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Colorectal cancer treated at Christchurch Hospital, New Zealand: a comparison of 1993 and 1998 cohorts
B Robinson, F Frizelle, M Dickson, C Frampton

This study is a collaboration between the Oncology Service and Department of Surgery in Christchurch Hospital, New Zealand where we reviewed and compared the management and outcome of patients treated for colorectal cancer during two time periods (1993–4 and 1998–9). Survival improved over the 5-year period (1993–4 to 1998–9) for the various stages (Dukes' stages) of the cancer as well as overall. The improvement in survival in the later group of patients (1998–9) has been associated with more operations by specialists in colorectal surgery, more frequent staging by computed tomography (CT) scanning, and greater use of chemotherapy.

Excess cost associated with *Staphylococcus aureus* poststernotomy mediastinitis
A Upton, P Smith, S Roberts

This study quantifies the cost associated with serious wound infections following cardiac surgery. Nine patients who developed deep-wound infections due to *Staphylococcus aureus* were compared with nine patients who underwent the same procedure but did not develop infection. Patients with infected wounds had a mean excess hospital-related cost of $45,677. This study emphasises the potential and substantial cost-savings associated with preventing surgical-wound infections.

Effect of volcanic gas exposure on urine, blood, and serum chemistry
M Durand, C Florkowski, P George, T Walmsley, P Weinstein

In this research we investigated changes in the chemistry of the urine, blood, and serum of volunteers who were exposed to volcanic gas. Aluminium and rubidium—which are abundant in volcanic gases but relatively scarce in body fluids—were found to be at significantly higher concentrations in urine following the exposure to gas. The results suggest these elements may be useful biological markers of volcanic gas exposure. This is potentially important for volcanologists (for whom volcanic gas can be an occupational hazard) who may work without always using respirators near fumaroles, lava flows, or other sources of volcanic gas.

Measurement of thiopurine methyl transferase activity guides dose-initiation and prevents toxicity from azathioprine
C Sies, C Florkowski, P George, R Gearry, M Barclay, J Harraway, L Pike, T Walmsley

Azathioprine is an effective and commonly prescribed drug used to treat conditions as diverse as inflammatory bowl disease, acute lymphocytic leukaemia, and some dermatological disorders. Approximately 10% of patients have a genetic make-up that means that treatment by standard dosage of this drug may be ineffective, or may lead

to serious toxicity. A blood test predicting which patients will be at risk of unwanted toxic side-effects (or may require higher drug doses) is now available, thus providing personalised medicine including the safe and optimal use of azathioprine.

Recurrent myoglobinuria due to carnitine palmitoyltransferase II deficiency: clinical, biochemical, and genetic features of adult-onset cases
D Kilfoyle, D Hutchinson, H Potter, P George

Dr Kilfoyle and colleagues have reviewed their experience in Auckland with carnitine palmitoyltransferase II (CPT II) deficiency—a rare, inherited metabolic disorder. Due to deficiency of the enzyme CPT II, patients have restricted ability to metabolise fatty acids within their skeletal muscles. Furthermore, following exertion, they are prone to dramatic episodes of muscle pain and sometimes acute kidney failure. CPT II deficiency can mimic other disorders, and the diagnosis relies on careful neurologic evaluation, muscle biopsy, and biochemical and genetic laboratory tests.

Getting started as a hepatobiliary surgeon: lessons learned from the first 100 hepatectomies as a consultant
J Koea

Liver surgery is often perceived as difficult and dangerous. Consequently training in liver surgery has been hard to obtain. However several recent technical advances have now made liver surgery safe. This paper describes the experience obtained with the first 100 liver resections carried out by a newly trained surgeon in New Zealand.

Elevation of serum liver enzymes after laparoscopic cholecystectomy
G Sakorafas, G Anagnostopoulos, V Stafyla, T Koletis, N Kotsifopoulos, S Tsiakos, G Kassaras

Laparoscopic cholecystectomy has been reported to cause liver changes in patients with a preoperative normal liver function. We examined the liver function (before and after operation) in 72 consecutive patients who underwent laparoscopic cholecystectomy (key-hole operation) as well as in 36 consecutive patients who underwent open cholecystectomy. Alterations in hepatic function occur after laparoscopic cholecystectomy and appear to be clinically insignificant. No alterations in liver function seem to occur after open cholecystectomy

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Good news for patients with colorectal cancer?

Ian Bissett

New Zealand has one of the highest incidences of colorectal cancer (CRC) in the world. This issue of the *Journal* provides some evidence that the lot of these patients may be improving. Bridget Robinson et al (*Colorectal cancer treated at Christchurch Hospital, New Zealand: a comparison of 1993 and 1998 cohorts*. URL: http://www.nzma.org.nz/journal/118-1210/1323) have presented the outcomes of two cohorts of CRC patients separated by 5 years and followed up for a minimum of 42 months.

The patients have all been treated in Christchurch Hospital either for their initial surgery or for subsequent chemotherapy and their outcomes compared. The authors suggest that the 1998 group does better—based on improved overall and disease-specific survival. There were, however, significant differences in the composition of the cohorts, including more patients with advanced disease and fewer patients receiving chemotherapy in the first group. There is no indication of the relative proportions of public and private patients in each cohort, but the great leap from 44% to 82% with the consultant as operator suggests that this 1998 group may have many more patients operated on in the private sector.

In an attempt to adjust for these differences the survival was analysed by disease stage and by using multivariate analysis (MVA). 'Consultant as operator' and 'administration of chemotherapy' were not significant variables in determining outcome after MVA, but cohort remained so. Indeed, this is strong evidence that the 1998 group's survival was better (independent of chemotherapy and Australian Clinico-Pathological [ACPS] Stage). This improvement over time has also been reported by other authors[1,2] which suggests that *improving surgical technique is one of the factors leading to improving survival*.

Outcomes in rectal cancer have been shown to be related to surgical technique[3], surgical training,[4]and unit volume.[5] For example, Porter et al[4] (in a study of 683 patients with rectal cancer in Canada) showed that when the results of colorectal trained surgeons with a high volume of surgery were compared with surgeons without specific training and performing low volumes of rectal cancer surgery cancer-specific survival was increased almost twofold and the local recurrence rate reduced by 75%. Similar results with respect to surgical technique have been reported in the New Zealand context.[6]

Those patients who develop liver metastases from CRC can now be offered further treatment. The 5-year survival for patients undergoing potentially curative resection of colorectal metastases is about 30%.[7] Historically, the obstacle to offering surgery to these patients has been the technical difficulty of the surgery and its significant mortality.

Jonathan Koea, in this issue of the *Journal*, has reported the short-term outcome of his first 100 liver resections as a consultant (*Getting started as a hepatobiliary surgeon: lessons learned from the first 100 hepatectomies as a consultant*. URL:

http://www.nzma.org.nz/journal/118-1210/1322). The largest group of patients in this series has liver metastases from CRC. Although the surgical morbidity is high (52%), the mortality is only 3% and comparable with other established centres. Similar results have been previously reported in New Zealand.[8]

Not all patients with CRC metastases to the liver are suitable for surgery but only those with disease that is confined to the liver and whose metastases can be resected leaving sufficient residual functioning liver. The cases reported in this issue of the *Journal* by Simon Janes give some hope for those patients whose tumour initially appears irresectable (*Metastatic colorectal carcinoma: clinicopathological downstaging following neoadjuvant chemotherapy*. URL: http://www.nzma.org.nz/journal/118-1210/1321).

Janes reports on three patients with metastatic CRC who show dramatic response to chemotherapy with no evidence of residual disease on microscopic examination of the resected liver tissue. In addition, Adams et al[9] reported on 701 patients (with initially irresectable liver metastases from CRC) and found that, after neoadjuvant chemotherapy, 95 patients (13.5%) were resectable and had 5-year survival similar to those who were initially resectable.

To summarise, advances are being made in the management of CRC on several fronts:

- Preoperative staging has improved thus allowing for tailored treatment of patients (especially those with rectal cancer);[10]
- Subspecialised training is improving surgical technique (both in the extirpation of the primary and hepatic metastases);
- Chemotherapy is increasing survival in those patients with more advanced disease;
- Hepatic resection for those patients with metastases can now be performed with minimal mortality and significant long-term survival;
- Guidelines for the surveillance of patients at heightened risk of developing CRC have become clearer; and
- Laparoscopic surgery has been shown to offer equivalent survival rates to open surgery.

We are making progress in managing CRC with improvements in multiple small steps—and this is good news for our patients.

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Colorectal cancer treated at Christchurch Hospital, New Zealand: a comparison of 1993 and 1998 cohorts

Bridget Robinson, Frank Frizelle, Michelle Dickson, Chris Frampton

Abstract

Aim To compare clinicopathological variables, management, and outcome of two cohorts of unselected patients treated for colorectal cancer (CRC) at Christchurch Hospital, New Zealand in 1993–94 and 1998–99.

Methods Retrospective review from hospital discharge codes, oncology referral database, and histology database. Data was stored in a Microsoft Access database.

Results 356 patients in 1993–94 and 317 patients in 1998–99 had a confirmed diagnosis of adenocarcinoma of the colon or rectum. At the minimum follow-up time of 42 months, 54% (40% of CRC) of the 356 patients in the first cohort, and 36% (26% of CRC) of the 317 patients in the second cohort had died. The Kaplan-Meier survival curves showed significant improvement in 1998–99 overall, as well as for Dukes stages A plus B, stage C, and stage D disease. Computed tomography (CT) scan-staging increased from 11.3% to 62.8%. On multivariate analysis, cohort, stage, vascular/lymphatic invasion, and elective surgery were independent prognostic factors for disease-specific mortality. Over the 5 years (1993–94 to 1998–99), surgery by consultant increased from 44% to 82%, adjuvant chemotherapy for Dukes stage C increased from 21% to 45%, and chemotherapy for metastatic disease increased from 2.4% to 23% of stage D and from 2.5% to 36.5% of those patients who developed metastases .

Conclusion The improvement in outcome is attributed to more specialised surgery, more frequent CT scan staging, and greater use of chemotherapy.

Colorectal cancer (CRC) is a major health problem in New Zealand—2554 new cases were registered in 1999, an age-standardised rate of 45.5 per 100,000 people. Furthermore, CRC is the second-most common cause of cancer death (www.nzhis.govt.nz/stats/cancerstats) in New Zealand, although its mortality rate has been relatively constant over the past 5 years (19.4 per 100,000 people)

Recent reports from Otago, New Zealand[1] and Western Australia[2] suggested no improvement in outcome over 15 years. However, subspecialisation in Adelaide, Australia[3] and advances in management in France[4] have been associated with improved survival. Greater uptake of elective screening, earlier diagnosis, specialisation by colorectal surgeons, and advances in chemotherapy for early and metastatic disease, and radiation for rectal cancer would all be expected to improve outcome.

The aim of this study is to review the management and audit the outcome of two cohorts of patients with CRC treated at Christchurch Hospital in 1993–4, and then 5 years later (beginning January 1998), in order to document differences in disease characteristics and management, and to identify trends in survival. The cohorts were

chosen to be 5 years apart, to have at least 3-year follow-up (for the second cohort). We also aimed to sample before and after site-specialisation of surgeons as well as the widespread uptake of adjuvant chemotherapy.

The study is a comprehensive audit of all patients with CRC. It will allow further understanding of prognostic factors, and enable comparison with other centres and assessment of any impact of advances in management on patient outcome.

Methods

This retrospective study includes all patients who received the primary diagnosis of adenocarcinoma of the colon or rectum between 1 January 1993 to 31 December 1994 and 1 January 1998 to 30 June 1999. Patients with CRC were located from the database in the Oncology Service and the Christchurch Hospital discharge codes (ICD 9 codes). This was cross-checked with the histology database in the Christchurch Hospital Pathology Department.

Patients were eligible for the study if they had their primary surgery at Christchurch Hospital or if they were referred to Christchurch Hospital by a Christchurch surgeon for consideration of adjuvant or palliative therapy. Thus, patients having surgery by a private surgeon in Christchurch, but who were not referred to the Oncology Service, were not included. Patients were excluded if the primary site was not confirmed as the colon or rectum, or if the surgery date fell outside the timeframe .

Patient notes were searched for information about prognostic factors, primary treatment, metastatic disease, and the date of death or last follow-up. Tumour staging and prognostic factors were derived from the histology report, and information about the primary surgery was derived from the operation report. Tumour stage was defined according to the Dukes, Australian ClinicoPathological Staging[5] (ACPS), and TNM staging systems.[6] However the Dukes stage was regarded as 'Stage D' if there was residual disease or metastases on other staging. Patients with residual disease after surgery were regarded as metastatic. Perioperative complications included any complication within 30 days of the primary surgery. Local recurrence was defined as recurrence in the tumour bed or anastomosis.

Metastatic disease was determined clinically and was not routinely confirmed by histology. Metastatic disease was defined as distant if both distant and local recurrence occurred concurrently. The date of diagnosis was taken as the date of definitive surgery and was the date of biopsy in non-resected patients. Follow up was taken to last-recorded attendance or death; cause of death was recorded from hospital records or GP records. Autopsy was uncommon. The data collector was not involved in the management of the patients.

