirms the need for careful ongoing safety monitoring of these patients.

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Management of symptomatic liver cysts

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SUMMARY

Non-parasitic liver cysts are seen in up to 5% of the population. They become symptomatic when they are large and can cause pain, nausea, vomiting, early satiety and obstructive jaundice. Treatment modalities include percutaneous drainage, open deroofing, hepatic resection and lately, laparoscopic deroofing. We assessed our management of eleven symptomatic patients over the last five years between May 1996 and August 2001. Two of these had mild symptoms and were kept under review. The remaining nine were treated surgically. Of these, eight were treated by laparotomy and open deroofing with argon laser coagulation of the cut edges while one was treated with left hepatic resection. Three of these had been previously treated with laparoscopic deroofing at other hospitals and had been referred after having developed recurrent symptomatic cysts. Two patients developed post-operative complications - bile leakage that resolved with conservative management. The patients were followed up for a median period of twelve months ranging from 3-62 months. One patient died of liver failure 12 months after surgery. There was no symptomatic recurrence. We conclude that open cyst deroofing gives marked symptomatic relief with a very low complication rate. In today's era of laparoscopic surgery, it has a definite role in the management of symptomatic liver cysts, more so in recurrent cysts following laparoscopic treatment.

INTRODUCTION

Non-parasitic liver cysts are seen in up to 5% of the population.[1] These usually tend to be asymptomatic. When the whole liver is involved, Polycystic Liver Disease (PCLD) is presumed to exist.[2] Large cysts may cause symptoms, predominantly pain. Nausea, vomiting, obstructive jaundice and early satiety may be caused by the pressure effects of large cysts.[3] Different treatment modalities have been used. They include percutaneous drainage, open deroofing, laparoscopic deroofing and hepatic resection. This study assesses our management of symptomatic liver cysts over the last five years.

METHODS

Between May 1996 and August 2001, nine patients underwent surgery for histologically proven non-parasitic cysts of the liver. Two patients with mild symptoms have not been operated on and have been kept under review. Patients were identified from the hepatobiliary database and records were reviewed for clinical presentation, preoperative investigations, surgery and follow-up. CT scanning was performed in all patients to determine the extent of the disease and to help exclude parasitic cysts. Of the nine patients who underwent surgical treatment eight were treated by laparotomy and open deroofing while one was treated by left hepatic resection for extensive involvement of the left lobe by a large multilocular cyst. The major aim of surgery was to remove as much of the cyst wall as possible to prevent recurrence. A CUSA (Cavitron Ultra Sonic Aspirator) was used for liver resection. Three patients underwent synchronous cholecystectomy for coexistent gallstones.

RESULTS

Eleven patients with symptomatic cysts (9 women, 2 men) with a median age of 55 years (age range 49-81 yrs) were identified from the records. The

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TABLE

Demography, clinical features, procedure and outcome

Patient No.	*Age Year/Sex*	*Presenting Symptoms*	*Previous Treatment*	*Procedure*	*Follow-up/ Results*
1	80/F	Pain, Nausea	Nil	Open cyst deroofing	3 months Symptom free
2	55/F	Pain	Nil	Open cyst deroofing	60 months Symptom free
3	49.5/F	Pain, Nausea	Nil	Open cyst deroofing+ Cholecyste-ctomy	47 months Symptom free
4	81/m	Pain	P.C.Aspiration, Laparoscopic deroofing	Open deroofing	22 months Symptom free
5	53/F	Pain, Nausea & vomiting	Laparoscopic deroofing	Open cyst deroofing	62 months Symptom free
6	78/F	Abdominal distension	PC. Aspiration, Laparoscopic deroofing	Open cyst deroofing+ Cholecyste-ctomy	10 months Symptom free
7	61/F	Pain, Abdominal distension	Nil	Left hepatic resection	62 months Symptom free
8	49/F	Pain	Nil	Open deroofing+ Cholecyste-ctomy	10 months Symptom free
9	51/F	Abdominal wall/ vein distension+ leg oedema due to IVC obstruction	Nil	Open cyst deroofing	12 months Died of liver failure
10	54/F	Mild Pain	Nil	Conservative Management	8 months
11	69/F	Mild Pain	Nil	Conservative Management	11 months

(P.C.: Per Cutaneous)

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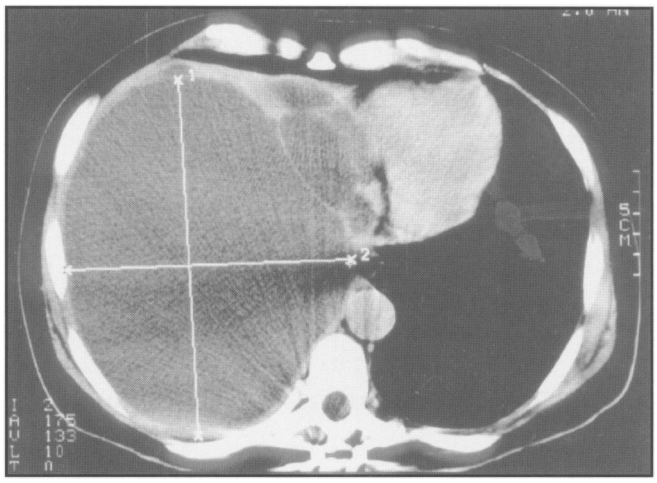

Fig 1. CT scan demonstrating multiple liver cysts in a patient with PCLD and one very large cyst. Surgical deroofing/cyst excision in such a patient achieves a very significant reduction on the mass effect and good symptom relief.

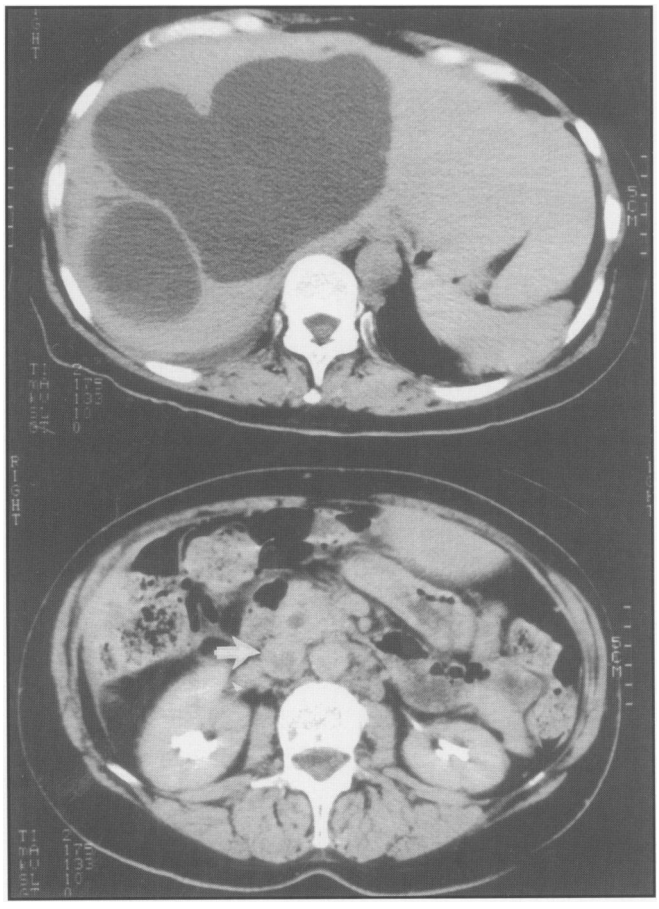

Fig 2. A large, centrally located cyst with vena caval compression and caval thrombosis.

main presenting complaints were pain (82%), abdominal distension (27.2%), nausea and/or vomiting (36.3%) (Table). Liver function tests were abnormal in 20% of patients. One patient with PCLD presented following a road traffic accident. She sustained a spinal fracture but also developed a large haemorrhage into a liver cyst (Fig. 1). One patient with a very large cyst involving the right lobe and segment IV of the left lobe developed a thrombosis in the inferior vena cava (Fig. 2). One patient had polycystic liver disease and two had polycystic disease of both the liver and the kidneys. One patient with PCLD and mild symptoms has been treated conservatively. Of the nine patients treated surgically, two had undergone previous repeated aspirations followed by laparoscopic deroofing and one patient had undergone laparoscopic deroofing alone. These procedures had been carried out at other hospitals and all three patients developed recurrent symptomatic cysts. Two patients had a postoperative complication – bile leakage that resolved with conservative management.

Patients have been followed up for a median period of twelve months ranging from 3 - 62 months. One patient with polycystic liver disease (PCLD) was admitted twelve months after surgery with jaundice and deteriorating general health and died of liver failure. There has been no symptomatic recurrence of cysts in the other patients.

DISCUSSION

Simple liver cysts are thought to arise as a congenital aberration of bile duct development. The dominant cyst is usually accompanied by several smaller cysts.[1] When however, the whole liver is involved, PCLD is presumed to exist, which has a close association with polycystic disease of the kidneys.[2]

Liver cysts are normally asymptomatic and are usually detected incidentally during abdominal imaging.[1] Symptoms appear to be due to pressure effects with pain as the predominant feature. The stomach or duodenum may be compressed by the enlarged liver giving rise to nausea, vomiting and early satiety.[3]

It has been observed that symptomatic liver cysts occur ten times more commonly in women, usually at age 50-60 years with pain as the predominant symptom.[1] Our experience was similar with symptoms occurring more commonly in women (4:1) with an age range of 50-60 years and with pain as the predominant symptom. Most symptomatic liver cysts are benign but carcinoma arising in the wall of a cyst has been reported.[4]

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Different treatment modalities have been used. Percutaneous aspiration appears to be a simple option. It is, however, associated with a high recurrence rate.[5] Percutaneous aspiration with introduction of sclerosing agents has shown good ressults.[6-7] Larssen *et al* injected alcohol in ten patients. There was reaccumulation of fluid in eight patients and this resolved over the next few months with no need for further alcohol sclerotherapy.[6] The rate of symptomatic recurrence seems to be definitely reduced after percutaneous sclerotherapy.[8]

The technique of open cyst deroofing or fenestration was first described by Lin *et al* in 1968.[9] It has been recommended by several groups and has been applied successfully for simple liver cysts.[10, 11] We have found it to be particularly successful when there are only one or several large cysts and a significant reduction in the 'mass' effect of the cysts can be achieved. For multiple smaller cysts (eg, 2-5 cms) as occurs usually in PCLD, deroofing/fenestration is not as effective, as the fibrous architecture of the liver and cysts remains intact and a significant reduction of the volume cannot be achieved. For these patients, resection is perhaps more appropriate.

More radical approaches like hepatic resection have been advocated for treatment of large cysts. It has been shown that hepatic resection is safe and effective and that symptomatic relief is complete and permanent except in cases of diffuse polycystic disease of the liver.[12] Total cystectomy and liver transplantation have been advocated in PCLD.[13, 14]

Laparoscopic deroofing of the liver cysts was first described in 1991.[15] It has been advocated as the treatment of choice.[16] Studies indicate that laparoscopic deroofing results in permanent cure in the majority of cases.[17] Zacherl *et al* operated on eleven patients and only one developed recurrence.[17] Klingler *et al* have reviewed the studies on laparoscopic treatment of liver cysts and pointed out that most studies have not quoted a recurrence rate.[18] They advocate that recurrence should be made the end point and have cautioned that the general application of the minimally invasive technique should await a thorough evaluation of the operative complications and outcome in terms of cyst recurrence.[18] Certainly, in our series, one third of the patients who required surgery had a previously failed laparoscopic procedure.

In conclusion, in view of the above findings, with no recurrence, marked symptomatic improvement and minimal complications after open deroofing, we conclude that open deroofing of liver cysts has a definite role in the management of patients with symptomatic liver cysts in this era of laparoscopic surgery and more so in the treatment of recurrent cysts after laparoscopic treatment.

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Treating Ulster's rural poor:

The County Infirmaries of Armagh and Down 1766-1851

G M Beale

SUMMARY

This paper considers the role of county infirmaries in providing health care for the inhabitants of two counties in south-east Ulster. It traces the establishment and management of these institutions from their beginnings shortly after the passing of the Infirmaries Act (1765) to the middle of the nineteenth century. From the available evidence, the accommodation, staff, patient numbers and diet of the infirmaries are considered and an assessment of their efficacy in offering a valuable service to their communities is discussed.

INTRODUCTION

In Ireland, until the 1760s hospital care was limited to the cities, and during the years when voluntary hospitals were growing in number in these centres of population, rural areas experienced total lack of provision. However, in 1765 an Act was passed to encourage the setting up of county infirmaries, thus providing the opportunity for those in more rural districts to benefit from some treatment and care.[1]

This Act made provision for the establishment of one infirmary for the relief of the sick and diseased poor in each county in Ireland. In 23 counties the Act directed that the hospital should be built in or near the county towns without any reference to the convenience or indeed inconvenience of such locations to the majority of the population – in effect many of these places were situated at the extreme end of the county. In seven counties a site remote from the assizes town was specified and the counties of Dublin and Waterford were completely omitted, probably because there were already hospitals in each.

The Primate, the Lord Chancellor, the bishop of the diocese and the rector of the parish in which the infirmary was directed to be built, together with donors of 20 guineas and annual subscribers of three guineas, were to form a corporation for the building and management of the establishments. Funds to construct and maintain these were to be the responsibility of the Grand Juries which were empowered to make presentments of up to £100.

To be admitted to the infirmary, prospective patients were required to be residents of the county and they also had to be in possession of a ticket which could be obtained from members of the corporation or from the surgeon himself. In theory, therefore, those meeting the criteria, could present themselves for admission at the infirmary. However, in practice, tenants, labourers and servants who worked on the estates and farms of members of the corporation received tickets whilst tenants and other dependants of non-members did not.[2]

The expediency of making provision for the sick poor was considered by the landlords and gentry of counties Armagh and Down within one and two years respectively of the passing of the Act relating to county infirmaries (1765).