Univariate comparisons between cohorts were conducted using Pearson's chi-squared test and independent t-tests. Kaplan Meier actuarial survival curves were compared between cohorts and prognostic groups using the Log rank test. The Multivariate analyses of all cause and disease specific survival was performed using Cox's Proportional Hazards regression models; a $p<0.05$ was considered statistically significant. The audit was approved by the Canterbury Ethics Committee.

Results

During the study period, 747 patients with the primary diagnosis of CRC appeared eligible for the study. The initial search for 1993–94 located 94 from the Oncology Service referrals and 284 from Christchurch Hospital records; while in 1998–99, 183 were from Oncology records, and the remainder from Christchurch Hospital—thus showing a shift to more private surgery. A similar number of patients were planned in the two cohorts, but after excluding patients whose diagnosis (adenocarcinoma of the colon or rectum) could not be confirmed there were 356 in the 1993–94 cohort, and 317 in the 1998–99 cohort.

More patients had been incorrectly coded in the 1998–99 cohort (Table 1). The median follow-up time for the 1993–94 cohort was 29 months (mean 39 months) and for the 1998–99 cohort 35 months (mean 30 months). Minimum follow up for surviving patients was 42 months for the 1998–99 cohort.

Table 1. **Patients with colorectal cancer in two cohorts, with exclusions**

	Cohort	
	1993 – 1994	**1998 – 1999**
Eligible	**378**	**369**
Exclusions	**22**	**52**
Not adenocarcinoma	1	9
Not colorectal primary	6	17
Cancer unknown primary	1	8
No malignancy	6	8
No histological diagnosis	5	6
No clinical records	2	2
Other	1	2
Study group	**356**	**317**

Table 2 Demographic features, presenting symptoms, stage, and histology of two cohorts of patients with colorectal cancer

		1993 – 94 Cohort		1998 – 99 Cohort	
Total		**356**		**317**	
Age	< 30	0		2	0.6%
	31 – 50	17	4.8%	15	4.7%
	51 – 70	153	43.0%	143	45.2%
	71 – 90	180	50.6%	147	46.4%
	> 90	6	1.6%	10	3.1%
Gender	Male	193	54.2%	163	51.4%
Presenting symptoms					
	Perforation	11	3.1%	10	3.2%
	Obstruction	62	17.4%	30	9.5%
	Change bowel habit	206	57.9%	165	52.1%
	Pain	188	52.8%	209	65.9%
	Rectal bleeding	134	37.6%	152	47.9%
	Anaemia	87	24.4%	75	23.7%
	Weight loss	83	23.3%	52	16.4%
Comorbidity		192	53.9%	142	44.8%
	CVD, IHD	104	29.2%	79	24%
	CORD	52	14.6%	24	7.6%
	PVD	43	12.1%	17	5.4%
	Diabetes mellitus	26	7.3%	32	10.1%
	Renal impairment	16	4.5%	7	2.2%
	Other	56	15.7%	58	18.3%

Primary site					
	Caecum/ascending	94	26.4%	81	25.6%
	Transverse	25	7.0%	29	9.1%
	Descending	32	9.0%	27	8.5%
	Sigmoid	98	27.5%	75	23.7%
	Recto/sigmoid	36	10.1%	19	6.0%
	Rectum	73	20.5%	88	24.7%
	Not specified	1	0.3%	0	
Dukes stage	A	26	7.3%	37	11.7%
	B	123	34.6%	114	36.0%
	C	109	30.6%	109	34.4%
	D	83	23.3%	52	16.4%
	Not staged	15	4.2%	5	1.6%
Vascular/lymphatic invasion		127	35.7%	99	31.0%
Differentiation					
	Well	3	0.8%	7	2.2%
	Moderate	87	24.4%	226	71.3%
	Poor	47	13.2%	65	20.5%
	Not stated	219	61.5%	19	6.0%

Table 3. Management of colorectal cancer

	1993–94 Cohort		1998–99 Cohort	
Indication for surgery				
Acute	115	32.3%	89	28.1%
Elective	230	64.6%	228	71.9%
Not stated	11	3.1%		
Operation				
Right hemicolectomy	93	26%	89	28%
Left hemicolectomy	14	4%	19	6%
Sigmoid colectomy	54	15%	21	7%
Anterior resection	67	19%	89	28%
Abdominoperineal resection	25	7%	19	6%
Hartman's procedure	13	4%	16	5%
Subtotal colectomy	20	6%	21	7%
Other / not stated	49	14%	47	15%
Not done	12	3%		
Surgeon				
Consultant	157	44.1%	249	82.4%
Registrar, supervised	95	27.4%	46	14.5%
Registrar, alone	69	19.4%	20	6.3%
Not stated	35	5.4%	3	0.8%
Oncology referral	85	23.9%	131	41.3%
Dukes stage B	15	12.2%	40	35.1%
Dukes stage C	60	55.0%	79	72.5%
Adjuvant chemotherapy;% of stage	25		57	
Dukes stage B	2	1.6%	7	6.1%
Dukes stage C	23	21.1%	49	45.0%
Radiation therapy	24	6.7%	28	8.8%
Combined chemo-radiation	3	0.8%	12	3.8%

Table 4. All cause mortality according to dukes stage and vascular/lymphatic invasion

		Median survival, all causes (months, ± SE)		Significance Log rank
Cohorts combined				
	Dukes A/B	87.7 ± 5.75		
*	Dukes A/B, VLI +	76.5 ± 15.2	)	
	Dukes A/B, VLI -	88.1 ± 7.4	)	0.3048
	Dukes C	40.5 ± 4.4		
	Dukes C, VLI +	29.0 ± 2.8	)	
*	Dukes C, VLI -	60.4 ± 8.3	)	<0.0001
Dukes A/B				
	Cohort 1993 – 94	27.0 ± 2.4	)	
	Cohort 1998 – 99	Not reached	)	<0.0001
Dukes C				
	Cohort 1993 – 94	32.0 ± 4.7	)	
	Cohort 1998 – 99	51.5 ± 5.7	)	0.0493
Dukes D				
	Cohort 1993 – 94	7.1 ± 1.2)		
	Cohort 1998 – 99	9.2 ± 2.8)		0.0165
*	Dukes A/B VLI +	Dukes C VLI -		0.278

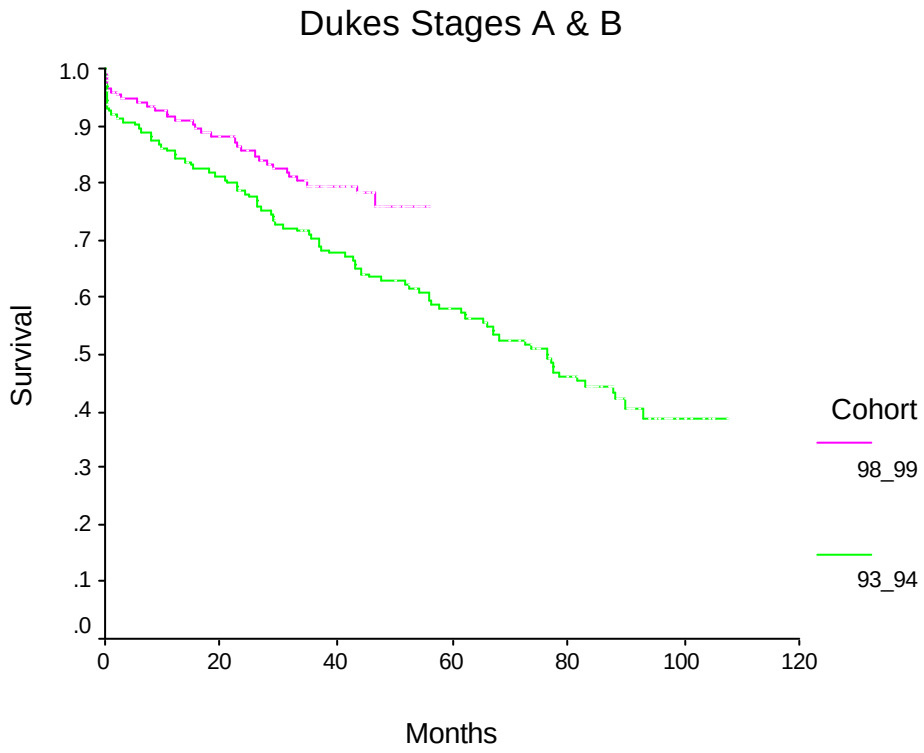
Table 5. Multivariate analysis for survival

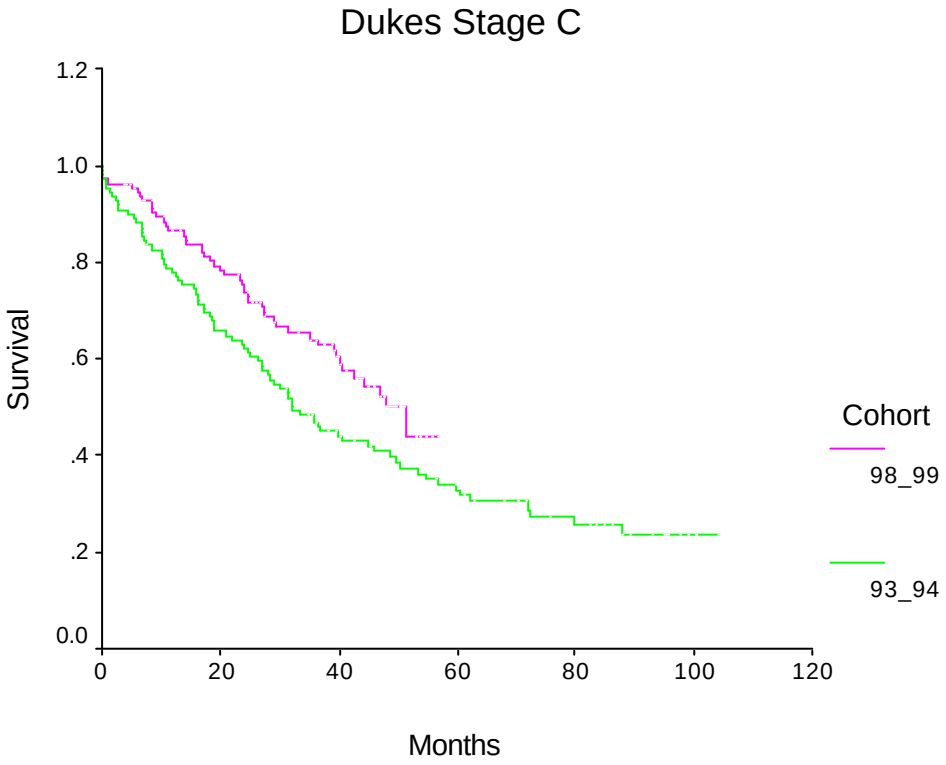
	Significance	
Variable	**All-cause mortality**	**Disease-specific mortality**
Cohort	0.015	0.002
Age	<0.001	0.129
Dukes stage	<0.001	<0.001
Vascular lymphatic invasion	0.022	0.046
Surgery elective	0.028	0.004
Surgery by registrar	0.217	0.460
Perforation	0.831	0.449
Comorbidity	0.028	0.890
Perioperative complication	0.217	0.171
Adjuvant chemotherapy	0.339	0.529

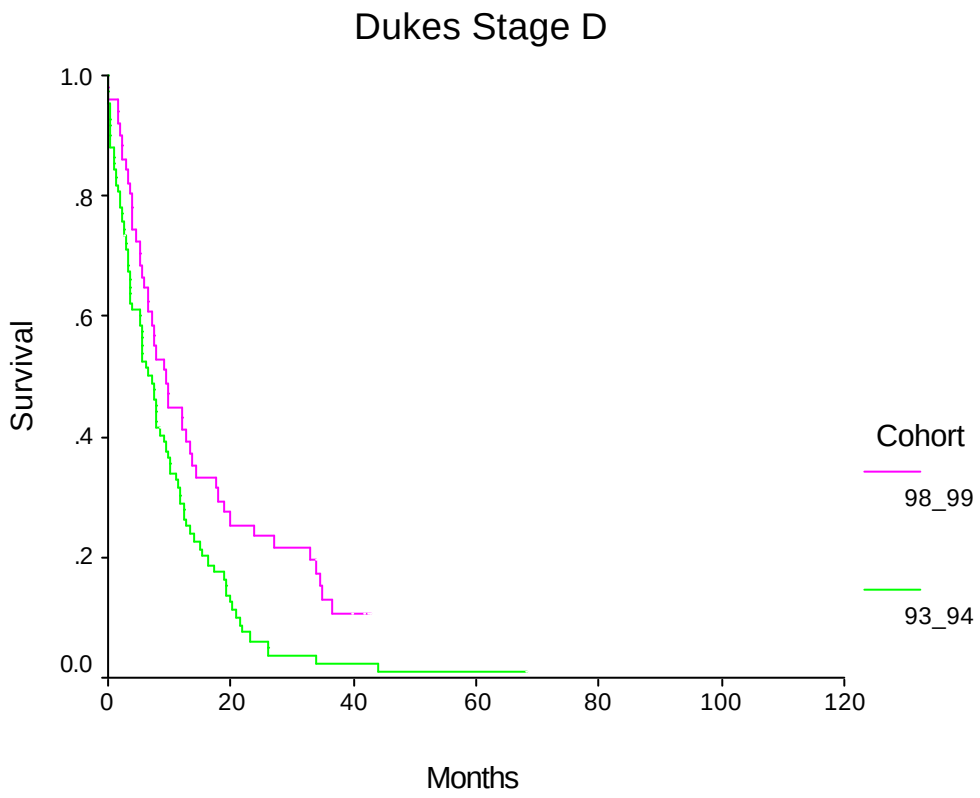
Cox Proportional Hazards Model

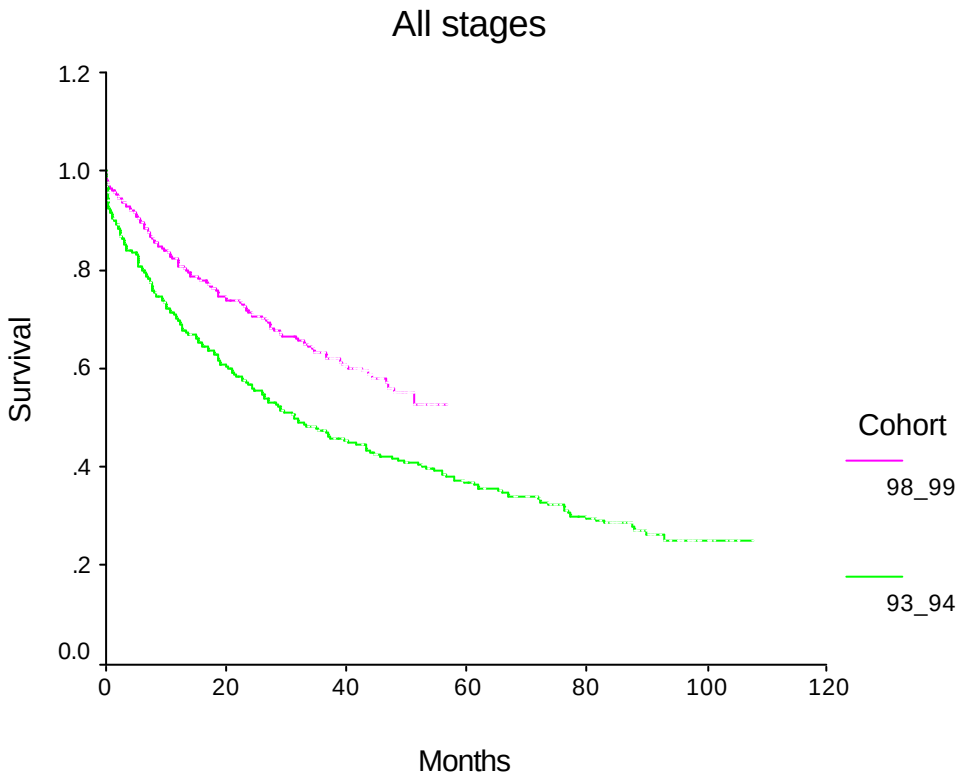
Figure 1. Kaplan-Meier survival curves for all-cause mortality by cohort, for the entire group, by Dukes A & B, Dukes C, and Dukes D stage disease

(a)




Dukes Stage C
Survival
1.2
1.0
.8
.6
.4
.2
0.0
0
20
40
60
80
100
120
Months
Cohort
98_99
93_94


Dukes Stage D
Survival
1.0
.8
.6
.4
.2
0.0
0
20
40
60
80
100
120
Months
Cohort
98_99
93_94


All stages
Survival
1.2
1.0
.8
.6
.4
.2
0.0
0
20
40
60
80
100
120
Months
Cohort
98_99
93_94

The demographic details, presenting features and comorbidity of the 673 patients are shown in Table 2. The mean age of the 1993–94 cohort was 69.7±11.1 (SD) years and of the 1998 – 99 cohort, 68.7±12.6 ($p=0.270$). The presenting symptoms were similar in the two cohorts. More patients in the earlier cohort had medical comorbidities, especially vascular disease and chronic respiratory disease ($p<0.001$). The site of the primary in the colon and rectum were similar in the two cohorts, with 58.1% in the sigmoid or rectum in the 1993–94 cohort, compared with 54.4% for the 1998–99 cohort.

Staging by ACPS moved 10 Dukes A in 1993-94 and 21 from 1998–99 to ACPS Stage B1. ACPS stage showed a trend to earlier stage in the later cohort ($p<0.0001$), as did Dukes stage ($p=0.016$). The primary tumour was less likely to be localised in the earlier 1993–94 cohort, with 58.2% T3 or smaller, compared with 69.7% for the later 1998–99 cohort ($p<0.001$). TNM nodal status showed no difference between the two cohorts.

In the 1993–94 cohort, staging ultrasound and a staging CT scan was done in 22.4% and 11.3% patients, respectively—while in the 1998–99 cohort, ultrasound and a CT scan was done in 16.4% and 62.8% (including 44.8% preoperatively) patients, respectively.

Histology reports indicated the presence of mucinous features in 14.3% in 1993–94, and 6.3% in 1998–99. Vascular or lymphatic invasion was recorded in one-third of patients including in 23.6% of stages Dukes A or B, and 46.8% of stage Dukes C for the combined cohorts. Reporting of differentiation was much more complete in the later cohort.

Table 3 shows the management of the 673 patients. The proportion presenting acutely who needed urgent surgery was similar for the two cohorts, yet the number with obstruction was less in the later cohort. Hospitalisation for pain or severe anaemia also resulted in acute surgery.

The type of operation performed reflects the site of the primary tumour and was similar for the two cohorts. There was a significant increase ($p <0.0001$) in the proportion of operations carried out by a consultant: 82.4% for the 1998–99 cohort compared with 44% for 1993–94 cohort.

In 1993–94, 62 patients had a stoma fashioned (reversed later in 13 patients), whereas in 1998–99, 85 patients had a stoma (reversed in 31 patients). Twelve patients in 1993-94 did not have surgery, and were analysed with the Dukes D group.

Perioperative complications within 30 days of surgery were recorded for 20.8% of the 1993–94 cohort, and 23.4% of the 1998–99 cohort. Chest infections occurred in 8.4% and 8.8% of patients in 1993–94 and 1998 – 99 cohorts respectively; heart failure in 1.9% and 4.1%; deep vein thrombosis/pulmonary embolism (DVT/PE) in 2.5% and 1.9%; myocardial infarction in 2.2% and 2.2%; and abscess or leak in 2.5% and 5.0%.

The proportion of patients with Dukes B and Dukes C disease referred to the Oncology Service was greater for the later cohort ($p<0.0001$). In the 1998–99 cohort, of the 23 patients with Dukes C disease not referred to Oncology Service, 12 were aged 80 years or older, 6 had comorbidities which contraindicated chemotherapy, 1 had had an incomplete excision, while no reason was evident for the remaining 4 patients.

Use of adjuvant chemotherapy was more frequent in the 1998–99 cohort ($p<0.0001$). By stage, 45% of the Dukes C patients received chemotherapy in 1998–99 compared with 21% in 1993–94. For Dukes B, the proportion was 6.1% in 1998–99, reflecting the uncertainty of benefit for this group. Radiation therapy was given only to patients with rectal cancer (total 39; 26% of cases in 1993-94 and 23% in 1998-99) or low sigmoid adenocarcinoma (total 13 cases). One patient with Dukes A rectal cancer received chemotherapy with radiation. Chemotherapy was given for metastatic disease at diagnosis in 2 (2.4%) patients in 1993-4, and 12 (23%) in 1998–9.

The minimum follow-up time for surviving patients from both cohorts was 42 months. For patients who recurred after potentially curative surgery (i.e. Dukes Stages A, B, and C), the median time to recurrence was 20.6±1.0 months for the 1993–94 cohort, and 16.3±3.6 months for the 1998–99 cohort; p=0.35 (Log Rank), p=0.45 (Breslow).

The median survival from recurrence was 4.4±0.5 months (1993–94) and 11.0±2.5 months (1998–99) (p = 0.018 [L/R], 0.018 [Breslow], all causes); and the data were very similar for disease-specific mortality. Chemotherapy was given for metastases developing on follow-up in 2 (2.5%) patients from the early cohort and 19 (36.5%) of the later cohort (Table 3). Fluorouracil-based chemotherapy was used except for 7 patients in 1998–99 who received irinotecan.

Liver metastases at diagnosis were resected in 3 patients in 1993–94, and 4 in 1998–99. Surgery was carried out for new liver metastases on follow-up in 17 patients from the 1993-94 cohort and 13 from 1998–99 cohort.

At 42 months, 53.9% of the 1993–94 cohort had died (39.6% of CRC), compared with 36.4% of the 1998–99 cohort (26.6% of CRC); $p\leq0.0001$. Table 4 shows the all causes median survival by Dukes stage for the two cohorts, by stage and also according to vascular lymphatic invasion (VLI).

Figure 1 shows the survival curves for the entire cohorts, then for stages A and B combined, Dukes C, and Dukes D. The median survival was significantly better for all stages for the 1998–99 cohort. Vascular/lymphatic invasion was prognostic. When the cohorts were combined, the median survival for Dukes C was worse when VLI was present, and the median survival of Dukes A/B with vascular lymphatic invasion was similar to Dukes C without vascular lymphatic invasion. When re-analysed by disease-specific survival, all the significant differences retained significance.

Table 5 shows the multivariate analysis for survival according to patient, disease, and treatment-related variables. Cohort, age, Dukes Stage, VLI, elective surgery and presence of comorbidity were predictive for all cause mortality, while age and comorbidity lost significance for disease-specific mortality.

The 11 patients excluded (because no histological diagnosis was made) were reviewed. All had been managed on a presumptive diagnosis of advanced colorectal cancer. Seven were male, 4 had presented acutely, their mean age was 77 years, and 4 had demonstrated metastatic disease. Six patients had comorbidity; 2 with heart failure, 3 with pre-existing cancers, and 1 with ischaemic heart disease and diabetes mellitus. Their median survival from diagnosis was 7 months.

Discussion

This study documents the clinicopathological variables, treatment, and outcome of two large cohorts of patients with colorectal cancer, treated in 1993–94 and 1998–99 at Christchurch Hospital. The patients were unselected, consecutive patients referred to the regional hospital serving Christchurch and its environs. The time periods were chosen to record any impact of greater site specialisation by the surgeons and the general acceptance of adjuvant chemotherapy. In the later cohort (1998–99), more were initially located from Oncology Service referrals, reflecting a shift to more surgery in the private sector.

The study shows an improvement in outcome for the later cohort, both overall and for each Dukes stage. Multivariate analysis showed that elective surgery, in contrast to emergency, was associated with better survival. This could reflect earlier disease (not yet obstructing, perforating, or penetrating serosa) which have been recognised as poor prognostic factors.[7–9]

Surgery by a training registrar rather than the consultant did not reach significance. The trend to more specialist surgery reflects the site specialisation in Christchurch Hospital, and the increase in private surgery. However it is likely that better surgical technique contributes to the improved outcome as also shown in two recent Australian studies.[3,10]

The more intensive radiological staging in the 1998–99 cohort would also improve survival for Dukes Stages C patients, by moving already metastatic patients from C to D stage—i.e. stage migration. It would also be expected to increase the number of Dukes D patients, which, however was not seen. There was a significant increase in use of adjuvant chemotherapy for Dukes C patients from 21% to 45%. However use of chemotherapy was not an independent prognostic factor probably because all patients were included, not just Dukes C.

The clinicopathological features are essentially similar to those of other South Island, New Zealand series.[1,11] The site of the primary is similar to the Otago study[1] and closely reflects distribution in the Eurocare European database— in contrast to the USA SEER database where right colon was more common and rectum less common.[12]

The proportion of operations by consultants in 1993–94 (44%) was similar to the Otago study (55%) of patients treated between 1990 and 1992,[1] but increased to 82% in the 1998–99 cohort

As expected, outcome was closely related to Dukes stage (as shown in Figure 1 and in the multivariate analysis in Table 5). However, the presence of vascular and/or lymphatic invasion in the primary tumour had independent prognostic impact, as previously reported in some series.[13,14] Patients with Dukes A/B disease who had VLI had an outcome similar to those with Dukes C disease, without evidence of VLI. Within the group with Dukes C, VLI was associated with a significantly poorer survival. Grade could not be assessed since it was poorly recorded in 1993–94, although it was recorded in 94% of patients by 1998–99.

Univariate analysis had shown the earlier cohort to have significantly greater number of comorbidities and to be of higher Dukes stage, but disease-specific mortality

showed similar trends to all cause mortality, and all survival comparisons between cohort were made by Dukes stage.

Adjuvant chemotherapy with 5FU/levamisole[15] and then 5FU/leucovorin,[16] was starting to be offered during 1993, and was routinely considered for the 1998–99 cohort as efficacy was confirmed.[17] Chemotherapy for metastatic disease was sometimes used before 1995, based on reports of survival benefit if used early.[18]

By 1998–99, the benefit of chemotherapy for advanced disease was accepted, and patients were being entered in clinical trials including the Saltz regimen[19] or received 5FU/leucovorin by Mayo or once-weekly regimens,[20] followed by Irinotecan on failure.[21] Surgery for liver metastases was similar for patients from the two cohorts.