THE ARMAGH COUNTY INFIRMARY

Under the terms of the Act, the Armagh County Infirmary was established in 1766 in Abbey Street to cater for the needs of the sick of the whole county. Before its establishment the inhabitants of the city had erected and maintained, by private contributions, a hospital called the 'Charitable Infirmary' which was located in Scotch Street and 'which they liberally assigned over to lord primate and governors of the new establishment and it was used until the erection of the present edifice'.[3]

Before a surgeon was appointed under the terms of the new legislation, the staff of the Charitable

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Infirmary were in attendance and they are thanked formally on their retirement in the early minutes of the new institution. Tributes were paid to Dr King, Senior, Dr King, Junior, Mr Samuel Maxwell, surgeon and Mr Joseph Boyde, apothecary for their 'Faithful, Diligent and Successful Attendance without fee or reward at the Charitable Infirmary since its first opening'.[4]

In 1777 it was described as:

> a building of three stories 90 feet in front & 50 feet deep, with a large court or area before it, inclosed from the street by a wall. The lower storey consists of a kitchen, rooms for servants and storerooms for provision and firing. The right wing contains two large wards of eight beds in each, and two rooms with one bed each for men. The left wing contains a ward of four beds and two rooms with a bed in each for women with apartments for the surgeon, his family and apprentices. There are two staircases, one communicates with the offices below from the men's wards and the other from the women's. There are also in the infirmary a room for surgical operations, another for preparing & keeping medicines. There is a room where the governors meet the first Saturday in every month & a large hall with a fireplace.[5]

The institution was administered by a board of governors which, from 1774, met every month. In May 1813, a standing committee was established 'to regulate the management of the infirmary' and from that time regular quarterly and annual meetings were held to consider such routine business as passing accounts and general organisation of day-to-day affairs.[6]

Furniture and equipment were purchased – beds, cupboards, lamps, curtains, tables and chairs – and building work, whitewashing, repairs and alterations were carried out regularly to improve the fabric of the premises.[7]

In 1767, the first surgeon appointed to the new infirmary on an annual salary of £100 was Joseph Shewbridge. He died in 1776 and was replaced by Michael Whyte of Mercer's Hospital. On his death in 1787, Richard Daniel also from Mercer's Hospital who had earlier relieved Mr Shewbridge was confirmed as surgeon and held the position for 17 years. Various appointments were made in subsequent years as vacancies arose.[8]

Other members of staff included the porter, the housekeeper who appears to have held an important position in the early years of the infirmary, and nursing assistants who, in the eighteenth century, might not have had the recognition they deserved. In 1773, for example, the Minutes of the Infirmary 'merely refer to the need for two women to assist in attending the patients and were considered along with a kitchen maid'.[9]

Patient numbers in the early years of the infirmary show that from 8 August 1767 until that same month in 1771 there were 111 interns, 14 of whom were still receiving treatment. As the years passed numbers of patients increased considerably as the following table shows:

TABLE I

Number of patients treated at Armagh County Infirmary 1817, 1818 and 1822 [10]

	1817	*1818*	*1822*
Interns	181	192	160
Externs	3,722	3,174	1,842
Accident victims	245	400	163
Children vaccinated	108	51	100
Ruptured poor		26	
Total	4,256	3,174	2,265

THE ARMAGH INFIRMARY AFTER SEVERAL DECADES

In the 1830s, it was reported by the Assistant Commissioners considering the state of Ireland's poor that the hospital was a well constructed three-storey building.[11] The basement contained various utility rooms to serve both the infirmary and the surgeon – for the former, a kitchen, housekeeper's pantry, potato and meal store, matron's sitting room, washhouse and scullery; and for the latter a butler's pantry, two other pantries, a kitchen and scullery. The first floor comprised a surgery, a female ward with 12 beds and a new ward not completed due to lack of funds, but capable of holding six or eight beds. Two men's wards, one containing 13 beds and another eight, a nurse's room and a matron's bedroom were all located on the second floor. On these floors also, the surgeon had his complement of rooms – a study, drawing-room, and board room on the first floor and on the second, five bedrooms and a garret with two rooms. These together with the basement rooms occupied five-twelfths of the accommodation of the whole building.

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Three wards were occupied. These were found to be 'clean, lofty, and well-ventilated and everything looked neat and orderly'.[12] Despite the elevated situation of the hospital and the favourable condition of the wards, it was on two occasions severely infested with malignant erysipelas – in 1823 and 1826. In the latter year, this disease could only be arrested by the total evacuation of the building and the burning of clothes and bedding.

The medical attendant and the apothecary were both well qualified. The former was a graduate of the Royal College of Surgeons in Ireland and a Doctor of Medicine. In addition, he held a certificate in midwifery. He was engaged in private practice, which was required not to interfere with his duties at the infirmary and the governors were to be advised of any intended absence of more than four days. The surgeon who was appointed by the governors received an allowance of £89 1s 10d from the government and since 1829 was paid an annual sum of £50 from the general funds of the charity in view of his work with out-patients.[13]

The latter, who was responsible for dispensing the medicines, was a licentiate of both the Dublin Apothecaries' Hall and the King's and Queen's College of Physicians in the same city. He was also a member of the London College of Surgeons.[14] The apothecary received a salary of £30 per annum and a further allowance of £20 for discharging the duties as registrar. Such medical staff were augmented by a matron, a male and female nurse, an assistant nurse, a cook and a porter.

The dispensing room was neatly maintained and contained a good supply of excellent medicines, including many of 'the more delicate preparations'. There was also an adequate stock of surgical instruments. Leeches were sometimes used and these were purchased in small quantities as required. Arrangements for vaccination were established and the surgeon was obliged to vaccinate all who applied for it.

An unlimited number of tickets entitling the bearer to receive relief at the hospital was issued by each subscriber and, unlike some areas, there was little difficulty in obtaining admission. The medical officer decided on which cases were eligible to be admitted and which would be treated as extern patients. The latter received aid at the dispensary on two days a week – Tuesdays and Saturdays between 11.00 am and 12 noon – but were not visited in their homes. Expectant mothers from the labouring class were attended by midwives, the majority of whom, it appears, possessed little skill.

Intern patients were confined to the infirmary. According to the Assistant Commissioners they were not required to work 'further than cleaning the wards and rendering assistance to the nurses'.[15] Visitors were permitted on Thursdays and where patients were seriously ill were allowed to remain in the building.

In March 1830 there were 35 patients in the infirmary and figures for the years 1825-1829 reveal the following numbers treated and the total annual expense :

In 1821 the inhabitants of county Armagh numbered 197,427,[17] so that while some provision had been made to alleviate the condition of the sick poor in the county, comparatively few benefited from the work of this institution even after more than half a century. But, whilst the numbers treated in the Armagh infirmary, by modern standards appear small, they compared favourably with, and in some cases much better, than those of similar institutions in other counties, for example the infirmary for county Antrim at Lisburn, which treated an average of 1,348 patients from a population of 262,860 during the same period.[18] By the time of the Assistant Commissioners' report several years later, the numbers of patients treated in the Armagh infirmary had risen as follows

However, concern was expressed by the Assistant Commissioners about certain management issues

TABLE II

Number of patients treated at Armagh County Infirmary 1825-29, and the total annual expense [16]

		£	s	d
1825	2,288	718	6	8
1826	2,576	711	13	10
1827	2,691	765	0	8
1828	2,341	753	19	0½
1829	2,567	852	0	4½

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Table III

Number of patients treated at Armagh County Infirmary 1832-34 [19]

	Intern	*Extern*	*Total*
1832	388	2,657	3,045
1833	438	2,289	2,727
1834	482	2,682	3,184

particularly regarding the diet rolls and the provision accounts in the Armagh establishment.

Two principal factors were noted: the striking excess of low diets over full diets (the only other variety allowed in the dietary in this hospital) compared with the diet-rolls in operation in the early years of 1832; and the large and increasing part which milk formed in both full and low diets, but especially in the latter. The rules by which the respective quantities of milk were charged against each patient in the weekly diet-roll were as follows:

1. Every patient, whether on full or low diet, was entitled to one pint of milk as his/ her regular daily allowance.

2. Each patient on full diet, and any on low diet, who might happen to have had no extra milk, were entitled to one pint of milk on Mondays and Fridays, 'Instead of meat or broth', in addition to his/ her regular allowance.

3. All patients on low diet, with very few exceptions, had each a pint of extra milk every day, as well as on Mondays and Fridays and in addition, very often a pint of butter milk every day.[20]

The milk was paid for from the funds of the infirmary at a cost of 2d per Irish quart. The same commodity was supplied to the Armagh Fever Hospital for $1^1/_2$d or $1^3/_4$d per quart. The surgeon at the infirmary was responsible for supplying all the milk required. He received payment from the treasurer through the matron, a situation in which the medical attendant was reckoned to be the contractor for that article. However liberally and honourably the surgeon might have fulfilled his contract for milk with the infirmary – and the Assistant Commissioners did not intend to convey any contrary insinuation – the principle of the transaction was considered objectionable coupled as it was with some circumstances peculiar to the case.

The medical attendant framed the dietary of the hospital and proposed it for sanction to the governors, by whom it was adopted in 1831. He ordered and regulated all additional allowances of milk to the patients in the infirmary and he held in his possession and cultivated for his own profit, all the land (four acres in total) belonging to the institution. Consequently, it was in his interest to augment the consumption of an article in the patients' diet which he alone could prescribe in any quantity he would choose to sanction. The Assistant Commissioners believed that this was a position in which the medical officer of a public charity never should have been permitted to place himself.[21]

The annual reports of the infirmary exhibited some interesting facts which received due consideration in the comments of the Assistant Commissioners. It appeared that the annual county grants had risen in the early years of the 1830s from £400 in 1831 to £500 in 1833, and the annual subscriptions increased from £92 to £131, and although during the same period £183 had been expended on building and repairs, £86 11s 11d on new articles of furniture and repairs to old items, yet one large ward remained unoccupied due to lack of furniture. The building work executed in 1831 and 1832, it was reported, appeared 'not directly connected with the accommodation of the patients, though it cost £154 10s 10d and left the institution £170 in debt.[22] Just over a decade later, plans for the establishment and management of additional accommodation to house scrofulous patients were approved by the governors on 23 June 1843. The project was supported from the bequest of the late Dr Edward Lill, rector of Clonoe parish, County Tyrone from 1739 until his death in 1791 and the new buildings were to be named the 'Lill Wards' in his memory.[23]

Dissatisfaction was also expressed with the surgeon's attitude towards out-patients. These were given prescriptions and received medicines at the hospital pharmacy on agreed weekdays as suggested earlier, but the sick poor were not visited in their own homes even though the medical attendant had, since 1829, been paid £50 per annum for administering this service. As a result of the inefficiency of this dispensary another was established by the gentry of the parish of Armagh.[24]

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THE DOWN COUNTY INFIRMARY

A general meeting of the gentlemen of county Down was held at Downpatrick on 21 April 1767 to discuss the establishment of an infirmary for that county. Subscriptions at this date totalled £810 10s 9d.[25] The newly-elected governors who were responsible for the management of the institution met on 1st July 1767 and resolved to take out a lease on a house in Saul Street, Downpatrick, to accommodate patients. Beds and furniture were immediately ordered and by 14 July of that year the infirmary was ready to receive patients.[26] A surgeon was appointed at a salary of £100 per annum.

Various rules were formulated to ensure the efficient management of the hospital. A register of all in- and out-patients was to be kept by the surgeon. This was to include their ages, diseases, the parish from which they came, by whom they were recommended, the time of admission and discharge, and their state of health when discharged. In agreement with the Act of parliament a bed was to be reserved in cases of emergency and in such cases the surgeon would be permitted to give advice and medicine. Several categories of persons were not permitted to be received as in-patients: 'pregnant women near their time; persons under ten years of age unless they were to undergo operations; persons under lunacy; ill of infectious diseases, as fevers, smallpox, measles, itch, venereal disease, last stage of consumption etc.'[27] Those who were admitted were allowed to remain more than two months only on recommendation of the surgeon.

Within the infirmary a certain discipline was initiated. Segregation of male and female patients was stipulated. Patients were required to go to bed at nine o'clock in winter and at ten o'clock in summer and to rise by eight o'clock in winter and seven o'clock in summer. Smoking was prohibited unless ordered by the physician and if such were the case this was to be carried out only in the kitchen. Cursing, swearing, playing cards, dice or any other game were not permitted and the housekeeper, who was responsible for the oversight of the domestic arrangements of the infirmary, was to ensure that no provisions of any kind, particularly strong liquors, were to be brought to the patients by their relatives and friends. Visiting was by arrangement with the housekeeper who was expected to keep a strict surveillance on the duration of the stay. Patients were required to assist with nursing duties and with routine household chores such as washing and ironing, cleaning and gardening. Rules concerning the behaviour of patients, nurses and servants were read once a week in all the wards.[28]

The patients' dietary was formulated early in the infirmary's history. Sunday, Tuesday and Thursday were flesh meat days, while Monday, Wednesday and Friday were designated 'meagre days'. The dietary was as follows :

> Breakfast: water oatmeal porridge, one pint, with a pint of milk or small beer – or a pint of milk pottage without sauce.
>
> Dinner: Eight ounces of beef or mutton or pork or veal, weighed when raw for each patient; either of them to be boiled and broth made of it, thickened with cutlings or grotts; a pint of which to be served to each. Roots are to be used when to be procured, as potatoes, turnips or parsnips. When there are roots, six ounces of bread, and eight ounces when otherwise. A pint of small beer when to be had conveniently.
>
> Supper: Water pottage a pint, or a pint of flummery or potatoes; with either of them a pint of milk pottage, or six ounces of bread and a pint of milk.

On 'meagre days' breakfast and supper were to be the same as on Sunday, Tuesday and Thursday, however dinner on the former was to consist of:

> 1. Ten ounces of bread and a pint of milk.
> 2. Or twelve ounces of plain pudding, one ounce of butter and a pint of small beer.
> 3. Or a sufficiency of potatoes and one pint of milk.
> 4. Or ten ounces of bread, two ounces of butter and a pint of small beer.
> 5. Or three ounces of skimmed milk cheese, eight ounces of bread and a pint of small beer.
> 6. Or one quart of broth, made the day before, and four ounces of bread.
> 7. Or a quart of grott gruel or barley, seasoned with salt and butter, and four ounces of bread. [29]

Two centuries later, the Metabolic Unit Dietitian at the Royal Victoria Hospital, Belfast investigated this diet and reported that, on average, it was very adequate, except for a deficiency in vitamins A, D and C. It was computed at an average daily intake of 2,400 calories per day, compared with 2,750 calories per day recommended by the BMA in 1950 for a man doing light work.[30]

At a meeting of governors on 12 January 1768, it was reported that since the opening of the

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infirmary, 15 patients had been received and six discharged cured; three were incurable and six remained in the house; 31 out-patients had also received advice and medicines, 17 of whom had been cured, two were discharged as incurable and 12 remained under care.[31]

In March 1768 the total income of the infirmary amounted to £571 8s ld, a sum which comprised subscriptions, Grand Jury presentments, a parliamentary grant, the proceeds of various functions and the interest of debentures. In addition to annual subscriptions, the governors hoped to attract certain 'casual benefactions' and consequently four boxes each inscribed 'Poor Box of Down Infirmary' were placed 'one in the church of Down, one in the meetinghouse, one in the infirmary and one in the market place of Down'.[32]

Gradually the governors deployed the finances to improve the facilities and appoint additional personnel. In October 1768, it was decided to convert one of the rooms into a ward to accommodate patients under salivation. The services of an apothecary were enlisted in April 1773 at a cost of 10 guineas per annum. By 1774, the original building in Saul Street, Downpatrick where the infirmary was housed, necessitated considerable repairs. At a meeting of governors held on 5 April of that year it was resolved to purchase from the Barrack Board, the old barracks in the town and convert them into an infirmary with accommodation for 20 patients, a number which had been suggested a year previously to meet the minimum requirements of the area. After some delay the barracks were repaired and opened as the new infirmary.[33]

By the closing years of the first decade of the nineteenth century, due to the dedication of the governors and the hospital personnel, the numbers of patients treated had risen considerably (see Table IV).

Despite attempts at improving both the fabric of the building and the comfort of patients,[35] by the end of the first three decades of the nineteenth century the state of the building was again a cause for concern.

NEW PREMISES

On 1 May 1830 after an inspection of the premises and on consideration of an architect's report, the governors decided to erect a new building which should include fever wards. Funds were to be raised by private subscriptions and by Grand Jury presentments. Financial problems had generally been eased at least slightly by the County Infirmaries (Ireland) Act, (1808)[36] which empowered Grand Juries to present an additional sum of £500 per annum. (This was increased by the Grand Jury Act of 1836 [37] to a maximum of £1,440).