Our study is limited by not capturing patients treated in the private sector who were not referred for an oncology opinion or treatment. The total number and proportion of the total group referred to the Oncology Service was greater in the later cohort, probably reflecting the greater perceived benefit of adjuvant therapies by that time.. However those with early stage disease and those who declined referral would not be referred. Patients referred at development of metastases were included if their primary surgery had occurred during the defined time point. Thus poorer-prognosis Dukes B and C patients may be relatively over-represented in the studied group. A bias favouring the later cohort could therefore occur if just better-prognosis patients were referred.

Conclusion

Over a 5-year period (1993–94 to 1998–99), we have demonstrated an improvement in outcome for patients with colorectal cancer treated in the Departments of Surgery and Oncology at Christchurch Hospital. There is also better histopathological grading, heralding a move to unified reporting.[22]

Greater specialisation of surgeons, more operations by consultants or supervised trainees, more frequent CT staging, and use of chemotherapy are all likely contributing factors to the improved patient outcome. In the future, a further improvement is hoped for with greater use of resection or local therapy for liver metastases, as well as availability of new chemotherapeutic, antiangiogenic, and targeted agents.

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Excess cost associated with *Staphylococcus aureus* poststernotomy mediastinitis

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Abstract

Aim To determine the additional cost attributable to *Staphylococcus aureus* poststernotomy mediastinitis (PSM) following sternotomy for cardiac surgery at Green Lane Hospital.

Methods A retrospective case-control study was undertaken. Nine patients with *S. aureus* PSM (cases) were matched with nine patients without PSM (controls) for gender, age, type of surgical procedure, time of procedure, and presence of diabetes mellitus. Patients' length and cost of hospital stay (for the admission associated with the initial surgery and any subsequent admissions associated with complications of that surgery) were obtained from the hospital's clinical costing system.

Results *S. aureus* PSM was associated with longer average length of hospital stay, 42.6±18.7 vs 10.4±4.0 days (p=0.005). The mean cost per patient in New Zealand dollars was $30,527±$10,489 for controls and $76,104 ± $31,460 for cases, and the mean excess cost associated with *S. aureus* PSM was $45,677 per patient.

Conclusions This study illustrates the significant cost of deep surgical site infection, both in terms of length of hospital stay and hospital revenue, and highlights the potential cost benefit of successful strategies to reduce surgical site infection such as *S. aureus* PSM.

Hospital acquired infection (HAI) are associated with considerable morbidity, mortality and consumption of healthcare resources.[1] The prevalence (10%) and the predicted cumulative incidence (6%) of HAI in Auckland are similar to rates reported in international literature.[2] Little is known about the cost of HAI in New Zealand. A recent study looking at the cost of HAI in Auckland estimated the costs of HAIs in medical and surgical admissions to Auckland District Health Board (ADHB) hospitals over 1 year to be substantial—i.e. NZ$13.05 and NZ$10.07 million respectively.[3]

We recently reviewed staphylococcal poststernotomy mediastinitis (PSM) at Green Lane Hospital's Cardiothoracic Surgery Unit. PSM is an infrequent complication of median sternotomy; the rate of staphylococcal PSM in our review was 1.2%. It is associated with prolonged hospital stay as well as increased morbidity and mortality (A Upton, unpublished data). Recent changes to the collection of hospital associated cost have allowed us to carry out a case-controlled analysis of the costs of PSM in a small group of patients.

Methods

Adult patients who developed *Staphylococcus aureus* PSM following median sternotomy for coronary artery bypass grafting, heart valve, or thoracic artery surgery between 1 July 2002 and 30 June 2003 were identified. The control group were patients who had similar surgical procedures performed during the same time interval. Where possible, controls were matched for gender, age, type of surgical

procedure, month of procedure, and presence of diabetes mellitus. Data to assess cost were extracted from the Auckland District Health Board (ADHB) clinical costing system: Power Cost Manager (PCM).

PCM is a 'bottom-up' costing tool which means that the cost of individual patient care is identified by capturing every item of utilisation on each patient, during his or her stay in hospital. Expenditure is then allocated according to utilisation. The costs of the admission for the initial sternotomy (initial admission) and any subsequent admissions related to complications of surgery (subsequent admission) were calculated.

The average length of stay (ALOS) following the initial admission and subsequent admissions, total costs for all admissions, mean cost per stay for initial admission, and subsequent admissions and the mean cost per individual patients for all admissions related to initial surgery were calculated. Cost of hospital admission and length of stay were compared using an unpaired t-test and a p-value of 0.05 was considered statistically significant.

Results

Nine patients, all male, were identified as having *S. aureus* PSM during the study period. Patient demographics, surgery details, the average length of stay, and mean costs are shown on Table 1. No control patients were re-admitted with infective or non-infective complications of surgery.

Table 1. Case and control patient demographics, surgery details, average length of hospital stay, and cost of initial and subsequent admissions

Variable	Cases N=9	Controls N=9	P value
Males (%)	9 (100)	9 (100)	
Median age, years (range)	63 (54–78)	63 (52–78)	
Diabetes mellitus (%)	5 (56)	6 (67)	
Elective surgery (%)	6 (67)	9 (100)	0.2
CABG (%)	7 (78)	7 (78)	
ALOS initial admission (days)	25.9±21.4	10.4±4.0	0.064
ALOS initial & subsequent admission/s (days)	42.6±18.7	10.4±4.0	0.005
Costs NZ$			
-Total	685,838	274,747	N/A
-Mean cost initial admission	57,616±38,124	30,527±10,489	0.069
-Mean cost subsequent admission	20,912±19,083	N/A	N/A
-Mean cost per patient	76,104±31,460	30,527±10,489	0.001

ALOS=average length of stay; CABG=coronary artery bypass grafting; NZ=New Zealand.

Discussion

For patients with *S. aureus,* PSM the ALOS for the initial admission, 25.9±21.4 days, showed a trend towards being longer than for control patients. When the ALOS for the initial and subsequent admissions were compared the study group had a significantly longer hospital stay, 42.6±18.7 vs 10.4±4.0 days (p=0.005). This increased ALOS was associated with a mean excess cost of NZ$45,677 per patient, doubling the cost of the procedure. Our results are comparable with a recent Australian study where the mean excess cost associated with deep sternal site infection was AUS$31,597 per patient. [4]

Interventions to prevent SSI are well described and include avoiding preoperative shaving of the surgical site the night before the operation, antiseptic skin preparation, timely intravenous administration of appropriate prophylactic antibiotics, and adherence to good infection control practises for the duration of the hospital stay.[5] Of all infection control practices, hand hygiene is one of the most important—and is simple, cheap, and effective. Despite this, observational studies have found that adherence to hand hygiene by healthcare providers is poor, with rates ranging from 5–81%.[6]

Preoperative application of intranasal mupirocin to eradicate nasal *S. aureus* carriage is a strategy employed by some units and has been shown in a randomised placebo-controlled trial to reduce *S. aureus* HAI in operative patients who were *S. aureus* carriers, but not to reduce the rate of *S. aureus* SSI overall.[7] As Auckland and other parts of New Zealand have relatively high rates of mupirocin resistance (up to 30%),[8] the benefits of this intervention may be minimal and not cost-effective. A number of patients undergoing median sternotomy have non-elective surgery; and in these patients, preoperative nasal swabs and mupirocin treatment may not be feasible.

This study is limited by the small sample size. More cases had non-elective surgery and this may have lead to an over-estimation of the length of the initial hospital stay. Despite this, we believe that our study demonstrates the substantial cost (both in terms of inpatient hospital stay and hospital expenditure) of *S. aureus* poststernotomy mediastinitis.

Further research into the costings of HIA in New Zealand is needed.

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Effect of volcanic gas exposure on urine, blood, and serum chemistry

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Abstract

Aims This pilot study tested the hypothesis that aluminium (Al), rubidium (Rb), arsenic (As), lead (Pb), mercury (Hg), fluorine (F), and chlorine (Cl), which are all known to be present in volcanic emissions, may be useful biological markers for occupational gas exposure in volcanologists.

Methods Ten human subjects were exposed to fumarole gases on White Island, New Zealand, for ~20 minutes. Sulphur dioxide (SO_2) exposure was recorded by personal monitoring tubes. Pre- and post-exposure urine, blood and serum samples (collected using standard protocols) were analysed in the pathology laboratory for trace element and halogen content.

Results Average personal exposure was measured at <75 ppm SO_2 and calculated at ~25ppm HCl, ~8 ppm hydrogen fluoride (HF), ~1 ppm Al, ~0.1 ppb Rb and ~4 ppb Pb. These concentrations almost certainly exceed those usually found in occupational exposure settings. Advanced levels of urinary Al and Rb were found following gas exposure and were statistically significant in the population at $p<0.005$ and $p<0.001$, respectively. The other chemical elements that were analysed (urinary Cl, F, and Hg; blood Pb, and serum Al) did not show such patterns.

Conclusions It is possible that urinary Al and Rb may be useful markers for exposure, a hypothesis which should be followed up in future work.

Volcanic emissions include a suite of toxic gases including sulphur dioxide (SO_2), carbon dioxide (CO_2), hydrogen sulphide (H_2S), hydrogen chloride (HCl), and hydrogen fluoride (HF)—plus aluminium (Al), arsenic (As), mercury (Hg), lead (Pb) and titanium (Ti) in gaseous and molecular aerosol form. The very high gas concentrations which may easily be encountered on active volcanoes mean that researchers may risk the development of reactive airways dysfunctional syndrome or other forms of occupational asthma if they do not habitually use respirators with acid gas cartridges. Despite this, volcanologists in the field rarely monitor occupational exposure to harmful gases.

Biological monitoring following exposure to potentially harmful gases and respirable particles is common in industry, but this is almost unheard of in volcanology. In this report, we present findings from preliminary work on White Island (New Zealand's most active volcano at present), which investigated the value of using blood, serum, and urine markers to study or monitor occupational exposure to volcanic gases.

Methods

White Island volcano—White Island lies in the Bay of Plenty 48 kilometres offshore at the northern end of the Taupo Volcanic Zone in the North Island of New Zealand. The generally mild activity between eruptions and the ease of access by boat made it an ideal natural laboratory for this work. Over

recorded history (1826–present), activity has been characterised by gas emissions from fumaroles (surface vents emitting volcanic gases, fed by a sub-surface hydrothermal system) and mud pools, punctuated by episodes of weak-moderate eruptions, which typically last for several months.[1,2] During the current work (February 2002) we observed moderate-strong gas emissions from fumaroles and the main vent inside the crater complex.

Gas emissions from the volcano are typical of other volcanoes of the same magma type (andesite), at ~430 tonnes per day (t d^{-1}) SO_2 and ~1550 t d^{-1} CO_2.[3] The emission of metals as gas or aerosols is significant and includes ~6000 kg d^{-1} Al, 600 kg d^{-1} Rb and 16 kg d^{-1} As.[4]

Subjects in this experiment were exposed to gases from one of three fumarole complexes in the central subcrater. All three are on the very lower slopes of the crater walls. Presently we cannot determine the elemental concentrations in the gases from each of the fumaroles, but these values are known for the main vent plume at White Island, which is fed by the same hydrothermal system as the fumaroles.[5]

Exposure and sampling procedure—Subjects (average age 27 years; no asthmatics and no smokers included) were on the volcano for 2 hours and each spent 20 minutes close (<10 metres) downwind from one of the three fumaroles, carrying masks around their necks but only using them if deemed necessary. Average exposure during this period was monitored with SO_2 diffusion tubes worn on clothing (Gastec Dositubes no. 5D).

The 'pre-exposure' (control) blood and urine samples were taken the day before the visit to the volcano, using standard protocols (urine sample period: 3.5 hours). The 'post-exposure' sample period began upon arrival at the volcano (and included the period of gas exposure itself), and ended after 4.75 hours when blood samples were taken.

Ethical approval for the work was given by Canterbury Ethics Committee, and participants gave informed consent after the implications of the work were explained.

Analytical methods—Urine chloride was measured using Integrated Chip Technology on an Aeroset Biochemistry Analyser (Abbott Laboratories, Abbott Park, IL 60064, USA). Fluoride was measured by Ion Selective Electrode (Orion Research Inc, Beverly, MA 01915–6199, USA). Urine aluminium, serum aluminium, and blood lead were measured on a Varian AA40 Graphite Furnace Atomic Absorption Spectrometer, and the urine rubidium was measured on a Varian AA100 Flame Atomic Absorption Spectrometer (FAAS) (Varian Techtron Pty Ltd, Mulgrave, Victoria 3170, Australia). Urine mercury was analysed by cold vapour generation using a Perkin Elmer Flow Injection analysis system attached to a Perkin Elmer A100 FAAS (Perkin Elmer Instruments, Norwalk, CT 06859–0010, USA). Creatinine was measured using the Jaffe reaction on an Aeroset Biochemistry Analyser.

Statistics—Wilcoxon's signed-rank test for matched pairs[6]—a non-parametric test for dependant variables—determined the statistical significance of post-exposure changes in blood, serum, and urine chemistry.