TABLE IV

Numbers of patients treated at Down County Infirmary 1807-9 [34]

	1807	*1808*	*1809*
In-patients cured	90	80	78
Much relieved	44	40	37
Incurable	7	8	10
Died in the house	2	2	3
Remaining in the house	20	21	21
Out-patients who received advice and medicine	1,540	1,460	1,450
Children inoculated with cowpox	150	180	194

On 2 June 1830, at a general meeting of governors, a site was selected. It was agreed to advertise for plans and estimates for the construction of an infirmary with a house and offices for the surgeon and, as intimated at an earlier meeting, the addition of wards to constitute a fever hospital.[38] The infirmary was to cost not more than £3,000 and the fever hospital not more than £1,000. Plans were examined on 5 October 1830, when it was decided that the accommodation for the surgeon was to be under the same roof as the infirmary, and the fever hospital was to be a separate building. Revised plans were examined at the governors' meeting on 3 November 1830 and those submitted by a Dublin architect, John B Keane, were approved. His estimate was £4,500. Construction costs were soon to dictate the plan of the new institution. On 16 February 1831, two tenders were discussed. Each was considerably higher than the estimated cost and the architect was instructed to revise his plan which was duly submitted to the governors the following month. Tenders for building the infirmary, fever hospital, entrance lodge, gates and boundary wall were received. The sealed tenders were not opened at a meeting held on 21 March 1831 as the governors

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had learned privately that it was unlikely that any contractor could complete the work for less than £6,000. A long letter signed by three governors and quoting an estimate of £6,000 was addressed to the Grand Jury. Funds in hand amounted to £694, with £1,846 laid out at interest; the probable sum to be realised from the sale of the present building was £300, thus making a total of £2,840. The governors therefore applied for a Grand Jury presentment of £3,000.[39] The surgeon, Dr Buchanan, was instructed to enlist the services of Mr John Lynn, at that time engaged in building the county gaol and Mr Bowen, a land surveyor, to prepare the estimates, serve all the necessary notices and bring the governors' application before the road sessions and subsequently to the Grand Jury.[40]

On 10 August 1831, a copy of the Grand Jury presentment for £3,000 payable in half-yearly instalments of £250, was received by the governors and commissioners for the completion of the work were appointed. Of the two tenders submitted, Mr Lynn's was accepted – for the infirmary, entrance lodge, gates and surrounding wall £3,950; and for the fever hospital, £2,050. The landlords and gentry of the county contributed to the construction costs of the new buildings demonstrating their concern for the welfare of their tenants.[41]

Whilst the exterior of the new premises appeared impressive, the interior, it seemed, revealed certain defects. The Assistant Commissioners reported somewhat critically that consideration for the comfort of patients had been sacrificed in order to provide 'a superb and spacious residence for the surgeon'. Indeed it was lamented that for such capital expenditure 'so little wholesome accommodation' was 'provided for those to whose exclusive benefit the establishment should have been appropriated'.[42]

Accommodation consisted of 11 wards – five, containing a total of 16 beds for females, and six with a total of 24 beds for male patients. The Assistant Commissioners reported that the wards were 'small and very imperfectly ventilated' and that in one ward occupied by four male patients 'the air was so oppressively loaded with cutaneous effluvium that one of the Assistant Commissioners could not without difficulty remain long enough in the room to measure its extent, which did not exceed 20 feet square'.[43] The yards of both the male and female wings of the hospital were confined and enclosed by high walls, apparently to provide a spacious stable yard and out-offices for the surgeon's residence.[44]

By the 1830s, two medical officers remained attached to the infirmary – a surgeon and an apothecary. The former was engaged in private practice but was expected to be in regular attendance at the hospital. (In alleged cases of neglect the poor had the right to complain to the governors). The apothecary's duties consisted of compounding medicines and attending to the patients under the direction of the surgeon. The Assistant Commissioners found the pharmacy to be well-maintained – high quality medicines were stocked including several of the most delicate and expensive preparations – and the institution possessed the correct equipment for preparing decoctions and infusions. The stock of surgical instruments was limited and consisted only of enema syringes, bougies, bandages, splints, trusses and lancets. When necessary, leeches were supplied to in-patients.

On the signed recommendation of a governor, any person was entitled to relief, although emergency cases were admitted immediately without recommendation. There was no limit to the number of recommendations which a subscriber could issue. At the time of the Assistant Commissioners' visit there were 21 patients in the house and 48 operations had been successfully performed in the preceding three years. Extern patients were seen at the infirmary and those unable to travel were attended at home by medical staff. The duties of the medical personnel, however, did not include visits to expectant mothers. These were generally looked after by midwives, whose skill was, in many cases, very limited.

Unfortunately the *Report of the Select Committee on the State of the Poor in Ireland* (1830)[45] and the *Report of the Commissioners for inquiring into the State of the Poorer Classes in Ireland* (1835)[46] do not provide information on the numbers of persons relieved in this infirmary during the years 1825-29, so a comparison between the Down and Armagh establishments cannot be made for this period. However, other sources reveal an increase in the numbers of patients treated and relieved during the years 1834-38 in the Down County Infirmary:

The infirmary committee reports for these years portray a very positive picture of the work of this

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TABLE V

Number of Patients treated and relieved in the Down County Infirmary 1834-38 [47]

	1834	*1835*	*1836*	*1837*	*1838*
Admissions	194	237	256	284	295
Discharged cured	142	178	227	230	238
Incurable	8	8	7	10	9
Relieved	25	34	12	31	25
Died	11	12	11	13	21
Remaining	28	33	33	32	34

institution, citing the afore-mentioned figures to reinforce their comments. The increase in accommodation since the construction of the new building, which amounted to an additional 16 beds – making a total of 40 – received particular praise, and the industry, zeal and retrenchment of the surgeon were also highly commended. The treatment of out-patients was of course an additional feature of each county infirmary and in Downpatrick this work continued and increased annually. In 1834, applicants who received advice and medicine amounted to 1,230, and the number of prescriptions dispensed totalled 3,652. These figures rose in 1835 to 1,408 applications and 3,926 prescriptions. By the end of 1838, there was a small decrease in applications, (1, 137) and also in the number of prescriptions dispensed (3,553). Vaccination of children was practised as part of the infirmary service here as elsewhere and available figures show that 54 children were vaccinated in 1834, 61 in 1835, and 74 in 1838.[48] This was performed on two days each week and was found 'generally efficacious'.[49] Members of the public were confident about its benefits and the prevalence of small pox in the early and mid-1830s may have been a factor in the increased numbers of children being vaccinated.

ASSESSMENT

There can be no doubt that it was of some benefit to the sick poor that there should be at least one hospital in every county, even though it may not have been particularly large or endowed with sufficient funds to admit all needy or urgent cases. The legislation under which such a system was established must, therefore, be considered humane, wise and beneficial. The idea of a uniform system throughout the country should also be seen as valuable. The infirmaries also contributed to the substitution of scientific medicine for the folk cures which were prevalent throughout the country. Medical officers were well qualified and were generally capable of discharging their professional duties efficiently. The professionalism of surgery was encouraged as the credentials of infirmary medical officers were required to be approved by the surgical staffs of Steeven's and Mercer's hospitals in Dublin and from 1796 infirmary positions were limited to those holding the licence of the Royal College of Surgeons which had been established twelve years earlier.[50]

The reports and figures for the two infirmaries in south-east Ulster show that the establishment of these institutions through the concern and generosity of the more fortunate members of the local community provided increasing assistance and medical care for those in need of medical attention.

One hospital to serve a population of 220,134 persons in county Armagh and one for 352,012 in county Down [51] extending over an area of 513 and 955 English square miles respectively nevertheless appears completely inadequate. The available figures for those treated at each infirmary in the years cited earlier, and viewed confidently by local personnel, seem meagre when the broader whole-county perspective is considered. In the period from 6 June 1841 to 30 March 1851 there was accommodation for 72 patients in the Armagh infirmary and for 50 in the Downpatrick building. During that period, a total of 7,847 cases had been admitted to Armagh, a proportion of one bed to 1,140 of the county population. The situation in county Down was even worse. There,

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during the same period, while fewer cases were admitted (6,215), the proportion of beds per head of population was 1 to 2,126.[52]

Distance was certainly a major factor. Although in these two counties the establishments were situated quite centrally (unlike that for county Antrim, situated at Lisburn in the extreme southwest as noted earlier), many patients would still be required to endure distances of at least 20 and in some cases 30 or more miles to receive treatment. In the Downpatrick infirmary, for example, on 5 January 1839 there were 34 patients. In the course of that year, 305 were admitted. Of this total of 339, 169 resided within five miles of Downpatrick, 64 resided between five and ten miles away and 106 lived at a distance of more than ten miles from the town. A similar picture was evident for 1840. Of the 341 patients admitted during that year, 144 lived within a distance of five miles, 89 from five to ten miles and 108 more than ten miles away. Thus it appears that a population contiguous to the infirmary, not perhaps one quarter that of the county, supplied 50 per cent of the patients admitted during 1839 and just over 42 per cent in 1840.[53] Figures for the Armagh infirmary for 1839 reveal that 641 patients were admitted during that year. Of these, 379 resided within five miles of the hospital, 212 from five to ten miles and 50 more than ten miles away. Therefore, in this county, over 59 per cent of patients lived within five miles of that institution.[54]

Denis Phelan, a Poor Law Commissioner, was critical of the Downpatrick infirmary. He felt that it was preposterous to assert that the population of county Down would send so few cases to that hospital in any one year, and equally that one of the most wealthy and commercial counties in Ireland could not, provided accommodation was sufficient and the establishment managed on different principles, contribute funds to support three times the number of patients treated.[55] Phelan believed that had no public expense been forthcoming to support the infirmaries, the resources in each county would have been deployed more extensively and such charities would have been better managed.[56] Undoubtedly the subscriptions for the years 1831-1833 were very low particularly as this county was considered by many to be one of the most prosperous in Ireland. The county grant for each of these years was £461 10s $9^1/_4$d and the subscriptions were as follows – 1831 : £26 17s 2d; 1832 : £5 5s; 1833 : £46 5s.[57] These figures for a so-called prosperous county were appalling. However, when the substantial subscriptions towards the building of a new infirmary during this period are taken into consideration, these apparently meagre amounts may not appear so niggardly.[58] Yet by March 1840, the amount of subscriptions remained comparatively low, at £35 4s, and contrasted sharply with those in county Armagh which, for the same year totalled £145 19s. Indeed, it is not surprising, given the total income of each infirmary for the 1839-40 period that the Armagh hospital admitted almost twice the number of patients than the county Down establishment during that year.[59]

Phelan was also critical of the extent of the surgeon's accommodation at Downpatrick and estimated that the rooms occupied by that gentleman would 'be capable of containing at least twenty-four beds, which is one more than the hospital usually holds'[60] A similar criticism was levelled against the Armagh institution by Phelan and Gulson who reported on the state of medical charities in various Poor Law unions in 1840. They stated that a considerable portion of the building was occupied by the surgeon and that 'this portion, independent of the offices appropriated to his use, would, if converted into wards contain at least 20 beds'. They continued 'If the entire hospital building were converted into wards for the sick, it might possibly be found adequate for the reception of all cases occurring within such parts of the county as are not so remote from it as to render their removal there difficult or impossible'.[61]

Generally, the concept of county infirmaries was a worthy one and capable of being expanded through future legislation. In the meantime it required some supplementary provision at a more localised level and this was evidenced by the rise and growth of the dispensary movement in these counties and throughout Ireland during the nineteenth century.

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Transduodenal excision of ampullary tumours

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SUMMARY

The commonly recommended treatment for ampullary tumours – pancreaticoduodenectomy results in significant morbidity and mortality. This study is a retrospective evaluation of the procedure of transduodenal local excision of ampullary tumours. Demographics, symptoms, histological findings and outcomes were retrospectively analysed in 15 patients. Survival analysis was done by the method of Kaplan-Meier and log-rank test.

The median age was 68 years (range 54-78). Endoscopic biopsy was accurate in only 41% of cases. CT scan demonstrated a mass in 50% cases. Definitive histology reported 4 adenomas, 2 carcinomas-in-situ and 9 adenocarcinomas. Median hospital stay was 13 days. There was no operative mortality. Mean duration of follow-up was 31 months (range 7-70 months). The procedure appears curative for adenomas and in-situ carcinoma. Overall 3 year actuarial survival for ampullary tumours is 65% while that for moderately differentiated carcinomas is 50%.

Pre-operative investigations provide inadequate histological information. Wide local excision is a safe operation with low morbidity and good survival in carefully selected cases. However, the role of local excision for carcinoma appears to be palliative rather than curative.

INTRODUCTION

Ampullary tumours are uncommon tumours arising from the surface of the papilla of Vater or from the inner epithelial lining of the ampulla itself.[1] Carcinomas of the ampulla of Vater account for approximately 6% of all periampullary tumours.[2] Villous adenomas of the ampulla have a reported incidence of 0.04-0.12 per cent.[3] The reported incidence of malignancy varies widely but seems to be around 25 per cent.[4,5] It is difficult to get an accurate preoperative histological grading of the tumour.[1,5] Villous adenomas of the ampulla are considered premalignant and there is controversy regarding optimum surgical management.[1,4] There are two main surgical options – local, transduodenal excision of the tumour (ampullectomy) or pancreaticoduodenectomy. This study is an evaluation of 15 patients with ampullary tumours who underwent local excision.

PATIENTS AND METHODS

Between April, 1995 and June, 2000 fifteen patients with tumours of the ampulla of Vater underwent transduodenal excision (TDE). The indications for TDE were either operative feasibility (i.e. tumour small enough macroscopically to allow confident complete local excision) or significant associated co-morbidity preventing a pancreaticoduodenectomy. Patients were identified from the hepatobiliary database and the records were reviewed for clinical presentation, preoperative investigations, surgery, immediate postoperative complications, pathological findings, hospital stay and follow-up.

The histology reports were reviewed with regards to tumour size, resection margins, pancreatic and lymphovascular invasion, the T stage (UICC) and tumour differentiation. Survival analysis was

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done by the method of Kaplan-Meier. Difference in survival between subsets was compared by the log-rank test.

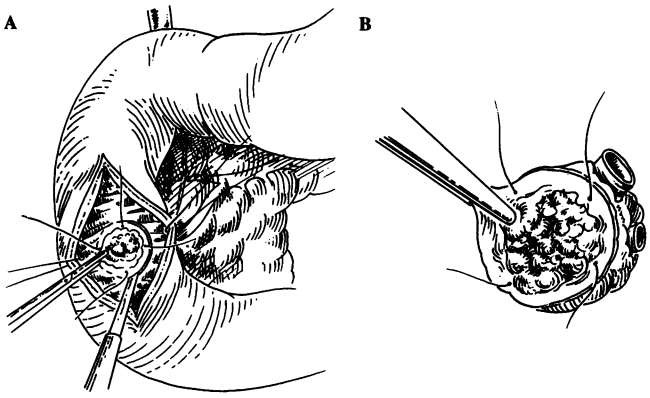

Fig 1. Stay sutures are inserted around the tumour as markers for wide diathermy excision (a) prior to excision of the papilla of Vater, encompassing part of biliary and pancreatic ducts and posterior duodenal wall (b).

Surgical procedure

The procedure involves a transduodenal approach via a longitudinal duodenotomy. Four stay sutures are inserted around the tumour as markers (figure 1a). A wide diathermy excision is performed around the stay sutures to ensure a clear margin. Excision involves a wide resection of the papilla of Vater, encompassing part of the biliary and pancreatic ducts and a part of the posterior duodenal wall (figure 1b). The bile duct and the pancreatic duct are sutured together to form a common septum and both ducts are then re-implanted (figures 2a and b). The duodenotomy is closed. Cholecystectomy is routinely performed to avoid cholecystitis secondary to duodeno-biliary reflux. A feeding jejunostomy is routinely inserted to allow enteral nutrition in the immediate post-operative period.

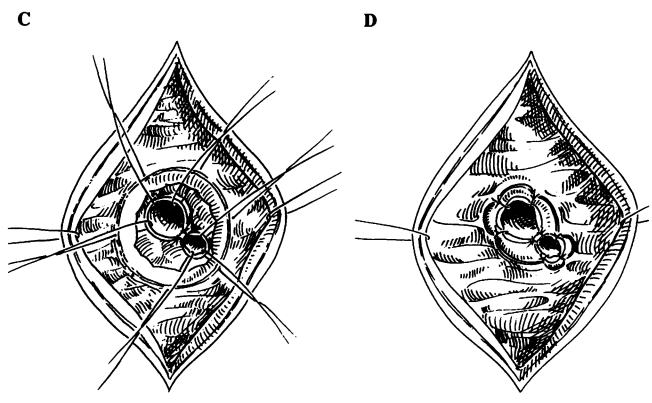

Fig 2. Bile duct and pancreatic duct sutured together to form a common Septum (c) prior to re-implantation in the duodenum (d).

RESULTS

Clinical Features

The clinical presentation, preoperative diagnosis, final pathological diagnosis, complications and outcome are summarized in Table 1. There were 12 males (80%) and 3 females (20%) with a median age of 68 years (range, 54 to 78 years). Ten patients (66%) had jaundice (of these 2 also had rigors). Seven patients (46%) complained of abdominal pain (of these 1 also had backache). In two patients the ampullary tumour was an incidental finding. The first of these (no. 2) was a 78 year old woman, found to have abnormal liver function tests during investigation of cardiac disease. The other was a 70 year old man (no. 13) who was initially admitted with fractured ribs and on examination was also found to have jaundice. One patient presented with haematemesis. One patient (no. 14) was operated on urgently as she was thought to have unresolving jaundice due to bile duct stones. Other presenting features were anorexia (n=4), weight loss (n=4), lethargy (n=3), nausea (n=3), anaemia (n=l) and steatorrhoea (n=l). The duration between onset of symptoms and surgery ranged from 3 to 56 weeks.

Investigations

CT Scan showed an ampullary mass in 6 (50%) of the 12 cases in which it was performed. Ultrasound Scan was performed in 9 patients and revealed a dilated biliary duct system in 8. Preoperative endoscopy was performed in 13 cases and biopsies were taken in 12 patients. Endoscopy was not done in 2 cases – 1 due to delay in surgery while waiting for ERCP and in 1 case jaundice was thought to be secondary to bile duct stones and the patient underwent intraoperative cholangiogram and duct exploration. Three patients were stented preoperatively at ERCP.

Complications and hospital stay

In the immediate post-operative period, one patient developed a subphrenic abscess which was drained percutaneously and one developed a wound infection. There was no postoperative hospital mortality. Median hospital stay was 13 days (range 7-49 days). In the long term, two patients developed incisional herniae and one developed a metastatic skin nodule with no evidence of recurrence intra-abdominally, 34 months after primary excision of ampullary carcinoma-in-situ (no. 6). This nodule was excised and the patient is alive and well at 41 months.

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TABLE

Demography, Clinical features, Pathology and outcome

Patient No.	*Age, y/sex*	*Clinical Features*	*Preoperative Diagnosis*	*Final Diagnosis T stage/ Differentiation*	*Complications*	*Follow-up in months/results*
1	72/M	J, Rigors, Lethargy	Adenoma, Severe Dysp.	AdenoCa T2/Moderate	None	17 months, Disease free
2	78/M	Incidental	Adenoma, Severe Dysp	Adenoma, Severe Dysp.	None	70 months, Disease free
3	77/M	P, N, V, W Lethargy,	Adenoma	Adenoma, Severe Dysp.	None	15 months, Disease free
4	69/F	Anaemia	Adenoma, Severe Dysp.	AdenoCa T2/Poor	None	8 months, Disease free
5	65/M	J, P, W, N, V	Inadequate	AdenoCa T1/Poor	None	10 months, Died of local recurrence
6	68/F	J, N	Adenoma, Severe Dysp.	Ca-in-situ	None	41 months, Scar nodule
7	66/M	J	Adenoma	AdenoCa T2/Moderate	Sub-phrenic abscess	56 months Disease free
8	64/M	Haematemesis	Adenoma Mild Dysp.	Adenoma, Mild Dysp.	None	29 months, Disease free
9	54/M	P, J		AdenoCa T2/Moderate	Wound infection	43 months, Disease free
10	71/M	J, W, Steatorrhoea,	Normal	AdenoCa T2/Poor	None	10 months, Disease free
11	61/M	P, Rigor with temperature	Adenoma, Mild Dysp.	Adenoma, Moderate Dysp.	None	52 months, Disease free
12	62/M	J	Adenoca	AdenoCa T2/Moderate	None	30 months, Died of local recurrence, liver involved
13	70/M	Incidental, J	Adenoma	Ca-in-Situ	None	53 months, Disease free
14	70/F	J, P, N, V		AdenoCa T2/Poor	None	7 months, Died of local recurrence
15	66/M	J, P, W		AdenoCa T2/Moderate	None	30 months, Died of local recurrence

(J-jaundice, P-pain, N-nausea, V-vomiting, W-weight loss, Dysp.-Aysplasia, Ca.Carcinoma)

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Histo-pathology

Preoperative endoscopic biopsy was accurate in only 5 patients (41%) of whom 4 had adenomas and 1 had an adenocarcinoma. Multiple biopsies were routinely undertaken at endoscopy. Amongst the remainder, preoperative biopsy revealed a villous adenoma with severe dysplasia in 5 patients of whom 2 eventually had carcinoma-in-situ, 2 had a moderately differentiated adenocarcinoma and 1 had a poorly differentiated adenocarcinoma. One preoperative biopsy was insufficient and 1 was normal. Both turned out to be poorly differentiated adenocarcinomas. In total, 4 patients had adenomas, 2 had carcinoma-in-situ and 9 had adenocarcinoma, of which 5 were moderately differentiated and 4 poorly differentiated. Of the 9 adenocarcinomas 1 was in stage T1 and 8 were T2. Frozen section biopsy performed in one patient (9) was reported as benign though definitive histology revealed moderately differentiated adenocarcinoma. Resection margins were clear in 14 patients. A re-laparotomy could not be undertaken in the one patient with involved resection margins due to significant associated co-morbidity. There was no pancreatic invasion, though lympho-vascular invasion was found in 3 cases. Mean tumour diameter was 2.5 cms (range, 1.5 to 4.2 cms). Mean duration of follow-up was 31.4 months (range, 7 to 70 months).

Outcome

The longest survival in this study was 70 months (no. 2) with a total of 4 patients alive after 50 months, 1 with a diagnosis of moderately differentiated adenocarcinoma, 1 with carcinoma-in-situ and 2 with dysplastic adenomas. Four patients (26 percent) died in this study. All the patients died of local recurrence. Two of these had T2, moderately differentiated tumours, and the other 2 had poorly differentiated tumours in stage T1 and T2. Survival was worst in the poorly differentiated group – 1 patient who also had involved resection margins surviving 7 months and another 10 months while both the patients with moderately differentiated carcinomas survived 30 months. Of the 3 patients with lymphovascular invasion 2 had poorly differentiated and 1 had a moderately differentiated carcinoma. The latter is alive at 43 months while of the patients with poorly differentiated carcinoma with lymphovascular invasion 1 is alive at 10 months and the other died at 7 months.

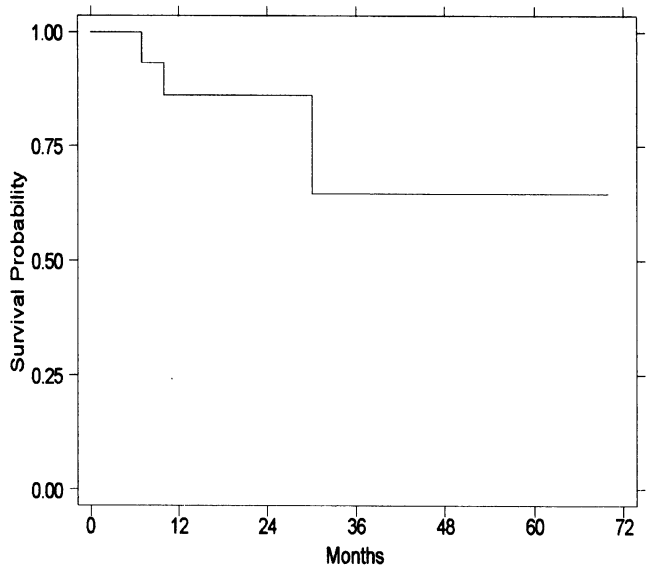

Fig 3. Overall actuarial survival (Kaplan Meier) – 1 year survival was 86% while 3 and 5 year survival was 65%.

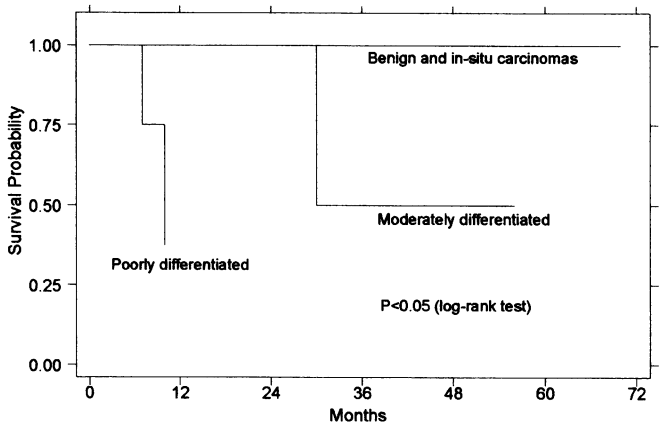

Fig 4. Survival by degree of differentiation.

The overall 1 year actuarial survival (Kaplan-Meier) for ampullary tumours (figure 3) was 86% (95% confidence interval 55-96%) while the 3 and 5 year survival was 65% (95% confidence interval 29-86%). Three year survival for moderately differentiated cancers (figure 4) was 50% (95% confidence interval 6-84%) while the longest survival for patients with poorly differentiated carcinoma was only 10 months in this study. Because of the relatively short follow-up and small series it is difficult to accurately interpret long-term survival at this point.

DISCUSSION

On the basis of autopsy investigations, the rate of neoplastic lesions of the ampulla ranges between 0.063-0.21%.[5] Halsted first reported

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transduodenal excision of an ampullary mass in 1899.[6] In 1935 A. O. Whipple reported a 2-stage resection of ampullary carcinoma.[7]

Although the ampulla is easily accessible by endoscopy there is a high reported incidence of false negative results for biopsy of carcinoma, ranging from 25-60%.[1, 5, 8, 9, 10, 11] The results in this study are similar, with a false negative rate of 59%. CT scan detection of a lesion is considered even less sensitive with a reported figure of around 20% in some studies.[1] Endoscopic ultrasonography aided diagnosis and staging has been widely recommended.[1, 12, 13, 14] However, Cahen *et al* reported an accuracy of only 44 per cent with endoscopic ultrasonography assisted staging and a false positive outcome for metastatic lymph nodes in 31% of their cases.[3] Endoscopic ultrasonography was not available for this study. Per-operative frozen sections are unreliable in excluding malignancy and can also give false positive results.[5, 15] It seems nearly impossible to exclude, with certainty, the presence of carcinoma in an adenoma without complete excision.[5]

While TDE is now accepted as the procedure of choice for benign adenomas, pancreaticodudenectomy is the commonly recommended surgery for ampullary cancer.[10] There have been recommendations for radical surgery even for benign lesions with some authors citing problems like a high incidence of malignancy, difficulty in accurate pre-operative confirmation, tendency for tumours to recur and concerns regarding the oncological adequacy of local resection for ampullary cancers.[8, 9, 16] A 3-year survival around 55 to 60 per cent and 5-year survival around 35 to 55 per cent has been reported after pancreaticoduodenectomy.[17-19] Beger *et al* reported 3- and 5-year survival rates of 72% and 52% respectively with R0 resections after radical surgery, but R0 resection was possible in only 62% of the malignant cases in their study, with an intra-abdominal complication rate of 25%.[5] The present study with overall actuarial 3 and 5 year survival projections of 65% would tend to favour the less radical approach.

Some reports also suggest that local resection is oncologically acceptable with comparable results and low morbidity in selective cases.[3, 5, 10] Tarazi *et al* reported a 2 year survival of 55 per cent and a 5-year survival of 41 per cent following TDE for carcinomas.[20] Newman and Pittam reported a 5 year survival of 41 per cent and a surviving patient 15 years after TDE for ampullary carcinoma.[20] Wise *et al* have reported a 3 year survival at 50 per cent and 5 year survival at 37.5 per cent.[22] Knox and Kingston have reported a better 1, 2, 3 and 5 year survivals following TDE compared to radical procedures.[23] Robertson and Imrie reported a median survival of 57 months with 44% five-year actuarial survival, after TDE.[24] Fifty percent of their survivors developed recurrent disease while there was a 25% incidence of post-operative deaths. Talamini *et al* in a large study of 28 years experience from the John Hopkins Institution reported an overall mortality of 3.8% after radical resection with no deaths in the last 5 years in consecutive 45 patients.[25] Morbidity in the latter part of their study had reduced to 38%. Five-year survival was 38% and they believed avoidance of transfusion improved the prognosis. Various studies have proposed that TDE is justifiable when the ampullary tumour is pT1(UICC-staging) and graded G1 or G2 (highly or moderately differentiated) with no lymphatic infiltration and complete resection (R0).[5, 26] The present study would tend to corroborate these suggestions. Unfortunately accurate TNM staging pre- or peroperatively is not feasible.

Howe *et al*, in a prospective study of the correlation between clinicopathological variables and survival of 123 patients presenting with ampullary carcinomas, found negative margins and negative nodes as independent predictors of improved survival.[2] Lymphatic drainage of tumours of the ampulla is distinct from pancreatic tumours in that, even in advanced cases, they seem to involve only a local group of lymph nodes near the ampulla, yielding a superior prognosis if the infiltration does not involve pancreatic tissue.[5, 27] Pancreatic involvement is closely related to extensive nodal involvement and ampullary cancers invading the pancreatic parenchyma may act more like pancreatic cancers resulting in a poor prognosis.[5, 27] In our study there was no pancreatic involvement in any of the cases and resection margins appeared clear in all but one case. Neither size nor duration of symptoms have been reported to accurately predict the presence of malignancy.[10] Interestingly, in the present study all 10 patients with jaundice had carcinoma or carcinoma-in-situ while none of the patients with villous adenoma had jaundice. This would be in keeping with some reports which suggest that malignant lesions tend to present

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with jaundice while benign lesions do not.[1, 9, 10] It would be interesting to see from larger studies in the future if elevated bilirubin could be utilised as a guide to the general decision making regarding the appropriate procedure and also as a predictor of survival in tumours of the ampulla.

In conclusion, our study suggests that obtaining an exact preoperative diagnosis for ampullary tumours is very difficult. None of the existing investigative tools seem to be entirely confirmative about the true histological nature of the tumour and the extent of the disease. Transduodenal excision of ampullary tumours seems curative for benign tumours and for in-situ cancers. It is a low risk alternative for patients with carcinoma who are poor surgical risks due to age or co-morbidity. Oncologically, local excision of carcinoma appears to be a palliative rather than curative procedure.

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Case Report

Gall bladder cancer – Radical surgery, the key role to improve outcome

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Gall bladder cancer is one of five most common malignancies of the gastro-intestinal tract. Most of the cancers are detected during histological examination after cholecystectomy. Females are more commonly affected than males with a ratio of 4:1. A direct association exists between the presence of cholelithiasis and the development of gall bladder carcinoma. In patients with gall bladder carcinoma the incidence of cholelithiasis ranges from 54-97 percent. Adenocarcinoma is the most common histological type but others can occur. We present four cases seen by a single surgeon in general surgical practice, during a four-year period. These cases demonstrate the varying histological types and the management of gall bladder carcinoma.