Outliers were defined by meeting both of the following standard criteria:

- By lying three standard deviations above the group mean, and
- By lying within the 75th percentile by at least 1.5 × the interquartile range.

Results

Exposure

During the acute exposure period near the fumaroles, SO_2 tubes recorded exposure between 6 parts per million (ppm) (Subject 3) and 75 ppm (Subject 4), with a group mean of 24 ppm. The recorded SO_2 exposure and calculated HF, HCl, Al, Rb, and Pb exposures are shown in Table 1. Mean exposures were calculated at ~2.5 ppm HF, ~8.5 ppm HCl, ~0.5 ppm Al, ~0.05 parts per billion (ppb) Rb, and ~1.5 ppb Pb. Since detailed chemistry of each fumarole on the volcano is not known, these calculations are subject to error perhaps in excess of 50%. Personal exposure away from the fumaroles was not measured but likely to be below 1 ppm SO_2.

Table 1. Average SO_2, HF, HCl, Al, Rb, and Pb exposure concentration recorded by diffusion tubes worn on subjects' clothing

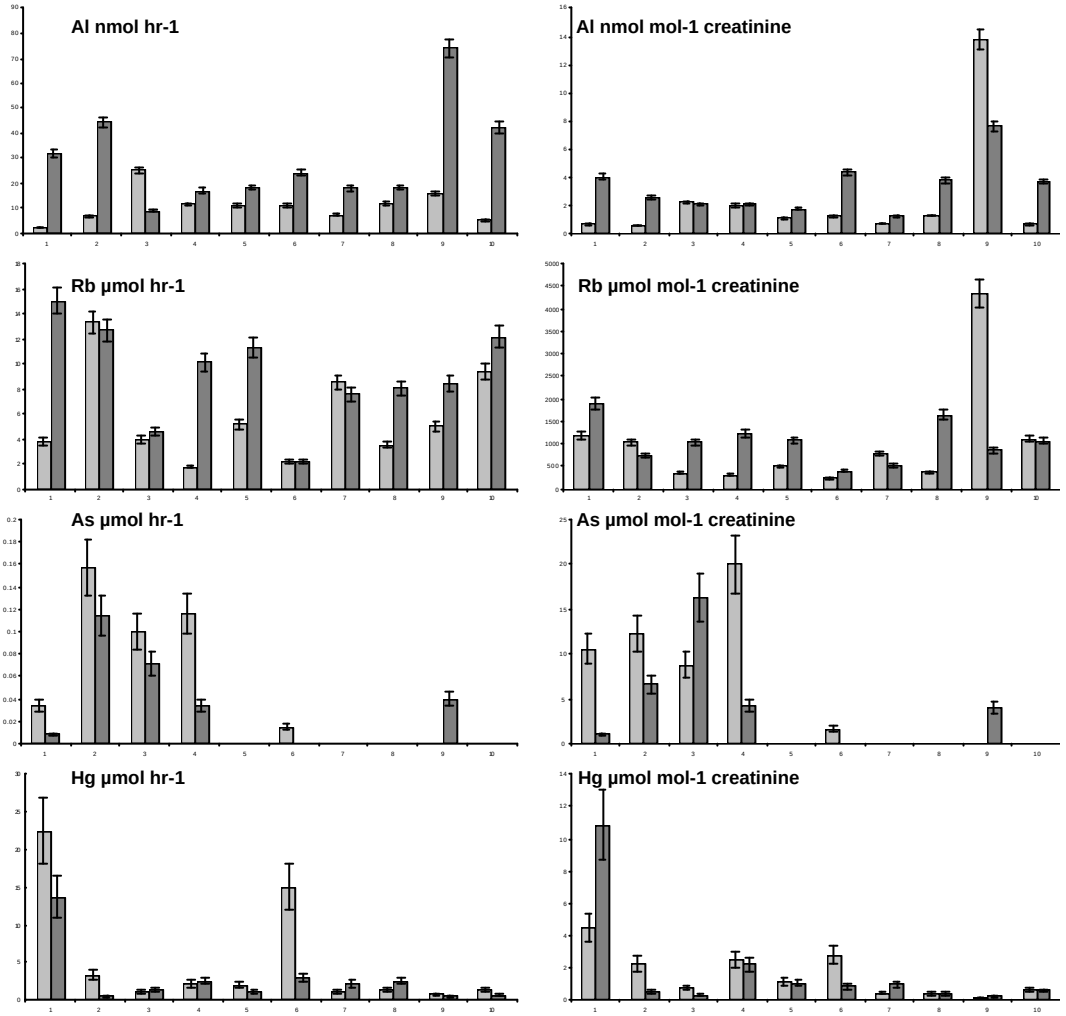
Subject No.	SO_2 ppm*	HF ppm[(a)]	HCl ppm[(a)]	Al ppm[(b)]	Rb ppb[(b)]	Pb ppb[(b)]
1	15	1.6	5.2	0.3	0.03	0.9
2	12	1.3	4.2	0.2	0.02	0.7
3	6	0.6	2.1	0.1	0.01	0.4
4	75	7.8	25.9	1.3	0.13	4.6
5	21	2.2	7.3	0.4	0.04	1.3
6	36	3.7	12.4	0.6	0.06	2.2
7	15	1.6	5.2	0.3	0.03	0.9
8	24	2.5	8.3	0.4	0.04	1.5
9	24	2.5	8.3	0.4	0.04	1.5
10	15	1.6	5.2	0.3	0.03	0.9

* Recorded by diffusion tubes. (a) Calculated from SO_2:HCl and SO_2:HF ratios in plume[1]; (b) Calculated from Al, Rb, Pb:SO_2 ratios in plume[4]

Table 2. Post-exposure changes in elemental outputs in urine, serum, and blood (statistically significant results in bold)

Element and analyte	Mean pre-exposure	Mean post-exposure	Mean change	Standard deviation
In urine				
Chloride mmol L^{-1} urine	128.5	84.4	–44.10	90.91
Chloride mmol hr^{-1}	47.56	46.58	–0.97	8.51
Chloride mmol mol^{-1} creatinine	7.79	5.35	–2.46	7.21
Aluminium µmol L^{-1} urine	0.03	0.063	**+0.03**	0.03
Aluminium µmol hr^{-1}	0.010	0.029	**+0.018**	0.0047
Aluminium µmol mol^{-1} creatinine	2.39	3.30	**+0.9**	2.82
Fluoride µmol L^{-1}	26.29	30.77	+4.48	19.01
Fluoride µmol hr^{-1}	11.25	13.93	+2.67	1.83
Fluoride mmol mol^{-1} creatinine	1.76	1.71	–0.05	1.53
Mercury nmol L^{-1}	5.09	2.82	–2.27	4.52
Mercury nmol hr^{-1}	1.56	1.800	+0.24	0.44
Mercury µmol mol^{-1} creatinine	0.28	0.22	–0.06	0.08
Rubidium µmol L^{-1}	14.54	19.25	+4.7	14.6
Rubidium µmol hr^{-1}	5.66	9.23	**+3.56**	1.17
Rubidium µmol mol^{-1} creatinine	1020.53	1049.53	**+29.1**	13.36
In serum				
Aluminium µmol L^{-1}	0.064	0.062	–0.002	0.018
In blood				
Lead µmol L^{-1}	0.13	0.14	0.01	0.03

Figure. 1. Al, Rb, As, and Hg outputs in urine. Outputs are shown as paired values (pre- and post-exposure) in each subject (1–10) as the excretion rate (µmol or nmol hr^{-1}) and the ratio of each element to creatinine (µmol or nmol mol^{-1} creatinine)



Trace elements and halogens in urine, blood and serum

Positive changes in the population mean outputs were seen in urine Al (all measures), urine Rb (all measures), urine F (micro-moles per litre of urine; µmol L^{-1}), and blood Pb (µmol L^{-1}). In the case of Al µmol L^{-1}, this shift was statistically significant with $p<0.005$; in Al µmol hr^{-1}, the positive change was significant with $p<0.025$; relative to creatinine, Al micro-moles per mol of creatinine (µmol mol^{-1}) increased across the population with $p<0.005$. Rb results were also statistically significant, with Rb the rate of output (micro-moles per hour; µmol hr^{-1}) increasing across the population with $p<0.025$; the population increase in Rb excretion mol^{-1} creatinine was signficant at $p<0.001$. Figure 1 shows individual results for urine Al and Rb.

Urine F and blood Pb showed positive changes in the population as a whole, but these changes were inconsistent across the population and were not statistically significant.

Analyses of other elements and analytes failed to show any clear positive or negative trends and none of the changes were statistically significant.

Discussion

Acute exposure to toxic gases and aerosols on volcanoes has rarely been properly documented, but can be high enough to cause acute illness and deaths from gas exposure have occurred. In the crater of Vulcano, Italy, for example, Baxter et al[7] measured concentrations of H_2S 60–150 ppm, HCl >10 ppm and HF 3–15 ppm close to active fumaroles where scientists were working. These concentrations exceed 10 minute occupational exposure limits by 2–15 times;[8] scientists worked near the active fumaroles for ~4 hours, wearing respirators about half the time. Prior to this study, two geologists had lost consciousness in the crater at Vulcano.[7] In 1997, four hikers died from H_2S poisoning in the Numano-taira crater on Adatara volcano in Japan.

Thus, volcanologists potentially face acute and chronic health risks when visiting actively degassing volcanoes. In this work, we aimed to simulate conditions of acute gas exposure experienced by volcanologists in active craters who were not always using gas masks. The period and intensity of exposure in this experiment could be at the lower end of that encountered by some volcanologists. However, America's National Institute for Occupational Safety and Health (NIOSH) 10-minute exposure limit for SO_2 (5 ppm; ref. 8) was exceeded by at least a factor of 2 in 9 of the subjects; and in the case of subject 4, by ~30 times.

This work is thought to be the first of its kind on an active volcano, but numerous proxy studies of industrially, or accidentally, exposed workers have been completed. Al exposure is common in metal processing industries, and numerous studies have found enhanced Al levels in serum and urine of occupationally exposed workers.[9–14] Pierre et al[15] stressed that the pattern of Al excretion rate varies between Al in different molecular forms, but at present we have no way of determining the form of Al in the White Island gases. Urine does, however, account for >95% of excreted Al in people with a healthy renal system, and is rapidly excreted.[15, 16]

Our results indicate an increased rate of urinary Al output in 9 of the 10 subjects (up to 70 nmol hr^{-1}; Subject 9), which was significant in the population to $p<0.025$. The population's enhanced Al concentrations in urine were significant at $p<0.005$. Subject 9 had the highest Al concentration in urine following exposure, at 0.15 µmol L^{-1}, twice that in the pre-exposure sample. This is, however, well below the mean urine Al reference value for unexposed individuals (m 0.237 µmol L^{-1}; r 0.04–6.2 µmol L^{-1}) determined by White and Sabbioni.[17] Al increased relative to creatinine in seven subjects by a factor of 1.6–64. The mean change in Al was 1700 nmol mol^{-1}, which was significant at $p<0.005$.

Given the rapid and thorough excretion of Al in urine, there is no reason to suspect the post-exposure signal is an artifact, or the result of a confounding factor involved prior to the study period. Although the influence of an unknown confounding source cannot be ruled out, the fact that Al was elevated in 8 of the 10 subjects suggests a common source for this change, rather than the unlikely effect of sources which act upon individuals (e.g. mobile Al in food, drinks, toothpaste or deodorants). Indeed, pulmonary Al absorption is more efficient than gastrointestinal absorption, and little is known of the bioavailabilty of Al in food and drink, except in water.[16]

Little is understood of the bioavailability, kinetics and excretion of Rb. Our results indicate statistically significant shift in the population's rate of Rb output (μmol hr^{-1}), at $p<0.025$. Cornelis et al[18] gathered the most recent reference values of which we are aware, indicating urinary Rb outputs of 0.5–1.95 μmol hr^{-1} are normal in healthy, unexposed individuals. Pre-exposure mean for our group, 1.61 μmol hr^{-1}, lies in the upper part of this range. The post-exposure mean, 2.64 μmol hr^{-1}, exceeds this reference range. Seven of the 10 subjects lay within this reference range prior to exposure; following exposure, only 2 lay within it; 8 subjects exceeding reference value outputs. In the population, this increase in Rb output μmol hr^{-1} was significant at $p<0.025$. The greatest change was in Subject 1, whose post-exposure urine Rb output was 4.3 μmol hr^{-1}, or more than twice the maximum reference values acquired by Cornelis et al.[18] Relative to creatinine, the group's mean positive change in Rb was 417 μmol mol^{-1}, which was significant at $p<0.001$.

If all these data are accurate, then the statistically significant population change in Rb to above reference value limits is potentially very important. Judgment should be made with caution though, especially with regard to the rather old reference values, which are the newest we believe have been published.

Although post-exposure increases in urinary Al and Rb outputs were statistically significant, there was not a clear correlation between excretions of the two elements. Reasons for these discrepancies may be related to a number of factors including differing levels of exposure or perhaps personal differences in renal function. Indeed, in the group as a whole, exposures recorded by the diffusion tubes did not correlate with the observed changes in urinary outputs. A clear correlation should not be expected, however, since respiratory absorption of gases and particles may vary considerably between individuals. It is also possible the tube readings were not an accurate indication of true respiratory exposure. Further uncertainties exist because it was necessary to estimate metal outputs from the fumaroles by using data from other vents.