CASE 1 An 82 year old female admitted with bleeding per rectum. She had recently been seen in the outpatients and investigated for bleeding PR. A barium enema carried out at this time was normal. The patient was later admitted as an emergency with haematemesis along with fresh bleeding per rectum. The patient was taken for an urgent upper gastrointestinal endoscopy which showed bright red blood in the duodenum. After resuscitation, the patient was taken to theatre for an exploratory laparotomy. The intraoperative findings were those of a duodenocolic fistula associated with an inflamed gangrenous gall bladder. The fistula was closed and a cholecystectomy performed. Histopathology showed one of the rarer types of gall bladder carcinoma, namely a well differentiated, keratinising squamous-cell carcinoma, forming squamous pearls (figure 1). The carcinoma had invaded through the wall to the serosal surface. Post operatively she made a good-recovery. A referral was made to the oncology team for post-operative radiotherapy. The patient was admitted again 3 months later with vomiting, upper abdominal pain and jaundice. Her condition deteriorated rapidly and she died four days later due to widespread metastatic disease.

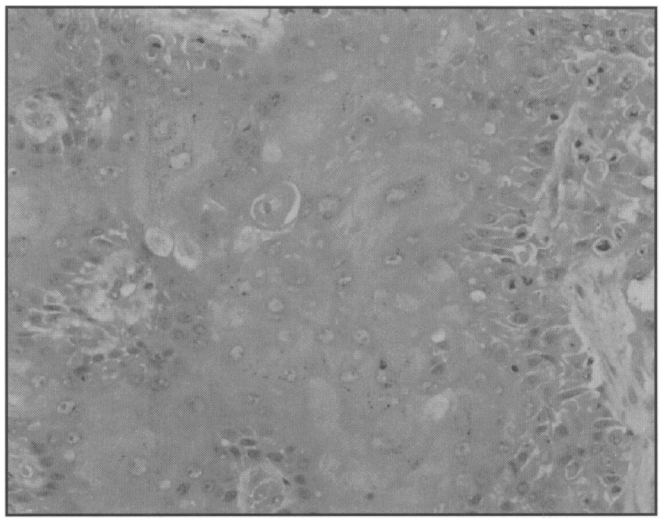

Fig 1.

CASE 2 A 69 year old female with a history of gall stones was admitted with recurrent episodes of pain in the right hypochondrium An ultrasound showed a soft-tissue echo in the region of the gall bladder. CT scan subsequently showed a solid lesion also in the region of the gall bladder not typical of a gall stone. It was decided to proceed with a laparoscopic cholecystectomy. During the procedure it was impossible to hold the gall bladder as it was hard and tense. The procedure was converted to an open procedure. The gall

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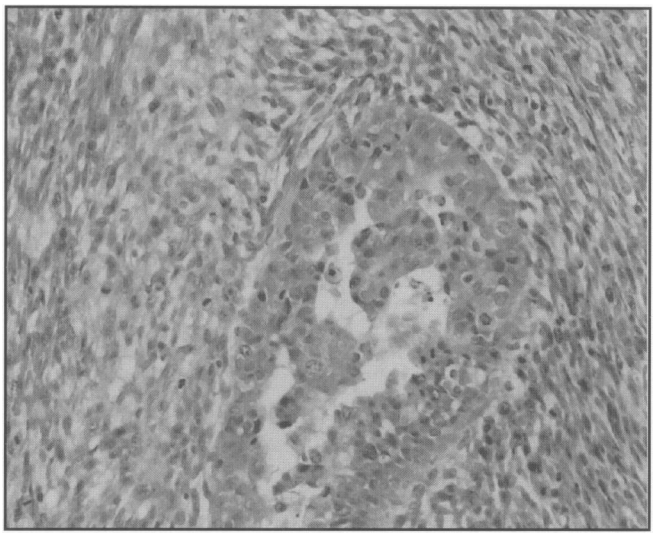
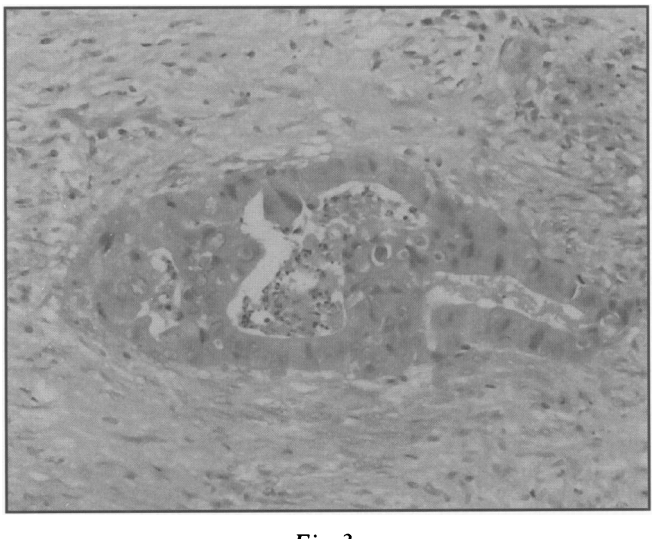


Fig 2.

bladder was solid and contained no bile, therefore along with cholecystectomy an adjacent cuff of the liver was removed. Histopathology showed a very rare, locally advanced primary malignancy of gall bladder with spread to the liver bed. The resection margins were clear. There was a biphasic pattern of malignant glands set in a malignant stroma in keeping with a carcinosarcoma (figure 2). This type of malignancy is probably primarily adenocarcinomatous with foci of sarcomatous change in poorly differentiated areas. Immediate post operative CT scan of the liver showed metastatic disease. The patient was treated with postoperative radiotherapy and palliative chemotherapy. Her last follow-up showed no change in the metastases in the liver on MRI.

CASE 3 A 75 year old female was referred with a history suggestive of obstructive jaundice secondary to gall stones. An abdominal scan showed multiple gall stones with a normal calibre common bile duct. The patient settled down on conservative management. A subsequent ERCP was normal. She underwent an elective laparoscopic cholecystectomy for gall stones six months later. Histopathology of the gall bladder showed a dysplastic lining mucosa from which a regular type, moderately well differentiated invasive adenocarcinoma was taking origin, and infiltrating to the circumferential limit (figure 3). The patient was offered further surgery but this was declined. The patient is being followed up and CT carried out one year after surgery does not show any evidence of metastatic disease.



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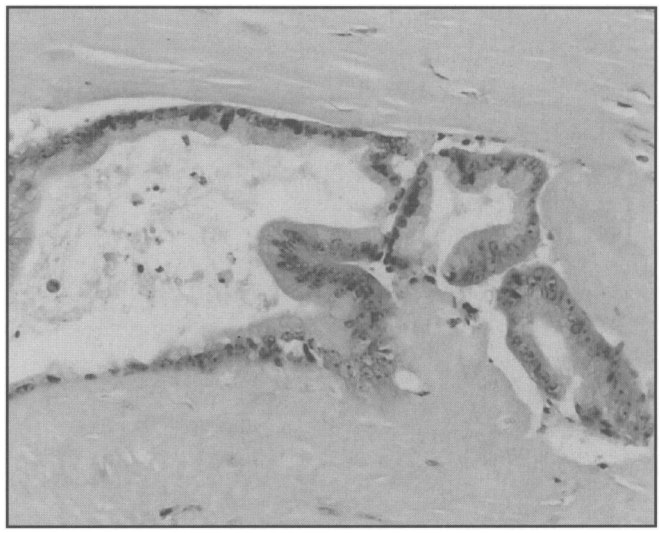

Fig 4.

CASE 4 A 70 year old female was admitted with a history of painless jaundice. An ultrasound scan showed a stone in the lower common bile duct. Considering the severity of jaundice and the size of the stone it was decided to proceed with open surgery. Cholecystectomy and common bile duct exploration were carried out and the stone was removed with the help of a choledochoscope. Histopathology showed a well differentiated mucinous adenocarcinoma seen throughout the full thickness of the heavily fibrosed gall bladder wall (figure 4). Postoperative CT scan showed no evidence of tumour in the lymph nodes or the gall bladder. The patient was offered the option of surgery for gall bladder resection but declined. The patient was given post operative radiotherapy and was well months after surgery.

DISCUSSION

Most clinicians view gall bladder carcinoma as an aggressive disease with very poor prognosis.[1] Recent advances in diagnostic imaging modalities,

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a better knowledge of the natural history of gall bladder disease [9] and reports of long term survival of more than fifty percent at five years after resection surgery have influenced many authors to advocate radical surgical treatment for gall bladder malignancies. Survival depends on the tumour type and on the ability to achieve a curative resection (R0) i.e. resection with a view to a cure leaving no tumour behind locally or regionally. The overall five-year survival rate is 52% after curative resection compared to only 5% after non- curative resection. The two patients with adeno carcinoma were alive and well, but the patient with squamous carcinoma died, and the patient with carcinosarcoma has metastases. This demonstrates the more aggressive nature of the unusual tumour types. The most common clinical staging used is the TNM staging which is as follows.

T0 No evidence of primary tumour

Tis Carcinoma in situ

Tl Tumour invades lamina propria or muscle layer

T1a tumour invades lamina propria

T1b Tumour invades muscle layer

T2 Tumour invades perimuscular connective tissue limited by serosa

T3 Tumour perforates serosa or extends directly into adjacent organs i.e. liver (<2cm)

T4 Tumour extends more than 2 cm into liver and/or into two or more adjacent organs

N0 no regional lymph node metastasis

N1 Metastasis in cystic duct, pericholedochal, and/or hilar lymph nodes (i.e. in the hepatoduodenal ligament)

N2 Metastasis in peripancreatic (head only), periduodenal periportal, coeliac and/or superior mesenteric lymph nodes

M0 no distant metastasis

M1 distant metastasis

STAGE GROUPINGS

Stage0 Tis N0 M0

Stage1 T1 N0 M0

Stage2 T2 N0 M0

Stage3 T1 N1 M0, T2 N1 M0, T3 N0 M0

As laparoscopic surgery has a potential to disseminate malignancy through port sites,[11] it is generally advised that patients suspected preoperatively of having carcinoma should not have laparoscopic surgery but rather undergo an open exploration with potential definitive resection. However, there is a high incidence of gall bladder carcinomas which are detected for the first time at histological examination. Most of the tumours discovered after laparoscopic surgery are early TI tumours but they may T2 tumours. The treatment for T1 disease still remains controversial [1,4] as some of the patient with early disease (T1b) might have lymph node involvement. Thus many authors would suggest that Tla could be successfully treated by simple cholecystectomy while patients with T1b require extended cholecystectomy.[4] For T2 disease, there is general agreement about the need for extended cholecystectomy as more than half of the patients are likely to have nodal metastases.[5] Tumours with penetration greater than or equal to T2 discovered after laparoscopic surgery should have further imaging to rule out disseminated disease. These patients should then undergo reexploration and a radical resection for potential cure.[12] It has been shown that aggressive resection for gall bladder carcinoma discovered laparoscopically is safe and effective. The role of resectional surgery for T3 T4 lesions is controversial as there are different reports as to the survival of patients after resectional surgery. Reports are present of improved survival after radical resection for stage T4 tumours from countries like Japan[10] but most reports from Europe[5] have failed to show improved survival. Thus major resections including regional and para aortic lymphadenectomy can be recommended only for selected patients with metastases limited to regional lymph nodes.[7] It is advisable that biopsy of para-aortic nodes is done before starting major resections as they are involved more frequently than expected and radical surgery in such patients offers no survival benefit. It is also imperative that the patients are in reasonably good health because of the high associated morbidity and mortality. Gall bladder cancers are generally not very chemo-or radio-sensitive. There have been reports suggesting that combining radiotherapy with aggressive resection for stage T4 tumours may improve survival.[3,8] As local recurrence is the main cause of failure, preoperative chemo radiotherapy has been tried in a prospective trial with encouraging findings.[13] Further prospective

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randomised trials will be required to evaluate the role of adjuvant therapy in the form of radiotherapy or chemotherapy, and their value with different tumour types.[5, 13]

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Case Report

Milk alkali syndrome

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The milk alkali syndrome was more commonly seen when milk and absorbable alkalis were the mainstays of treatment of symptoms due to acid-related upper gastro-intestinal disease. The syndrome became rarer after the introduction of the non-absorbable alkalis and H_2 receptor antagonists but it did not disappear altogether and should always be suspected when patients present with hypercalcaemia, renal impairment and metabolic alkalosis. Calcium carbonate is widely available in over-the-counter antacid preparations and is used in the prophylaxis and treatment of osteoporosis. An excessive intake can cause the milk alkali syndrome and it is possible that because of its increasing use more cases of the milk alkali syndrome will be seen in the future.

We report a case of the milk alkali syndrome in a female who took excess calcium carbonate as treatment for heartburn and vomiting. She was treated with intravenous saline and diuretics and made an apparently full recovery. She also received disodium pamidronate but it is unlikely that this contributed to her improvement.

CASE REPORT A 34 year old female presented in March 2001 with a short history of headache, vomiting, dizziness and leg pain. These symptoms started after the sudden death of her father-in-law two and a half weeks before. Her general practitioner found the creatinine to be 466 micromols/l (normal 40-110) and CO_2 to be 45 mmol/l (normal 22-30) and arranged for her admission. She had a history of inactive ulcerative colitis and of heartburn and dyspepsia for which she took 2 to 4 Rennie tablets (1.4 to 2.7 g of calcium carbonate) per day. She drank approximately twenty four units of alcohol a week. Physical examination only showed dehydration and blood pressure of 180/98 mmHg lying and 170/94 standing.

Investigations showed Hgb 11.6 g/dl (normal 11.5-16.5), WBC 7.0 x 10^9/l (normal 4.0-10.0), CRP 8 mg/l (normal 0-10), Na 136 mmol/l (normal 135-145), K 2.3 mmol/l (normal 3.5-5.0), Cl 90 mmol/l (normal 98-108), CO_2 38 mmol/l (normal 22-30), urea 18.4 mmol/l (normal 3.3-8.8), creatinine 267 micromol/l (normal 40-110), corrected Ca 3.39 mmol/l (normal 2.10-2.60), PO_4 0.83 mmol/l (normal 0.85-1.55), alkaline phosphatase 87 units/l (normal 35-120), parathyroid hormone 13 pg/ml (normal 10-85), and angiotensin converting enzyme 72 units/l (normal 27-100). Protein electrophoresis was normal and no Bence-Jones protein was found in the urine. Ultrasound scan of abdomen showed normal kidneys and renal tracts, and that of neck showed no enlargement of the parathyroid glands. X-rays of chest, hands, and skull were normal and isotope bone scan was normal. A barium meal as an outpatient showed mild gastro-oesophageal reflux and some crico-pharyngeal spasm.

She was treated with intravenous saline and bumetanide and urine output increased from 20 mls/hour on admission to a maximum of 240 mls/hour on day 6. The corrected calcium initially showed little change and disodium pamidronate was given on days 3, 4 and 5 (total dose 90 mg). By day 7 the corrected calcium was 2.76 mmols/l and creatine was 171 micromols/l. The blood pressure settled without specific treatment. She was questioned further about her calcium intake and it was found that during the time that she had been unwell she had been taking 36 Rennie tablets (24.5 g of calcium carbonate) per day. She was discharged on day 9 with a corrected calcium of

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2.80 mmols/l on no treatment other than ranitidine. She was advised not to take calcium-containing antacids.

At the outpatient clinic she reported feeling well with no heartburn. Corrected calcium was normal by day 14 (2.48 mmols/l) and remained normal thereafter. The parathyroid hormone level rose to 143 pg/ml on day 14, 163 pg/ml on day 25, and 114 pg/ml on day 63, before returning to normal at 60 pg/ml on day 203. Creatinine was normal by day 63 (95 micromols/l). No evidence of malignancy was found on investigation and the eventually normal calcium and parathyroid hormone would be very much against primary hyperparathyroidism. The final diagnosis was one of the milk alkali syndrome.

DISCUSSION

Sippy suggested in 1915 that patients with gastric and duodenal ulceration should be fed a milk and cream mixture hourly during the day and be given antacids hourly midway between feedings and in the evenings.[1] Some patients on this treatment developed headache, vomiting, dizziness and muscle and joint pain, and in 1923 Hardt and Rivers found that this subgroup had renal failure and metabolic alkalosis.[2] The hypercalcaemia which is now known to be central to the milk alkali syndrome was first described by Cope in 1936.[3] Over the next forty years the milk alkali syndrome was predominately a disease of men with peptic ulceration who were treating themselves with large amounts of milk and sorbable alkali such as sodium bicarbonate.[4] The incidence of the syndrome fell following the introduction of modern treatments and in the years 1985 to 1989 it averaged 2% of all patients admitted with hypercalcaemia.[4] Over the following four years, however, the incidence rose to an average of 12%, that for 1993 alone being 38%. The majority of patients in the later years were female and their calcium source tended to be calcium carbonate rather than milk. Biochemical evidence for this change was seen in a reduction in average phosphate concentration at presentation – milk contains phosphate, calcium carbonate does not.[4]

Calcium carbonate is a popular and effective antacid which is readily available over the counter. It is increasingly being promoted and prescribed for osteoporosis and other conditions. In limited amounts it is not toxic. It is poorly soluble in water but does dissolve in hydrochloric acid so that although only 1% of a dose is absorbed when gastric acid is lacking, 17% is absorbed when gastric acid is present.[5] Those who have had the milk alkali syndrome do not absorb more than normal controls. The lowest dose of calcium carbonate required to produce the milk alkali syndrome is probably around 10 g (4 g elemental calcium) per day. Individual susceptibility is dependent on factors such as pre-existing renal disease and concomitant treatment with thiazides.[6] Our patient was taking 24.5 g per day (36 Rennie tablets), a dose just over twice the manufacturer's recommended daily maximum of 16 Rennie tablets per day (10.9 g of calcium carbonate). The milk alkali syndrome is not listed as a complication on the product packaging but it is on the manufacturer's website [7] and perhaps the dosage warnings to the consumer should be stronger.[8] Patients should be advised to take no more than 3 to 3.75 g of calcium carbonate (1.2 to 1.5 g of elemental calcium) per day.[4]

DIAGNOSIS AND PATHOGENESIS

The diagnosis of the milk alkali syndrome depends on the history of ingestion of excess calcium and alkali, the finding of hypercalcaemia, renal impairment and metabolic alkalosis (of varying severity), and the exclusion of other causes. The pathophysiology of the syndrome is complex. While the increased intake of calcium must play a part, the central abnormality is a reduction in the ability of the kidneys to excrete calcium. As part of this reduction is due to the hypercalcaemia itself the possibility exists that a vicious circle will develop. The reduced excretion of calcium results both from a reduction in glomerular filtration rate and from an increase in tubular reabsorption of calcium due to alkalosis. Hypercalcaemia lowers the glomerular filtration rate directly by inducing renal vasoconstriction, and indirectly by reducing extracellular volume. (Stimulated calcium-sensitive receptors in the collecting ducts cause an isotonic polyuria by blocking the action of antidiuretic hormone, while similar receptors in the loop of Henle cause an increase in sodium loss (admittedly also increasing calcium loss and magnesium loss).) Further depletion of the extracellular volume occurs from the vomiting which is not uncommon in the milk alkali syndrome. Vomiting will also make worse any metabolic alkalosis caused by excess intake of alkali or by increased bicarbonate absorption from the renal tubules induced by hypercalcaemia. Suppression of parathyroid hormone, renal

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impairment and drinking milk will tend to increase phosphate levels, and hyperphosphataemia, hypercalcaemia, and alkalosis may lead to ectopic calcification. Nephrocalcinosis is common in chronic milk alkali syndrome (although it may not be obvious on plain radiography) and can result in permanent renal damage. The extent and reversibility of the renal failure depend on the duration and severity of the milk alkali syndrome. Some residual renal impairment occurs in many cases. It did not occur in this case due to the short duration of the illness.

The production of parathyroid hormone is regulated by calcium-sensitive receptors on the parathyroid chief cells and varies inversely with the plasma ionised calcium level. It might be expected that with hypercalcaemia the production of parathyroid hormone would fall and the plasma level would be suppressed. In our patient the parathyroid hormone level at presentation was towards the lower limit of normal but was not suppressed. The reason for this is not clear but it has been seen before.[4] Alkalosis does reduce the level of ionised calcium and perhaps the stimulation of the calcium-sensitive receptors was less than expected. Beall and Scofield found rebound hyperparathyroidism in two of seven patients with the milk alkali syndrome treated with saline diuresis.[4] The increase in parathyroid hormone followed hypocalcaemia in both cases. In the one patient for whom details were given the maximum decrease in calcium occurred on day 4 and the maximum rise in parathyroid hormone on day 8. They considered this rebound might be unique to the milk alkali syndrome and suggested that it was due to the absence of any force driving the calcium up once excess intake was stopped and rehydration started. Our patient also was found to have a rebound in parathyroid hormone following treatment but the peak occurred on day 25 and hypocalcaemia was not demonstrated. She received disodium pamidronate as well as saline and while pamidronate does not affect parathyroid hormone release from chief cells *in vitro*,[9] it does cause a rise in parathyroid hormone when given to patients with Paget's disease,[10] malignancy-associated hypercalcaemia [11] or hyperparathyroidism.[12] This rise (which peaks around day 7) is associated with a fall in calcium and presumably is caused by it. Pamidronate may have caused the rise in parathyroid hormone in our case although the longer time to peak level is unexplained. Bisphosphonates act by inhibiting osteoclastic bone reabsorption and have been found to be useful in hypercalcaemia due to malignancy[11] or hyperparathyroidism.[12] As this reabsorption is not thought to be excessive in the milk alkali syndrome, it is unlikely that the pamidronate helped our patient. Most cases of milk alkali syndrome begin to respond within 24 to 48 hours of treatment with intravenous saline and the elimination of calcium-containing alkali. It is common to administer a loop diuretic with the saline although this may not be very effective in the presence of renal failure. Haemodialysis may occasionally be required.

CONCLUSION

The incidence of the milk alkali syndrome may be increasing due to increased use of calcium carbonate. The elderly and those with co-existing disease will be more at risk. Most patients show a substantial improvement in renal function with treatment. The diagnosis can be missed if a detailed history of calcium and alkali ingestion is not elicited. Full details of all medication should be obtained whether prescribed or not as physicians and patients are often unaware that many non-prescription medications contain calcium and alkali.

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Case Report

Coeliac disease presenting with colonic lymphoma

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Coeliac disease is associated with an increased risk of small bowel lymphoma and adenocarcinoma.[1] The earliest association between coeliac disease and malignant lymphoma was reported by Fairley and Mackie (1937).[2] Histological stains enabled the identification of T-cell lymphoma, now designated as enteropathy-associated T-cell lymphoma (EATL) as the most common neoplasm (96%) associated with coeliac disease in one series,[3] and B-cell lymphoma accounting for the remaining 4%. The cause for this association remains uncertain. HLA genotyping has indicated that lymphoma is more common in DQA1*0501, DQB1*0201 individuals.[4]

Small bowel malignancy typically occurs in the fifth to seventh decades of life. Recent studies using population screening have provided an estimate of prevalence of coeliac disease (in particular, 1 in 122 in Northern Ireland [5]; 5.3 in 1000 in Sweden [6] and 4.9 - 5.7 in 1000 in Italy [7]). The common presentations of lymphoma are an exacerbation of their underlying disease (e.g. diarrhoea, pain, abdominal mass, weight loss) or a surgical complication (e.g. perforation, obstruction). We report a case of coeliac disease presenting with colonic lymphoma.

CASE REPORT A 63 year old man presented with one-month history of nausea, vomiting, diarrhoea and weight loss. He had a history of heavy alcohol consumption and previous bouts of morning diarrhoea for two years. Physical examination was unremarkable. Full blood picture, electrolytes and liver function tests were normal; the albumin was low. Following admission, he developed intermittent pyrexia and persistent diarrhoea despite anti-diarrhoeal medication.

On admission, antibodies to endomysium and tissue transglutamase (31Eu/ml, normal: 0-25) were positive. Endomysial antibodies were measured by immunofluorescence with a titre 1:5 or greater taken as positive, and tissue transglutamase was measured by immunosorbent assay (ELISA). OGD was performed, and duodenal biopsy showed partial villous atrophy. Colonoscopy showed a large flat ulcer at the distal transverse colon and biopsies revealed mucosal inflammation with no evidence of malignancy. He was commenced on a gluten-free diet. Ten days later, he developed two large episodes of bright red bleeding per rectum which required blood transfusion; however he continued to bleed and 48 hours later, laparotomy was undertaken.

At laparotomy, the ulcerated area of colon was identified and transverse colectomy was performed. It was also noted that a segment of ileum was thickened. No procedure was carried out on the small bowel. Histological examination confirmed an ulcer with appearances suggestive of malignant lymphoma. The lymphoma was covered by thick inflammatory exudates; probably explaining the initial benign colonoscopic biopsies. Some of the cells were positive for CD68. The majority of cells did not stain for either B- or T-cell markers. Therefore, it was regarded as a non-B, non -T cell lymphoma.

Due to the appearance of the small intestines at laparotomy, a small bowel series was carried out which was normal. Postoperatively, he became

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very depressed and his appetite waned and he was commenced on enteral feeding. Three weeks later he had a sudden deterioration and died due to pneumonia. Autopsy failed to show any further evidence of systemic lymphoma.

DISCUSSION

Lymphoma accounts for approximately 0.2 to 0.6% of large bowel malignancies.[8] The mean age of presentation is 55 years with a male preponderance.[9] So far, two risk factors have been identified: inflammatory bowel disease[10] and immunosuppression (post-kidney transplant, HIV, immune disorder).[11, 12] In coeliac disease a lymphocytic infiltrate develops in the gastric and colonic mucosa;[13] to date no association has been described between coeliac disease and colonic lymphoma. Immunological changes (rises in CD3+ and CD25+ lymphocytes and pro-inflammatory cytokines) have been noted in rectal mucosa of untreated coeliac patients, after a gluten challenge in the form of gluten enema had been given.[14]

As described above, microscopic inflammation is present in the colon of those with coeliac disease. It is possible that such inflammation could predispose to malignant transformation. As yet, this hypothesis remains untested. Colonic adenocarcinoma has been described in patients with coeliac disease.[15] In this report, three patients suffering from coeliac disease were found to have a right sided colonic adenocarcinoma. One patient was diagnosed with coeliac disease ten years previously and ulcerative colitis six years after that. The remaining two had the diagnosis of carcinoma and coeliac disease made within months of each other. There is one other documented case of colonic lymphoma in coeliac disease.[16] This was histologically a very different lesion from this case, being a diffuse differentiated T-cell lymphoma, which was treated primarily by chemotherapy.

There are several histopathological classifications of lymphoma due to the diverse morphology and cellular polymorphism of the disease. Descriptions such as malignant lymphomatous polyposis, tumours of mucosa-associated lymphoid tissue, tumours of 'centrocyte-like cells', 'maltoma' and polymorphic B-cell lymphomas have been used. Most immunohistochemical studies of gastrointestinal lymphoma have reported that the majority of tumours are of B-lineage via immunoreactivity with one or more B-cell markers.[17] However, some cases of high-grade lymphoma failed to stain with anti-leukocyte common antigen. In this case, tumour cells may stain positive for other antibodies that recognise leucocyte common related antigen. Yet, there is no specific combination of antibodies that allows positive identification of any of the histological subgroups.[18]

Prognostic data of primary colorectal lymphoma in the literature is scarce. Although histological stage significantly correlates with survival, in several series different pathological classifications were used. In another series, the presence of tumour cell MT2 immunoreactivity appeared to be a better determinant of prognosis than histological grade.[17] Surgical resection is recommended for localised colo-rectal lymphoma as it may provide important prognostic information, offer a chance for cure, with or without adjuvant therapy, and prevent surgical complications.[18] The value of chemotherapy, either alone or as adjuvant therapy for colonic carcinoma has not been prospectively evaluated. Radiotherapy and/or chemotherapy may also be of value for lymphoma with advanced stage and high-grade lymphomas.[17]

CONCLUSION

We have highlighted an uncommon disease occurring in the context of coeliac disease. This is the first report of coeliac disease in association with solitary colonic lymphoma, although there may be a possibility of the tumour occurring coincidentally in a patient with coeliac disease. A recent retrospective study in Northern Ireland had demonstrated that a third of patients with apparently spontaneous small bowel lymphomas had unrecognised coeliac disease.[19] This case may suggest that a similar search for coeliac disease in patients with colonic lymphoma might be appropriate.

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Case Report

Intestinal obstruction following blunt abdominal trauma

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Blunt abdominal trauma is a rare but recognized cause of small bowel obstruction. We report a case of intestinal obstruction in a 33 year-old male who initially was reluctant to volunteer the history of abdominal trauma. The omission of this important information significantly influenced the patient's diagnosis and management.

CASE REPORT A 33 year-old male with no past medical history was admitted with a three day history of central abdominal crampy pain radiating towards the right iliac fossa. At that stage he made no mention of abdominal trauma. Clinically he was tender with rebound in the right iliac fossa. Haematological and biochemical investigations were normal apart from a raised white cell count of 14.7×10^9/L. Plain abdominal X-ray was normal. Ultrasound scan of his abdomen showed some free fluid in the abdomen and pelvis. Non-specific bowel wall thickening was noted in the right iliac fossa. Because of the amount of free fluid a gastrograffin meal was performed; this was normal. A provisional diagnosis of appendicitis was made and the patient underwent an appendicectomy through a grid-iron incision. Approximately 500 mls of clear fluid were aspirated from the peritoneal cavity. The distal ileum was thickened and inflamed, there was no Meckel's diverticulum and the appendix appeared normal. Only an appendicectomy was performed. Apart from an ileus which persisted for three days postoperatively the patient made an uneventful recovery. On the day following surgery he admitted that he had been assaulted approximately four days before admission; he had received at least one blow to the abdomen. A CT scan of his abdomen was performed which again showed small bowel thickening in the right iliac fossa, but no other abnormality. Subsequent pathology of the appendix was reported as normal.