In contrast to the Al and Rb results, other elements studied here showed little relation between likely exposure and a response in urine or blood. Many studies have now shown the value and reliability of using fluoride concentrations in urine or plasma to evaluate the influence of environmental fluorine compounds.[15,19–22] These studies fall into two categories, in which occupational time-series exposures or laboratory controlled exposures (usually short term; hrs) are analysed. In the former case, Kono et al[20] found that occupational exposure to 2 ppm HF in air caused a statistically significant post-exposure change in urine F outputs.

Ehrnebo and Ekstrand[23] found a positive shift in plasma F concentrations which correlated with exposure measured by personal monitors. Tangible health effects have also been observed in people exposed in the work place or the laboratory. In studies of F exposure and respiratory symptoms, Søyseth et al[21] and Lund et al[22] both found statistically significant associations between exposure, plasma F concentrations and impaired respiratory function. Collectively, these studies suggest the current work might have found a positive response in urinary F outputs following exposure—tube results suggested subjects were exposed to ~1–8 ppm HF during the experiment.

To the contrary, we found no statistically significant post-exposure shift in urinary F by any measure. Only in Subjects 1 and 7 was the elevated total output accompanied

by increased F concentration in urine (μmol L^{-1}); in both these cases, the increased concentration was negligible.

Blood Pb has been observed to correlate with air Pb in occupational and other settings,[24,25] but here there was no uniform nor statistically significant change in concentrations in our results. Mean population concentration was unaffected by the exposure. Subjects 6 and 8 (both males) had blood Pb concentrations slightly above normal for males (0.22 μmol L^{-1}), according to reference values obtained by Apostoli et al[26]; both were already above this value when the experiment began. None of the female subjects exceeded the normal female value of 0.15 μmol L^{-1}. Serum Al was also apparently unaffected and remained well within reference intervals.[27] These intervals have, however, been criticised by Poulson et al,[28] but new levels have not yet been set. No clear pattern was discernible for blood Hg, nor Cl, and both remained within normal limits in all the subjects.[29,30]

Thus, with the exception of Al and Rb, there was little intra-element or intra-subject consistency observed in the results. This makes it difficult to resolve the relationship between exposure and body fluid response at this stage.[4]

Conclusions

This research found enhanced levels of urinary Al and Rb following volcanic gas exposure, which were statistically significant. Other elements analysed here (urinary Hg, Cl, F, blood Pb, and serum Al) did not show such patterns. The result raises questions of why such differences exist, and how future work could test these findings further.

These questions should be resolved in the future, provided improvements in our experimentation are made; notably in:

- Better control of possible confounding factors,
- Improved monitoring of personal exposure in real time with active analysers, and
- An extended sampling strategy with more subjects, elements and several bracketed sample periods, so the kinetics of excretion could be observed.

It is also necessary to have a better understanding of the preferential uptake, retention and excretion of various elements in this multiple element exposure. The molecular form of each element in the volcanic plume is also very important in determining rates of uptake, retention, and excretion—and this can only be resolved with improved techniques in geochemical analysis of the volcanic gas.

Despite these limitations in the present study, our results suggest that when people are acutely exposed to volcanic gases, respiratory absorption and urinary excretion of Al and Rb occurs (perhaps preferentially to other elements).

Given the patterns in urine trace elements we observed following acute exposure, it seems reasonable to extrapolate that chronic exposure might produce more consistent indications of a relationship between exposure and urine and blood chemistry. In that case, quantitative human health risk assessments could follow, but more research would be required before urine and blood chemistry could be used as biomarkers of a potential human disease burden.

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Measurement of thiopurine methyl transferase activity guides dose-initiation and prevents toxicity from azathioprine

Christiaan Sies, Christopher Florkowski, Peter George, Richard Gearry, Murray Barclay, James Harraway, Linda Pike, Trevor Walmsley

Abstract

Aim To establish an assay service for thiopurine methyl transferase (TPMT) activity in order to facilitate dose initiation of thiopurine drug therapy and to define appropriate reference intervals and optimal cut-offs for the New Zealand population.

Methods 407 patients underwent radio-enzymatic assay testing of TPMT activity prior to initiation of thiopurine drug therapy. Those with low activity also underwent genotyping for the abnormal *2, *3A, and *3C alleles.

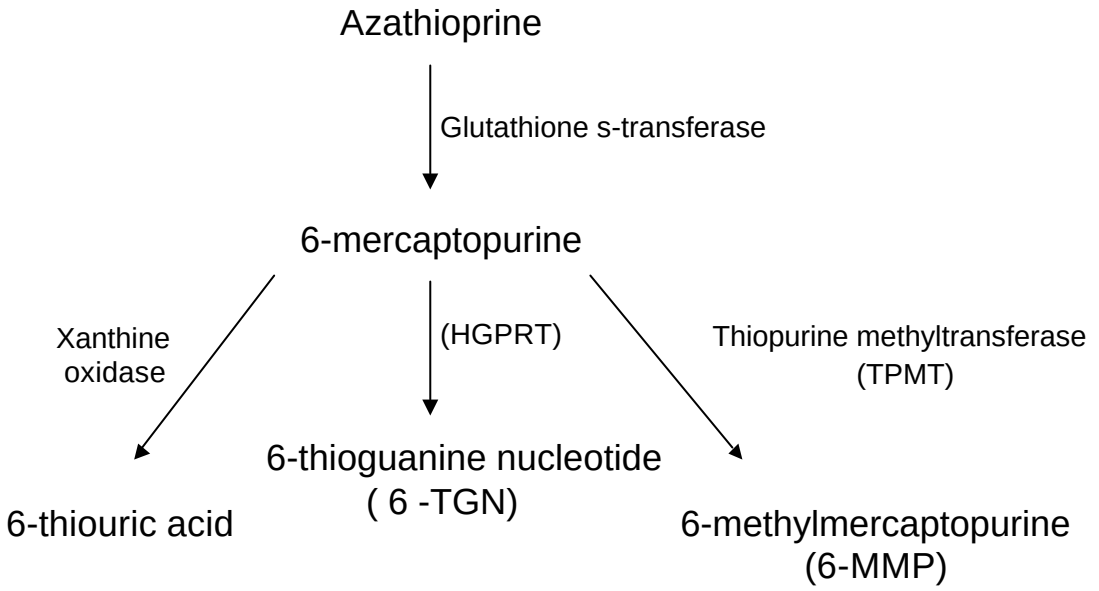
Results A trimodal distribution of enzyme activity was seen consistent with the known polymorphic genetics for this enzyme. Three cases of homozygous deficiency were identified. The 'normal' range is 9.3 to 17.6 units/ml red blood cells (RBCs), but many heterozygotes have activity above the lower limit of his range. TPMT activity above 10.7 units/ml RBC identifies a normal genotype with 100% probability.

Conclusion The normal range for TPMT has been established. The measurement of TPMT activity helps to guide dose initiation and may prevent toxicity from azathioprine.

Azathioprine, 6-mercaptopurine (6-MP), and thioguanine are collectively known as thiopurines and are used in the treatment of inflammatory bowel disease, acute lymphocytic leukaemia, myasthenia gravis, autoimmune hepatitis, a variety of dermatological disorders, and as an immunosuppressant in solid organ transplant patients.[1,2]

Azathioprine is converted to 6-MP (Figure 1) which can then undergo one of three metabolic transformations. The enzyme thiopurine methyl transferase (TPMT) has a trimodal variation in the general population and is central to the understanding of the mechanisms of toxicity associated with thiopurine drugs. Deficiency is inherited in an autosomal recessive manner with 1 in 300 subjects having homozygous deficiency, and around 8–10% of the community having intermediate enzyme activities. Subjects with heterozygote deficiency will metabolise increased amounts of 6-MP through the pathway to 6-thioguanine nucleotides (6-TGN). Although 6-TGN production underlies the therapeutic action of azathioprine, excessive amounts (as when TPMT is homozygous deficient) are extremely toxic and can result in myelosuppression, neutropaenia, and potentially death.

Figure 1. The metabolism of 6-mercaptopurine via three possible enzyme pathways: xanthine oxidase; hypoxanthine guanine phosphoribosyltransferase (HGPRT); and thiopurine methyltransferase (TPMT)



There is considerable potential to adjust thiopurine drug-starting doses with knowledge of TPMT activity and to avoid potential myelotoxicity. We therefore undertook to establish a routine assay for TPMT activity and establish appropriate reference intervals and cut-offs for the New Zealand population.

Methods

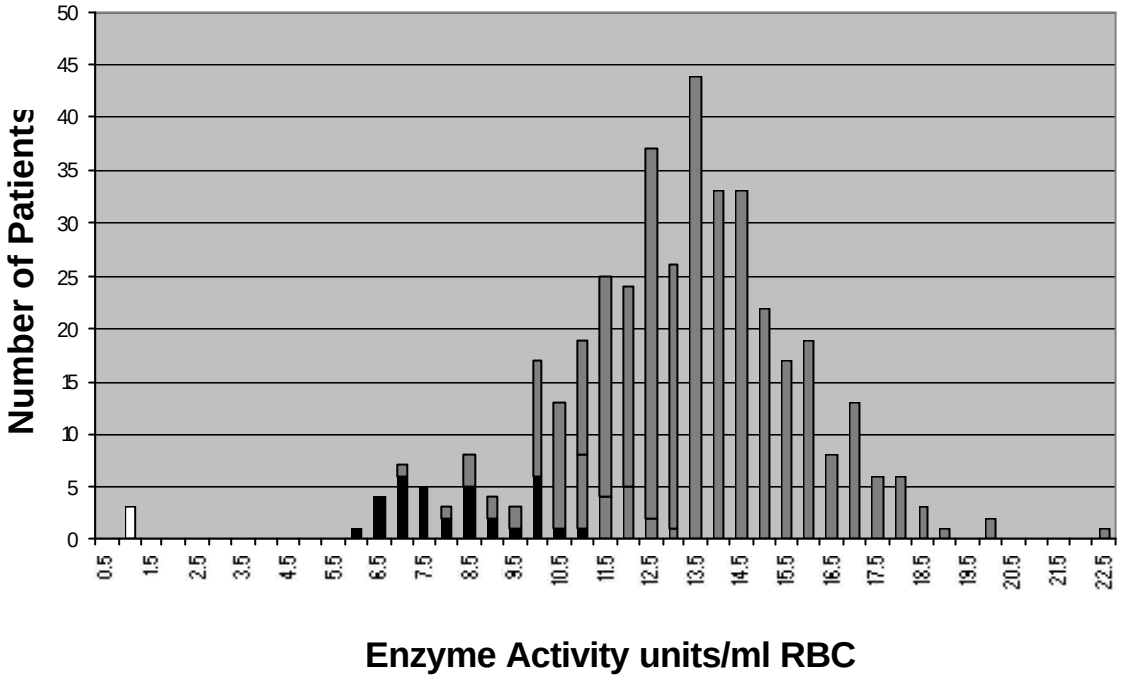
TPMT activity is typically measured in lysed red blood cells, which reflect the level of TPMT enzyme in human liver, kidney, and normal lymphocytes.

A method for measuring erythrocyte TPMT activity has been established based on the transfer of methyl groups from S-adenosyl-L-[methyl-^{14}C] methionine to 6-mercaptopurine, extraction of the radiolabelled ^{14}C-methylated reaction product into isoamyl alcohol/toluene, followed by liquid scintillation counting.[3,4]

This assay has been used to assess the risk of possible thiopurine toxicity in patients and to guide dose adjustments. Subjects with lower enzyme activity (<12 U/ml RBCs) also underwent TPMT genotyping to define the level of TPMT activity that separates true normals from those that may be either normal or heterozygous deficient. The gene encoding TPMT is located on chromosome 6 (6p22) and consists of 9 introns and 10 exons.

At least nine single-nucleotide polymorphisms (SNPs) that lead to decreased TPMT activity have been identified in the coding sequence. In addition, another SNP that leads to decreased TPMT enzymatic activity has been identified at the intron IX/exon X splice junction[5]. Testing for the common *2, *3A, and *3C alleles was also undertaken, using a multiplexed allele-specific polymerase chain reaction, which account for 90% of the known mutations in the Caucasian population.

Figure 2. Histogram indicates the number of patients confirmed as homozygous deficient (white); confirmed heterozygous (black); normal genotype (grey); not genotyped (chequered) vs TPMT enzyme activity



Results

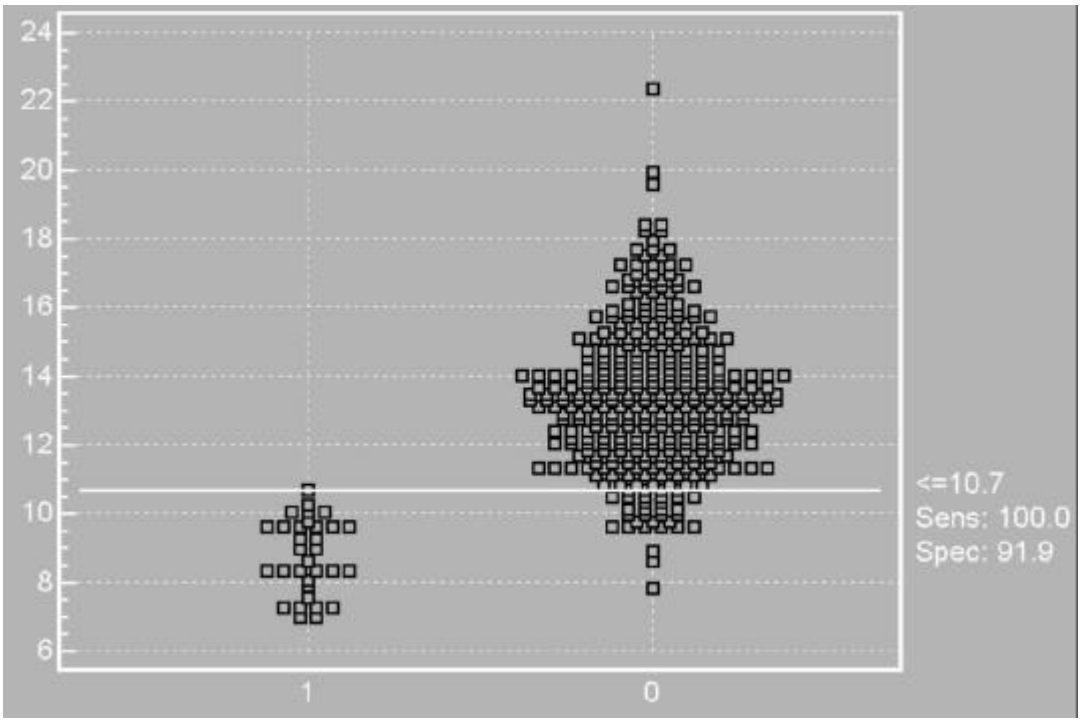
Over a 2-year period, 407 patients samples from throughout New Zealand were referred to Canterbury Health Laboratories for TPMT phenotyping; these patients were either about to receive azathioprine or had already started treatment. Their TPMT activities are depicted in Figure 2, showing the expected trimodal variation in the general population. Around 90% of the patient population had normal to high activity with these usually having the wild type genotype (*1/*1). Around 8% have reduced or intermediate activity, usually due to a *1/**2, *1/**3A, or *1/*3C genotype. Those with either very low or undetectable activity were found to be homozygous for the *3/**3 mutation accounting for 0.7% of the patient population.

ROC (Receiver operator characteristic) curve analysis of the data shown in Figure 3 indicates that for a patient with a TPMT activity of greater than or equal to 10.7 units/ml RBC, the probability of a normal genotype is 100%.

Prior to the introduction of the TPMT assay, a patient in Christchurch with inflammatory bowel disease was commenced on azathioprine 1.5 mg/kg; 13 days later he developed severe myelosuppression, with a haemoglobin of 61 g/L, WBC of 1.6, and neutrophils of 0.6; and required 3 days of barrier nursing and a 3 unit blood transfusion. Subsequent TPMT testing revealed that this patient was one of the 1 in 300 people who have no TPMT activity. Subsequently two other homozygous deficient patients were identified by TPMT assay prior to the initiation of therapy and

avoided potential toxicity, with azathioprine being introduced at 10% of the usual dosage.

Figure 3. Diagram of TPMT activity vs patients that are heterozygous (1) or normal (0), with optimal cut-off defined by receiver operator characteristic (ROC) analysis. The cut-off of 10.7 unit/ml RBC identifies TPMT deficient subjects with 100% sensitivity



Discussion

We have established a TPMT assay in Canterbury Health Laboratories and used this with a view to prevention of myelotoxicity and to guide initial azathioprine dosage.

The data presented correlates well with similar studies on healthy populations, which show a 89:11:0.3 ratio respectively.[6] TPMT activity appears to show no significant difference between the gender or age of the patient.[7] Thus the normal range of 9.3–17.6 unit/ml RBC, as defined in our population, can be used for children as well as adults.

TPMT activity testing may be useful for dose prediction and preventing toxicity. We identified three homozygous deficient patients, one of which might have avoided complications had the assay been undertaken prior to initiation of azathioprine. In those patients with intermediate activity (i.e heterozygous deficiency), the thiopurine starting dose should be lowered by 50–60%.[8]

Patients with Crohn's disease have been successfully treated with azathioprine using this regime even when found to be TPMT deficient.[9] Conversely, for patients found to have significantly higher enzyme activity, a higher starting dose may be appropriate

and 6-TGN monitoring will also guide future dose adjustment. Once initiated on thiopurines, future dose adjustments should be guided by monitoring of 6-TGN levels, also available from our laboratory. Regular monitoring of the white cell count should still be performed as toxicity can still occur suddenly, often being induced by intercurrent illness or initiation of additional medications.[10]

Standard protocols for treatment with thiopurines usually involve initial administration of low doses followed by gradual increase. This is less than ideal, given that 90% of patients may be receiving potentially inadequate treatment and the remaining 10% may be exposed to potentially unnecessary toxic effects.[11] Although frequent monitoring of full blood counts is usually in place for children with acute leukaemia other patients (such as those with dermatological disorder) may go unnoticed until myelosuppression has occurred.

Data for the year ending June 2002 shows that there were 14,203 prescriptions, dispensed on 37,105 occasions, for azathioprine (personal correspondence with Pharmac). If one assumes that these patients were on this drug for the full 12 months, this equates to about 3500 people on this drug. Over the last 5 years, there have been 35 reports of adverse effects of azathioprine of which 5 had a haematological component (New Zealand Centre for Adverse Reactions Monitoring (CARM), personal communication, 2004), which suggests that only a minority of adverse effects are reported.

After review of our data, we will perform confirmatory genotyping for the most common allelic variants on all samples with activity of less than 12 units/ml RBC. To date, all subjects with an activity above 10.7 units/ml RBC have normal genotypes, although below this level there is a considerable overlap between heterozygous deficient and genotypically normal subjects. Although some studies relate adverse effects specifically to the genotype, it is probably more important to know enzyme activity as genotypically normal subjects have a very broad range of enzyme activities that may impact differently on the choice of starting dose.[12,13]

Some national guidelines already recommend that ‘azathioprine dose should be optimised both with regard to efficacy and myelosuppression risk by prior measurement of thiopurine methyltransferase (TPMT) activity.’[14] Others have argued that it may be unethical, even legally culpable, not to undertake some assessment of TPMT status prior to thiopurine drug initiation.[4]

In addition to the medicolegal risk, the cost of treating neutropaenic patients is considerable. Economic analysis has indicated that the prevention of myelosuppresion in TPMT homozygotes, by screening each patient prior to initiating treatment, has a favourable cost-benefit ratio.[15] In the UK, it has been stated that at a cost of £40 for measurement of TPMT and with a frequency of 1 in 300 for homozygous deficiency, £12,000 would be spent to prevent one fatal toxicity[16] and avert a proportion of toxicity in heterozygous deficient individuals. Extrapolating the same figures to New Zealand and with an assay cost of $57.75 per assay, this would equate to a cost of $17,250 per fatal episode averted.

Conclusion

The combination of TPMT enzyme activity measurement with genotyping allows for dose prediction and adjustment to prevent dangerous side-effects in patients found to have lower than normal activities.

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Recurrent myoglobinuria due to carnitine palmitoyltransferase II deficiency: clinical, biochemical, and genetic features of adult-onset cases

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Abstract:

Aims To create awareness of adult-onset carnitine palmitoyltransferase II (CPT II) deficiency by describing the clinical, biochemical, and genetic features of three New Zealand patients with this disorder.

Methods Review of case notes, creatine kinase (CK) values, CPT II assay results, genetic mutation analyses, and the literature.

Results Three patients with CPT II deficiency were encountered by the authors over a 7-year period. Onset of symptoms was between ages 10 and 17 years. Each patient reported exertional myalgia, and had had at least two episodes of myoglobinuria following exertion or infection. Interictal neurological examinations, CK values, and routine muscle histology were normal. CPT II activities ranged from 3.8 to 9.7 pmol/min/mg protein (normal±SD=162.9±51.0 pmol/min/mg protein). Genetic analysis showed that one patient was homozygous and two were heterozygous for S113L, the common mutation in CPT II deficiency.

Conclusions CPT II deficiency should be suspected in patients with persistent exertional myalgia who have one or more episodes of myoglobinuria. The diagnosis is confirmed using a combination of enzyme assay and genetic testing.

Myoglobinuria is a dramatic clinical syndrome due to metabolic or other injury to skeletal muscle, with release of the cytoplasmic contents of muscle fibres into the extracellular space (rhabdomyolysis). Myoglobin appears in the serum and urine, the serum creatine kinase (CK) rises markedly, and acute renal failure and electrolyte alterations may occur. A wide range of insults to skeletal muscle may produce myoglobinuria.[1]

Carnitine palmitoyltransferase II (CPT II), an enzyme found in the inner mitochondrial membrane, is critical for the transfer of long chain fatty acids into the mitochondrion for β-oxidation. In 1973, DiMauro first reported deficiency of CPT II (OMIM 600650) in a 29-year-old man with recurrent myoglobinuria.[2] More than 150 patients with CPT II deficiency have now been reported.[3] In most patients, symptoms are confined to skeletal muscle and comprise exertional myalgia and episodes of myoglobinuria. Rarely, patients present in the neonatal period, infancy, or early childhood with fasting-induced hypoketotic hypoglycaemia, hepatic dysfunction, and cardiomyopathy.[4,5]

To illustrate the clinical, biochemical, and genetic features of the common adult form of CPT II deficiency, and to create awareness of the disorder, we present three patients diagnosed in New Zealand between 1989 and 1999.

Patients

Patient 1—In 1999, at age 17, this man was referred to a neurologist for investigation of exertional muscle symptoms. In retrospect, he recalled episodes of diffuse aching in his legs after walking as early as age 10. At age 16, he played four games of soccer over 2 days in a tournament. During the final game he developed diffuse aching in his legs and he was barely able to complete the game. That evening, he passed red urine. His myalgia resolved over 3 days.

Over the next 2 years he intermittently developed myalgia during or up to 12 hours after games of soccer. In between these episodes, his muscles were free of symptoms. Neurological examination at age 17 was normal. Serum CK after a soccer training session in 1999 was 12,000 U/L (normal range 0–200). At age 18, he developed rhabdomyolysis (peak CK 71,900) without acute renal failure during a viral infection. He recovered fully with intravenous fluids alone and the CK fell to normal. Following this episode he began to experience daily low-grade myalgia, made worse by late nights and for 1-2 days after exertion. A combination of small frequent meals and light training in the gym seemed to improve this symptom. There was no family history of muscle disease.

Patient 2— In 1976, at age 17, this woman developed diffuse myalgia, charcoal-coloured urine, and acute renal failure in association with a post-puerperal breast infection. She required short-term dialysis but made a complete recovery. At age 29 she embarked on a hike having eaten little in the days beforehand on account of pharyngitis. She developed myalgia within 1 hour, but continued hiking. That night she felt unwell and ate little. The next day, further hiking produced incapacitating myalgia, limb weakness, and myoglobinuria. The CK on admission to hospital was >60,000 U/L and her creatinine was 0.19 mmol/L (normal range 0.05–0.12).

The CK and creatinine levels normalised over the next 7 days. On review at age 40, she reported low-grade myalgia several times per week, not associated with exertion, and responsive to frequent carbohydrate snacks. Exertion, such as gardening, could produce more intense myalgia lasting up to 24 hours. The neurological examination was normal. There was no family history of muscle disease.

Patient 3: This man presented in 1997 at age 21 with a history of about 30 episodes of exertional myalgia since age 15. Episodes would begin after 1-2 hours of exercise as a ‘tight’ sensation in the exercised muscles. The myalgia would increase to become moderately intense over 30 minutes, then fade over about 12 hours. About 20 of the episodes had been accompanied by very dark brown/red urine suggestive of myoglobinuria. One typical episode of myalgia occurred during a febrile respiratory illness. Fasting or sleep deprivation could produce minor myalgia. CK on one occasion following uneventful exercise was 1770 U/L. Neurological examination and interictal CK at age 21 were normal. There was no family history of muscle disease.

Methods and Results

Muscle biopsies—Muscle biopsies were obtained under local anaesthesia from biceps muscle in all three patients. Cryostat sections from flash-frozen muscle were stained or reacted for haematoxylin and eosin, modified Gomori trichrome, NADH-tetrazolium reductase, ATPase (after preincubation at pH 4.3, 4.6, and 9.4), periodic

acid-Schiff (PAS), acid phosphatase, and oil red O.[6] In all three patients, the muscle architecture and staining patterns were normal.