The patient was discharged on day six, because of the thickening of his terminal ileum an outpatient small bowel series was organized. The patient was admitted 14 days after surgery with acute central abdominal crampy pain. On examination his abdomen was distended, and clinically he had small bowel obstruction. FBP, U&E, CRP and amylase were all normal. A small-bowel series (Figure) showed dilated proximal and distal small bowel and a short stricture in the terminal ileum just before it entered the caecum. As this was a tight stricture a laparotomy was performed

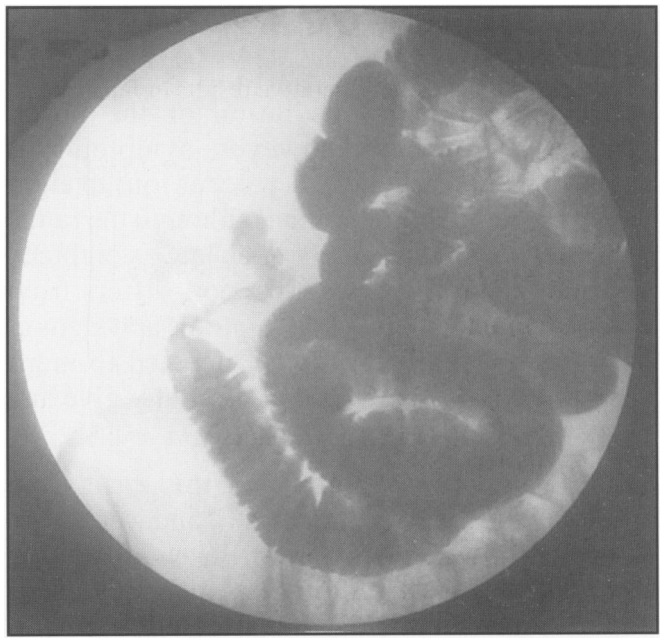

Fig. Image from the patient's small bowel series, demonstrating dilatation of proximal and distal small bowel and a short stricture at the terminal ileum just before it enters the caecum.

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through a midline incision. A hard mass was noted in the region of the terminal ileum and caecum and there was gross dilatation of the small bowel. A right hemicolectomy was therefore carried out with primary anastomosis. Post-operatively he made an uneventful recovery and was discharged on the eighth post-operative day.

Histology showed necrosis, ranging from partial to focal full thickness, of the terminal ileum wall, which had undergone repair by fibrous scarring. The surrounding fat showed evidence of extensive fat necrosis. A small extramural haematoma was also present. Microbiological investigations, including those for tuberculosis were negative. There was no evidence of any neoplastic process, nor of any stigmata to suggest Crohn's disease. The findings were consistent with a fibrous stricture secondary to trauma.

DISCUSSION

Blunt abdominal trauma is a recognised but rare cause of small bowel obstruction. Mechanisms responsible include falls, steering wheel and seat belt injuries or assaults, including child abuse.[1] Importantly, bruising or other visible signs of injury may not be present.[2]

In most reports the patient is managed conservatively with resolution of the initial symptoms. Typically however, symptoms of small-bowel obstruction then occur four to eight weeks after the initial trauma, although the range is as early as thirteen days or as late as eighteen years after the injury.[2] This report differs from others in that the patient's symptoms and signs at the time of presentation were deemed to merit surgery and the patient did not initially give any history of trauma.

On readmission, symptoms in this case were similar to those in other reports [3,4] and were those of small-bowel obstruction. A small-bowel contrast study is the radiological investigation of choice, and identifies the affected segment. Diagnostic confusion can occur since a small bowel series may fail to distinguish post-traumatic stenosis from Crohn's disease, as radiologically they may appear similar.[5] Treatment is always surgical, with excision of the stenosed bowel segment and primary anastomosis.[5]

The pathological mechanism causing small bowel obstruction is local ischaemia. This heals with fibrosis and stricture which causes the delayed onset of symptoms. Two separate mechanisms for local ischaemia are known. In the first, injury to the mesentery impairs the blood supply to the bowel, resulting in a stenotic segment, often adjacent to a mesenteric tear. This method of injury is more common in the proximal jejunum and distal ileum. The mesentery is fixed at these points, and may be more likely to tear in response to a shearing force.[2]

In the second, the mesentery is not torn but direct trauma causes sufficient damage to the small bowel to result in haernorrhagic mucosal infarction. Subsequent healing by fibrosis gives cicatricial stenosis and secondary small bowel obstruction.[5]

In previous reports histological examination of the stenotic segment showed fibrosis, ulceration and transmural chronic inflammatory infiltrates with granulomata in the submucosa. Diagnostic difficulty can occur. Distinguishing features of traumatic stricture from Crohn's disease are haemosiderin-laden macrophages and fat necrosis.[2]

In conclusion, this report highlights some well-recognised features of post-traumatic stenosis of the small bowel. Trauma may be trivial. Initial symptoms may resolve and definitive presentation with obstruction occurs weeks after injury. Small bowel series and surgical intervention are the preferred investigation and treatment. However this case is unusual in that the history of trauma was not initially forthcoming. It must be remembered that significant injury can occur without visible signs of trauma. Reported levels of assault and violence are increasing in our society.[6] Even when no history of trauma is given by a patient it should be considered as a possible cause of symptoms when young people present with abdominal pain, or when investigation or surgery demonstrate unexpected findings.

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Case Report

"Bird Fancier's Mouth", an unusual case of obstructive sialadenitis

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We report an unusual case of a patient who developed obstruction of the duct of her left submandibular salivary gland, with subsequent sialadenitis, from impaction of a bird feather. This was most likely the result of her habit of nuzzling her cockatoo and sucking its feathers. Following removal of the feather and antibiotic therapy, she made an uneventful recovery.

CASE REPORT A 49 year old female presented at the Accident and Emergency Department, having been referred by her General Practitioner. She complained of pain on the lower left side of her face and mandibular region, radiating into her ear. Examination revealed a low grade pyrexia of 37.5°C, with tender swelling of her left submandibular salivary gland. Inspection of the floor of the mouth revealed a black linear object protruding approximately 3cm from the orifice of the left submandibular duct. It appeared to have a flexible tip and initial concerns were of some type of worm.

The black structure was grasped with a pair of forceps and dislodged easily from the duct, releasing a discharge of blood and pus from the orifice. Inspection of the foreign body revealed it to be an inert structure. Initial thoughts that it may have been a mass of matted animal hair or a worm were unfounded when it was teased out and found to represent a feather.

On specific questioning, she gave no history of recent travel abroad, but owned a small puppy and a cockatoo. She admitted being very affectionate with her animals, kissing and nuzzling them frequently, including sucking at her cockatoo's feathers.

The patient was treated with Co-amoxiclav and Metronidazole and made an uneventful recovery.

DISCUSSION

Obstruction of the ducts of the salivary glands, leading to sialadenitis, is a far from rare occurrence. Such obstruction is most commonly due to calculus formation in the duct, with stasis leading to infection [1] although neoplasms of the gland [2] or an epidermoid cyst [3] may result in salivary stasis and infection. Obstruction of the punctum by dentures,[4,5] a fingernail [6] and a fishbone [7] have also been documented as causes of obstructive sialadenitis. Rarely, isolated submandibular suppurative sialadenitis can present in the premature neonate.[8]

This case is very unusual because of the bizarre nature of the foreign body. Close contact with animals including birds may cause a variety of specific zoonoses, but this case demonstrates an illness caused by a mechanical complication of close contact with a cockatoo.

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Case Report

Perforation of the sigmoid colon secondary to localised amyloidosis

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Accepted 12 August 2002

Amyloidosis is a heterogeneous group of disorders characterised by systemic or localised extracellular deposition of an abnormal protein material in the interstitium of organs and tissues, often resulting in functional impairment.

Although the gastrointestinal tract is susceptible to the deposition of amyloid materials with systemic disease, localised amyloidosis of the gut is very rare.[1] Complications associated with amyloidosis of the gastrointestinal tract are uncommon and colonic perforation is exceptionally rare. We report a case of perforation of the sigmoid colon secondary to localised amyloidosis and review other reports in the literature.

CASE REPORT An 88 year-old male patient presented with an acute onset of severe generalised abdominal pain. Over the previous five years he had undergone investigation for episodes of abdominal pain and rectal bleeding. Previous endoscopic examinations had revealed both sessile polyps and areas of ulceration in the sigmoid colon. Biopsies on each occasion had demonstrated colonic amyloidosis. He had no other relevant past medical history.

On admission, he was distressed but apyrexial. Abdominal examination revealed generalised tenderness with marked guarding and rebound, and absent bowel sounds. Rectal examination revealed no abnormalities. Initial haematological investigations and abdominal X-rays were normal.

At laparotomy he was noted to have generalised faecal peritonitis with a perforated sigmoid colon. The remainder of the colon and small bowel was grossly normal. A Hartman's procedure was performed and the peritoneal cavity was thoroughly lavaged. Postoperatively, he was treated with intravenous antibiotics and made a satisfactory recovery.

The gross specimen consisted of a 26 cm length of sigmoid colon which showed focal mucosal ulceration, perforation with a surrounding serosal reaction and marked thickening of the bowel wall

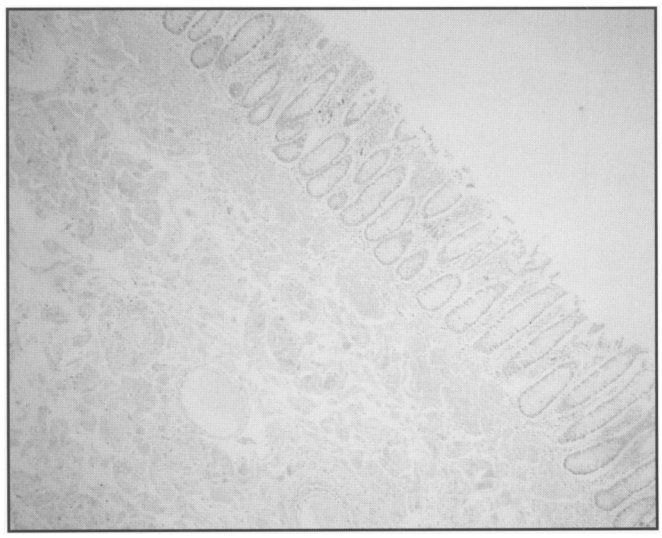

Fig 1. Congo red stain demonstrating submucosal amyloid (Magnification x 144).

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over a 15 cm segment. In addition, there was a 0.5 cm adenomatous polyp. Histology revealed mucosal ulceration and expansion of the submucosa by amorphous eosinophilic material (fig 1) which also extended between smooth muscle bundles in the muscularis propria. This material resembled amyloid histologically. There was a localised peritonitis adjacent to which deposits of amyloid were also present (fig 2). Congo red staining was positive both before and after treatment with potassium permanganate (KMnO4) and the typical apple green birefringence on examination under polarized light was observed. Immunohistochemistry showed lambda (λ) light chain positivity but

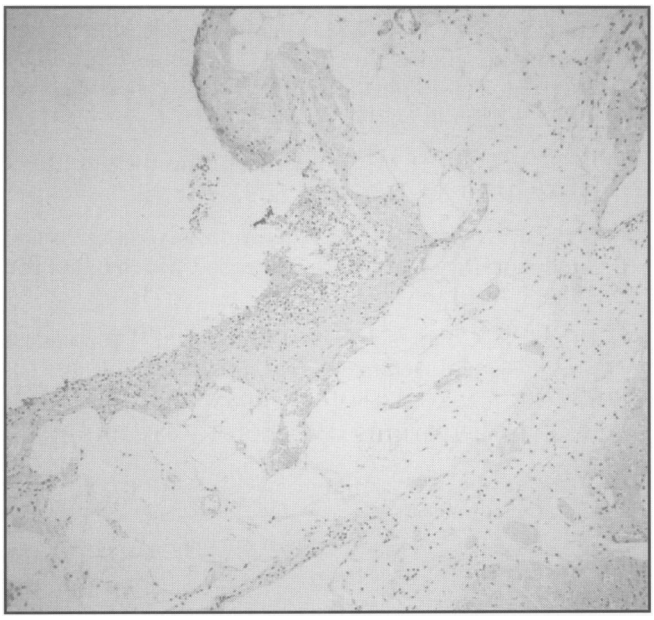

Fig 2. Haematoxylin and eosin preparation demonstrating serosal deposition of amyloid and evidence of peritonitis (Magnification x 60).

negativity with Kappa (κ) light chain, AA protein, AP protein and Transthyretin. Electron microscopy showed rigid non-branching fibrils 10-15 mm in diameter in keeping with amyloid.

Subsequent investigations to exclude other concomitant conditions revealed an ESR of 30 mm/hr, normal plasma protein electrophoresis and urine testing was negative for Bence Jones proteins.

DISCUSSION

Many classifications of amyloidosis have been proposed. In general, however, amyloidosis can be divided into two categories – systemic and localised. The systemic category, which commonly involves the gastrointestinal tract, includes primary (idiopathic) amyloidosis, secondary (reactive) amyloidosis (occurs in association with chronic inflammatory conditions, such as rheumatoid arthritis, ankylosing spondylitis, connective tissue disorders, tuberculosis, osteomyelitis, neoplasia or inflammatory bowel disease), amyloidosis associated with multiple myeloma or other plasma cell dyscrasias and familial types of amyloidosis. The protein deposited in primary (AL) amyloidosis is a normal immunoglobulin light chain (intact or N-terminal fragments of Igκ or Igλ) that is overproduced by an aberrant B-cell clone. In reactive (AA) amyloidosis the protein deposited is a normal serum protein, amyloid A component (AA), an acute-phase reactant that is produced in the liver in response to inflammation. Overproduction of transthyretin is indicative of senile amyloidosis or familial types of amyloidosis. Dialysis-associated amyloid is associated with the accumulation of β2-microglobulin.

Localised amyloidosis is site-limited and does not progress to systemic involvement. It commonly affects the skin, respiratory tract or genitourinary tract. The gastrointestinal tract is rarely involved, with fewer than 20 cases reported in the literature. Congo Red staining and its resultant green birefringence when viewed with high intensity polarised light, is pathognomonic for amyloidosis. The potassium permanganate (KMnO4) method or immunohistochemistry may be used to investigate amyloid protein types. Failure of pre-treatment with KMnO4 to abolish Congo Red positivity is more in keeping with AL amyloid, but it is not specific. The amyloid deposits in this case showed positivity for lambda (λ) light chains using immunohistochemical techniques. Although this is commonly associated with systemic amyloidosis, it is also often seen in localised amyloidosis. In view of the absence of detectable abnormal proteins in the serum and urine, and since other chronic inflammatory conditions, such as collagen diseases and multiple myeloma were excluded, this case was diagnosed as localised amyloidosis of the gastrointestinal tract.

Histopathologically, deposits of amyloid are either found in and around the walls of small submucosal blood vessels or within the mucosal layer and/or muscular layers of the gut wall. In most cases, the submucosal blood vessels are the

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earliest and most frequent site of amyloid deposition. This can lead to blood vessel narrowing or occlusion, with resulting ischaemia, infarction or perforation.

Gastrointestinal amyloidosis, whether systemic or localised, can present in a variety of ways. The commonest symptoms of amyloidosis affecting the large bowel are abdominal pain, rectal bleeding, weight loss and watery diarrhoea, however, involvement of the intestinal musculature may cause pseudo-obstruction. Intestinal infarction, ischaemic colitis and mass lesions mimicking malignancy have all been reported. Intestinal perforation is an exceptionally rare complication with only six previous reports in the literature.[2-7] This patient had been noted on previous endoscopic examinations to have had both sessile polyps and areas of ulceration in the sigmoid colon and subsequently presented with perforation secondary to severe ulceration.

Localised amyloidosis is essentially a benign condition; however, systemic amyloidosis is almost invariably fatal and treatment is mainly supportive. Death usually follows a cardiac event or renal failure. Median survival in primary systemic amyloidosis is between 12 and 15 months and most patients succumb within 3 years of diagnosis.[8] In amyloidosis associated with multiple myeloma the prognosis is even worse, with a median survival of only 4 months.[8] Outlook is better for secondary amyloidosis where survival up to 5 years is common [9] and there are occasional case reports documenting long-term survival. No specific therapy is available, however, for systemic forms of amyloidosis; treatment of the underlying disease is of prime concern.

Surgical intervention for amyloidosis affecting the gastrointestinal tract should be reserved for emergency procedures only, such as in patients with massive bleeding, perforation or obstruction, as there may be an associated haemorrhagic diathesis, or anastomotic dehiscence resulting from poor local healing. In the present case, the diagnosis had been made five years previously, but active surgical intervention was undertaken only when the patient presented with an acute abdomen.

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Case Report

Histoplasmosis as a presentation of Human Immunodeficiency Virus Infection

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Accepted 12 August, 2002

Opportunistic fungal infections account for a significant amount of morbidity associated with HIV disease. In Northern Ireland approximately 10% of our HIV positive patients have acquired their disease in foreign climes, particularly sub-Saharan Africa and the United States of America. This, coupled with increasing travel in general abroad, increases the likelihood of them acquiring opportunistic infections not often encountered in the United Kingdom. We report here a case of localised oral histoplasmosis without evidence of disseminated disease in a patient who had just been diagnosed as having HIV infection. Reactivation of latent histoplasma infection occurred as a result of previous exposure in South Africa following gradual depletion of his immune function by HIV infection.

CASE REPORT

History

A 51 year old heterosexual male presented to our department in May 2000. He had been diagnosed with palatal histoplasmosis one week previously in South Africa prompting a HIV test which returned as positive. He had immediately flown back home to Northern Ireland for treatment. His symptoms started in 1996 when he developed recurrent mouth ulcers and overgrowth of his gums. This persisted and in 1999 he developed a cough, intermittently productive of green sputum, recurrent fevers, and boils in the axillae and groins. In January 2000 his symptoms had increased in severity to such an extent that they were affecting his ability to eat and drink. He was unable to expectorate sputum because of pain in his mouth. He attended both his general practitioner and dentist over the following months where he was diagnosed as having recurrent chest infections and blocked sinuses respectively. He failed to respond to antibiotic treatment. Upon referral to an oral surgeon in April a palatal biopsy revealed histoplasmosis infection. A subsequent HIV test was positive.

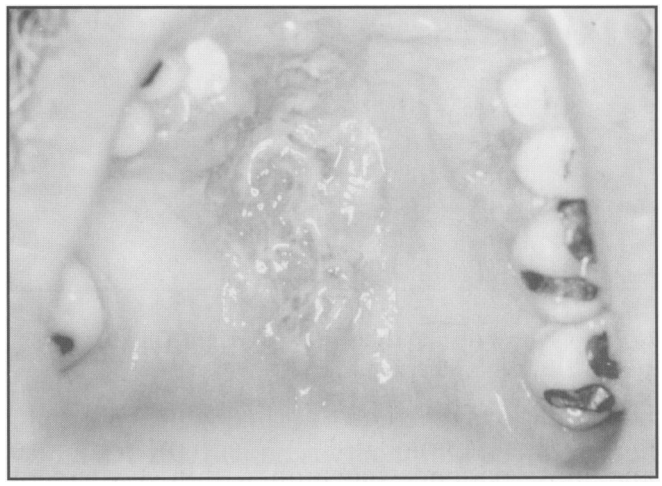

Fig 1. Necrotic ulcerated lesion on the hard palate.

Since leaving the United Kingdom in the 1960s he had lived and worked in different African countries, finally settling in South Africa. He had had multiple heterosexual encounters which included professional sex workers.

Examination revealed a well looking man with an ulcerated necrotic area on the roof of his mouth (figure 1). A raised nodule 0.5 cm in diameter was present on the dorsum of the right hand. The rest of the examination was unremarkable.

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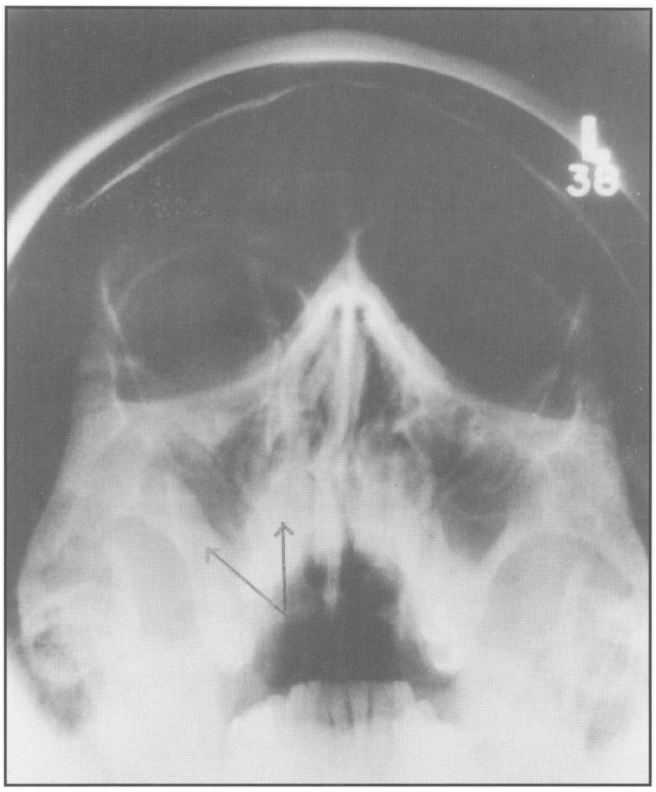

Fig 2. X-ray of maxillae showing right sided mucosal antral thickening.

Investigations revealed a normal white cell count but a reduced lymphoctye count –0.9 x 10 /L (1.5 – 3.5). His CD4 count was 0.06 x 10^9 /L (0.5 – 1.6). Confirmatory HIV testing was positive. Microscopy of sputum showed occasional pus and epithelial cells. Culture of sputum, blood and a swab of the palatal ulcer showed no growth. Analysis of urine for histoplasma antigen was negative. A chest radiograph was normal but a radiograph of facial bones showed maxillary antral mucosal thickening of the lateral wall (figure 2). Histology of a palatal biopsy obtained from South Africa showed an inflammatory infiltration of mainly histiocytes in the subepithelial stroma with areas of necrosis. PAS staining revealed small fungal organisms lying within the cytoplasm of the histiocytes (figure 3). Biopsy of the lesion on the hand showed it to be molluscum contagiosum.

Treatment with intravenous amphotericin B encapsulated in lysosomes at a dose of 0.5mg/kg was given for two weeks. Thereafter oral antifungal treatment in the form of itraconazole 200mg daily was the commenced. Prophylaxis for *pneumocystis carini* infection with cotrimoxazole was changed to dapsone 100 mg daily following development of a widespread maculopapular rash. His cough settled within the

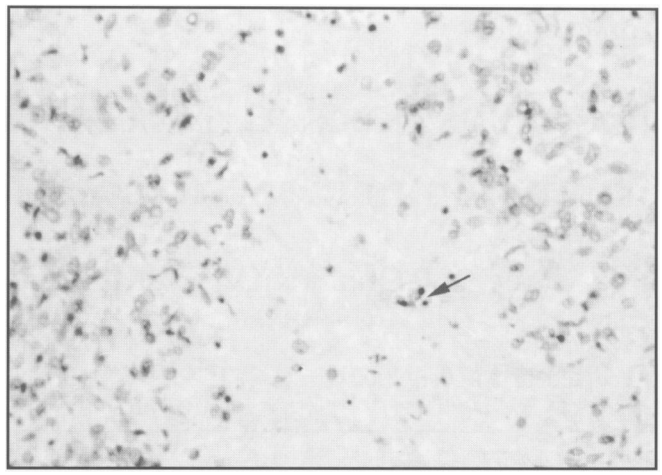

Fig 3. Palatal biopsy with PAS staining showing a granuloma with a necrotic centre in which small fungal organisms of histoplasma may be seen (x 40).

first week and the palatal lesions had gradually regressed. Repeat blood investigations showed his CD4 count to have increased to 0.11 x 10/L. After discussion with the patient an antiretroviral regime was chosen and commenced.

DISCUSSION

This 51 year old man had symptoms suggestive of oral histoplasmosis for four years prior to a definitive diagnosis. This led to the diagnosis of co-existent HIV infection. He responded very well to antifungal treatment. Attempts to diagnose infection at other sites (for example, paranasal sinuses) were not undertaken as his response to treatment was so prompt.

Histoplasma capsulatum is a dimorphic fungus, distributed worldwide between latitudes 45 north and 30 south of the equator. It is endemic in certain areas of north and south America, where it remains a major health problem.[1] It is acquired by inhalation of fragments of the mycelial form which are deposited in the pulmonary alveoli and converted to the yeast form at body temperature. CD4 T lymphocytes are crucial to the host's defence, hence the susceptibility of immunocompromised individuals.[2]

In immunocompetent individuals 90% of infections are asymptomatic. In HIV positive patients histoplasmosis usually presents as a disseminated infection and is categorised as an AIDS defining illness in such patients. It has been reported as the second or third most frequent opportunistic infection in HIV positive patients living in endemic areas.[2]

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The pattern of clinical presentation is varied – fever, weight loss, respiratory complaints, lymphadenopathy, hepatosplenomegaly, skin and oral lesions [3] and central nervous system involvement can occur with 5 - 10% of patients presenting with symptoms of septic shock.[4]

Blood tests may show anaemia, neutropenia or thrombocytopenia reflecting bone marrow involvement with the fungus. Liver function tests may be abnormal.

Diagnosis is based on culture of the fungus from blood, sputum or other clinical specimens. Histopathological examination of biopsy material (eg. lung, skin), bone marrow aspirate or lavage fluid may also be diagnostic.

Detection of anti-histoplasma antibodies in serum by either immunodiffusion techniques or a complement fixation test yields a sensitivity of 70-80%. However 30-50% of immuno-compromised individuals fail to develop detectable titres of antibody.

Detection of histoplasma antigen in the urine or serum yields sensitivities of 90 and 50% respectively. It is useful in immunocompromised patients and allows serial monitoring to assess response to therapy, however it is not widely available.[5]

Treatment with amphotericin B at a dose of 0.5 to 1.0 mg/kg for a total dose of 0.5 to 1.0 gm gives a response rate of 85-90%. Amphotericin B encapsulated in liposomes is being increasingly used as it causes fewer adverse reactions. Itraconazole orally at a dose of 400 mg daily showed a response rate of 85%, however patients with severe life threatening illness or central nervous system involvement were excluded from this study.[2]

Suppressive therapy with itraconazole a dose of 200 to 400 mg daily has been shown to be highly effective in preventing relapse whether initial treatment was with amphotericin B or itraconazole. Amphotericin B given by weekly or biweekly infusion resulted in 85-90% relapse free survival but may require an indwelling intravenous catheter. Long term continuation of maintenance treatment is recommended.[3]

Future therapies may include chloroquine which has been shown to greatly augment the ability of human macrophages to inhibit the intracellular growth of histoplasma yeasts. Nikkomycin Z is highly active against Histoplasma capsulatum in vitro. It has been shown to treat murine histoplasmosis successfully but has not yet been trialed in humans. A vaccine, made from the glycoprotein yeast wall, has been shown to confer protective immunity in mice against experimental infection. A human vaccine may be of benefit in the immunocompromised patient or military personnel in endemic areas, or those exposed to histoplasma occupationally.

The incidence of HIV infection in Northern Ireland continues to rise with a significant number of patients originating from Africa and America. Travel to distant climes, is increasing. It is very likely that in the future more cases of fungal infection, previously viewed as exotic, will be seen by doctors and dentists here.

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Book Reviews

The Dad's Survival Guide: the early years. Ian Banks. The Blackstaff Press. ISBN 0-85640-696-1. £9.99.

Like a hirsute Lord Reith; his mission: to inform and educate, Ian Banks returns to a bookshop near you. From TV to VD; you name it, he's covered it. The prolific Dr Banks latest offering weighs in at 192 pages, and is presented in the disarming and humorous style that is his moniker. Settling into an armchair, your reviewer elected to approach the project from the perspective of someone with no medical knowledge. "As a radiologist" you chorus, "you're practically there already." Quite.

There are chapters dealing with contraception, antenatal care, delivery, and others dealing with the odyssey that is being a father during those early childhood years. Banks' style is never less than engaging, and he writes with the assured style of someone who was that soldier at every stage: a medical man who has been there, seen it, done it, treated it, bought the tee-shirt if not the actual 'kiss-me-quick' hat.

The section at the back of the book is styled as the ultimate survival package for childrens' problems and their illnesses. It is well laid-out, immediately accessible, and written in a didactic but logical form. Everything from allergies through vaccination, meningitis, and rashes, to worms is included, with practical help and guidance on teasing out the serious from the trivial.

One excellent feature is the fathers' quotation box. Each is located in the book margin and vary in content from the funny to the very moving. I loved the (perfectly true) observation by one father that the worst three things about having a new baby in the house were 'lack of sleep, lack of sleep, and lack of sleep; in that order'.

In the chapter "So, who looks after the children?" Banks tackles the very traumatic themes of divorce, single parenting, and the changing role of the father. The accompanying quotations make for grim but thought-provoking reading, and would be, in my view, a sufficient reason in itself to purchase this book.

Dr Banks set himself the not inconsiderable challenge of producing a text, which is not just medical, but asks pertinent questions of us as fathers in society. Someone once said "looking for the answers just gives me indigestion, when I spent so much time just dealing with the question." Dr Banks entertains and informs. Lord Reith would approve, I suspect.

B KELLY

Law for Doctors, Principles and Practicalities: M. A. Braithwaite. 2000 Royal Society of Medicine, Press Ltd. ISBN 1:85315-465-2.

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A crowded undergraduate curriculum means that, in general, doctors on qualification have scant knowledge of the many and various ways their careers will interface with the law over a professional lifetime and doctors already in training and career grades in all disciplines of medicine may only come to know of the medicine/law interface when they are asked to be involved either in relation to personal practice or on behalf of a patient.

Two recent concise books serve to assist in providing doctors at all stages of their career with a knowledge of law relevant to medical practice and the practical aspects of medical evidence.

Law for Doctors, Principles and Practicalities is a well referenced eighty-four page guide to medical law for doctors. It is clearly and concisely written and progresses from a chapter on Structure and Sources of English Law through Negligence, Foreseeability and Causation, and Financial Compensation to new procedural rules, in particular the Woolf Reforms, and the role of expert witnesses. Reference is made to differences between English Law and Law in Northern Ireland and Scotland. Chapters on Confidentiality and Disclosure, Complaints, whistle-blowing and disciplinary proceedings, the Coroner's Court and Doctors and the Criminal Law will be of interest and value to all doctors.

In summary this book provides essential legal background reading for most legal matters affecting doctors with good references for more detailed reading if required.

Medical Evidence, a Handbook for Doctors deals with the practical aspects of a doctor's involvement in giving evidence in a range of Court scenarios. The Coroner's Court, Tribunals, including Mental Health Review Tribunals, the Council Court and the Civil Court are dealt with in individual chapters in a publication extending to some 135 pages.

There is much useful information on the respective roles of the professional and expert witness, the preparation and format of medical reports and appearing in court. Twenty-five key reference sources are listed at the back of the book.

No doctor should be involved in writing reports or appear in a variety of courts without being familiar with the contents of this book.

Law for Doctors, Principles and Practicalities and Medical Evidence – A Handbook for Doctors are complementary and very readable publications. In an era where doctors' practice increasingly interfaces with legal matters, and where there is an increasingly litiginous society, these books should find a place, not only on every doctor's bookshelf, but more widely among healthcare workers and healthcare management. Too often in medicolegal business an advanced stage is reached with key healthcare participants displaying little knowledge of legal procedures and process. Knowledge of the content of these publications will assist doctors in all aspects of medicolegal work and serve to allow them to perform to best ability when inevitably court attendance will be required at some stage in a medical career.

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D P NICHOLS

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M I WIGGAN

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