CPT II assay—This was based on the 'forward' assay: palmitoyl CoA + [^{14}C]carnitine → palmitoyl-[^{14}C]carnitine + CoA, catalysed by CPT II.[7] Fifty milligrams of frozen muscle was homogenised in 1.5ml 0.25M sucrose/10mM Tris-HCl. The homogenate was spun at 4300G for 45 minutes at 4°C and the pellet resuspended in 600µL 150mM KCl/10mM Tris-HCl. To 400µL was added 20µL 20% octylglucoside; this was vortexed and kept on ice for 30 minutes. The remaining 200µL was kept for measurement of protein concentration. Reactions were carried out in duplicate at 30°C in a 500µL volume containing: Tris-HCl 105mM, ATP 4mM, reduced glutathione 0.25mM, $MgCl_2$ 4mM, rotenone 40µg/ml, KCN 2mM, bovine serum albumin 1%, palmitoyl CoA 50µM, and DL-carnitine HCl 0.5mM (including 0.0625-0.125µCi [^{14}C]DL-carnitine). Reactions were started with 100µL of tissue sample and were stopped after 15 minutes with 500µL 1.2N HCl.

Palmitoylcarnitine was extracted by addition of 500µL butan-1-ol, vortexing 60sec, centrifugation at 1200G 8min, removal of 300µL of the butan-1-ol phase into a 1.5ml tube containing 60µL water, vortexing, centrifugation, and removal of 250µL of the butan-1-ol phase into a glass counting vial containing 5ml Ultima Gold. Control reactions had 500µL 1.2N HCl added at time zero. Palmitoylcarnitine was measured as discharges/minute relative to 25µL of the 'hot' DL-carnitine reagent. Results were given as pmol palmitoylcarnitine produced/minute/mg protein.

The CPT II activities in patients 1, 2, and 3 were 8.5, 9.7, and 3.8 pmol/min/mg protein respectively; all less than 6% of the control mean. The mean±standard deviation activity obtained in 18 healthy controls was 162.9±51.0 pmol/min/mg protein (range 93.9–294.9). Healthy controls consisted of patients who underwent a diagnostic muscle biopsy and were ultimately considered free of any neuromuscular disorder.

DNA analysis—DNA was prepared from blood (patient 1) or frozen muscle (patients 2 and 3) by a guanidine thiocyanate method,[8] and the five exons were amplified by PCR as previously described.[9] All PCR products were sequenced on an ABI 3700 Avant DNA sequencer, using dye terminator chemistries (Version 3.1) in accordance with the manufacturer's instructions. Analysis of these results indicated that patient 1 is homozygous for the common S113L mutation and that the other two patients are heterozygous for this mutation Further analysis to define the mutations on the remaining two alleles is in progress.

Discussion

The three patients in this report illustrate the clinical, biochemical, and genetic features of adult-onset CPT II deficiency.

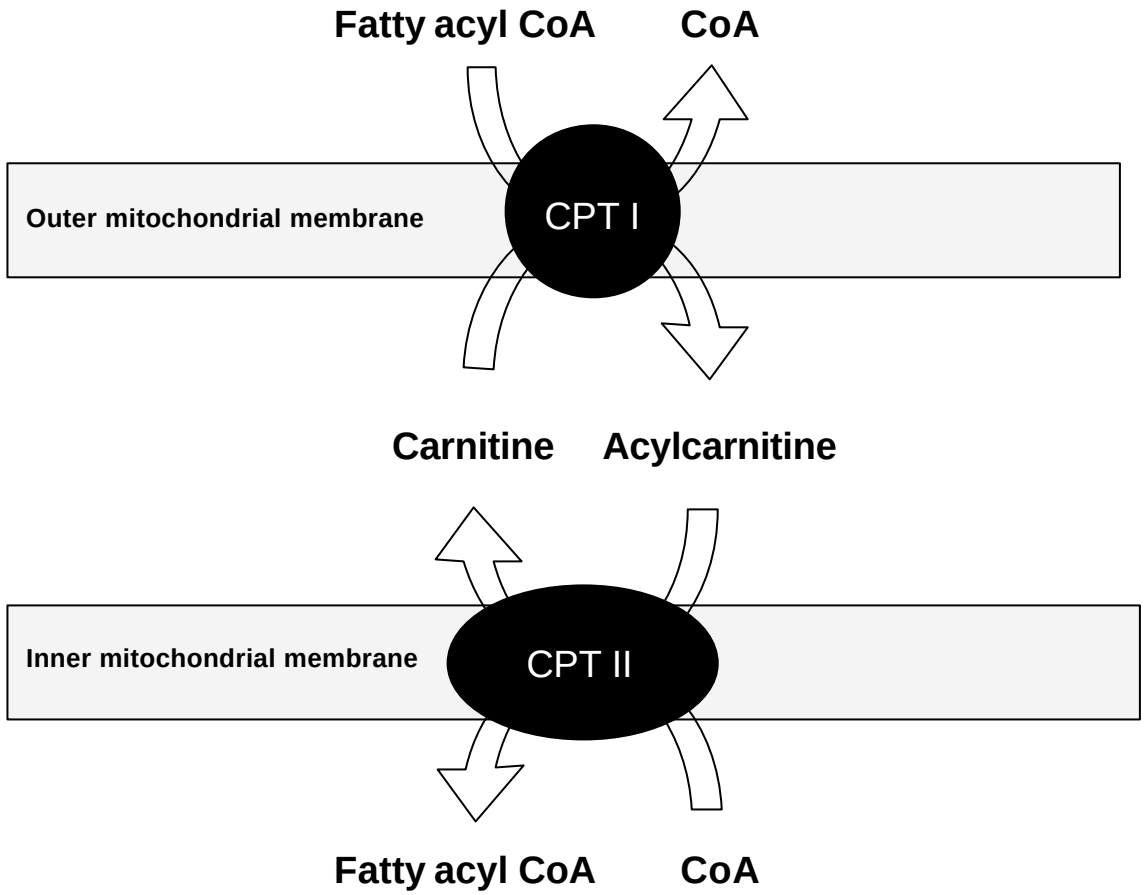
The following features, present in our patients, are typical of the disorder:

- Age at onset of symptoms (10-17 years);
- Myalgia provoked by exertion;
- Episodes of myoglobinuria following exertion or infection;

- Normal interictal neurological examination and CK level, and
- Normal muscle histology.

Fatty acids are the predominant source of energy for muscle during sustained exercise.[10] Two distinct CPT enzymes within muscle facilitate the transfer of long-chain fatty acids across the mitochondrial membrane into the mitochondrial matrix prior to β-oxidation[11] (Figure 1).

Figure 1. The transfer of long-chain fatty acids into the mitochondrion via the CPT system (simplified)



CPT I, encoded on chromosome 22, is located in the outer mitochondrial membrane and catalyses the formation of fatty acylcarnitine from fatty acyl-CoA and carnitine.[12] CPT I is the rate-limiting step in β-oxidation and its activity increases when intracellular levels of malonyl-CoA are low during fasting. CPT II, encoded on chromosome 1p32, is located on the inner mitochondrial membrane and catalyses the reverse reaction, reforming fatty acyl-CoA within the mitochondrial matrix.[13] Patients with CPT II deficiency cannot adequately increase fat oxidation during fasting or exercise to meet the energy requirements of muscle.

In most patients with CPT II deficiency, onset of symptoms is within the first two decades.[14] Exertional myalgia or stiffness, not immediately responsive to rest, is the commonest symptom. In many patients, it is the dramatic occurrence of myoglobinuria which first brings the patient to attention. Myoglobinuria in CPT II deficiency usually occurs after exertion, but can occur with febrile episodes, during fasting, or spontaneously. Eighty percent of the patients reported in the literature have been male,[14] perhaps reflecting their higher overall levels of physical activity, or the modifying effects of sex hormones. Interictal electromyography, not performed in our patients, is usually normal.

The combination of persistent exertional myalgia and one or more episodes of myoglobinuria is highly suggestive of a metabolic myopathy. The commonest of these are CPT II deficiency, myophosphorylase deficiency (McArdle syndrome), and phosphorylase b kinase deficiency.[15] The combination of myalgia and myoglobinuria can rarely occur in mitochondrial myopathies.[16] A range of features helps to distinguish CPT II deficiency from myophosphorylase deficiency.

Compared to CPT II deficiency, patients with myophosphorylase deficiency:

- Have more rapid onset (minutes) and resolution of exertional myalgia[17];
- May experience the 'second wind' phenomenon, whereby brief rest after onset of muscle symptoms allows resumption of exertion which is better tolerated;
- Commonly have a permanent mild elevation of CK;
- Often have no myoglobinuria, or just a single episode (probably due to their more intrusive exercise intolerance);
- Only develop myoglobinuria following exertion; and
- Usually have a subnormal rise in venous lactate following forearm ischaemic exercise.

The gene encoding human CPT II has an open reading frame of 1974 base pairs and encodes a protein of 658 amino acids.[18] To date, more than 25 disease-causing mutations of this gene have been described.[3] A common mutation, S113L, has been found in 40-73% of alleles in different series of adult-onset CPT II deficiency.[19,20] The S113L mutation dramatically reduces the catalytic activity of CPT II.[21] This mutation was present in four of the six alleles in our patients. We presume that the remaining alleles in patients 2 and 3 contain other unidentified mutations.

There is no entirely satisfactory treatment for CPT II deficiency. Episodes of myoglobinuria are treated with intravenous fluids and careful attention to electrolyte levels, and acute renal failure is treated conventionally. All episodes of acute renal failure in our patients resolved entirely. Patients are usually advised to avoid fasting, and especially the combination of fasting and exercise. Two of our patients observed that frequent snacks ameliorated their muscle symptoms. Pre-exercise oral glucose loading does not improve exercise tolerance,[22] but a high (65%) carbohydrate diet for 3 days improved exercise performance in four patients.[23] Enzyme replacement or genetic modification—each promising in another metabolic disorder of muscle, acid maltase deficiency[24,25]—are not yet possibilities.

To summarise, CPT II deficiency is probably underdiagnosed and should always be considered in patients with myoglobinuria or persistent exertional myalgia.

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Getting started as a hepatobiliary surgeon: lessons learned from the first 100 hepatectomies as a consultant

Jonathan Koea

Abstract

Aim Liver resection has historically been regarded as difficult and dangerous surgery associated with significant perioperative mortality and morbidity rates. Partly as a result of this, adequate training in hepatic surgery has been difficult to obtain with most surgical trainees exposed only to hepatic trauma and damage control scenarios. This report describes the first 100 liver resections undertaken as a surgical consultant.

Method Clinical, diagnostic, pathological, and follow-up data were collected prospectively on 100 patients undergoing liver resection, and was stored in a computerised database. Factors associated with morbidity and trends in operative and perioperative variables over the period of the study were then analysed.

Results Malignant tumours were the most common indication for hepatic resection (88 cases) with 40 resections being undertaken for metastatic colorectal cancer. A further 34 resections were performed for cholangiocarcinoma, gallbladder cancer, or hepatocellular carcinoma. Fifty-six patients underwent a lobectomy (right lobectomy 38, left lobectomy 18)—while a further 13 patients underwent extended resections and 31 patients underwent segmental hepatic resections.

The median blood loss for all patients was 375 ml (range 100–5800 ml), and 48 patients required red cell transfusion at any time during their hospital admission. The median hospital stay was 7 days (range 4–38 days), with 52% of the patients developing complications of which 7 patients experienced a major complication, and a 3% mortality rate. The risk of complications was directly related to the magnitude of resection, with 11 of 31 patients undergoing segmental resections developing complications.

In comparison, 28 of 56 patients undergoing lobectomy (and all 11 patients undergoing extended resections) developed perioperative complications. Over the study period there was an increase in the use of segmental resections and extended resections with a decrease in blood loss, in-flow occlusion, and mortality. However, hospital stay and morbidity rates remained constant. On multivariate analysis operative blood loss ≥1000 ml, resection of ≥4 hepatic segments, and the presence of abnormal parenchyma (cirrhosis, steatosis or fibrosis) were independent predictors of perioperative morbidity and mortality.

Conclusions Hepatic resection can be undertaken safely, and increasing experience as a hepatic surgeon is associated with greater utilisation of parenchymal sparing and extended resections (without the routine use of in-flow occlusion).

In 1977, Foster and Berman published a major review of 621 patients undergoing hepatectomy at 98 institutions in North America over the preceeding half century.[1] These authors reported an operative mortality of 25% for right and extended right

hepatectomies and 9% for left hepatectomies. Significantly, one-third of all deaths were due to intraoperative haemorrhage. That monograph confirmed the historical impression that surgery on the liver was dangerous and almost impossible to undertake safely. One early writer reported that the liver was so '…friable, so full of gaping vessels, and so evidently incapable of being sutured that it always seemed impossible to successfully manage large wounds of its substance.'[2]

This prohibitively high blood loss associated with hepatic resection and the risks associated with massive blood transfusion proved to be the major stumbling block to its widespread application. However, as experience was gained in hepatic resection, mortality rates improved. For example, in 1980, Hanks et al[3] reported a mortality rate of 42% and a median blood loss of over 5 litres in 7 patients undergoing major hepatic resection at Duke University in South Carolina between 1947 and 1969.

In contrast, Ryan et al[4] reported a mortality rate of only 8% in 52 patients undergoing hepatectomy over a period of 10 years in 6 Dallas hospitals, although over one-third of these patients developed significant intraoperative hypotension and the overall mean blood loss was 3400 cc. In addition, the performance of hepatectomies in dedicated Units, the application of knowledge of hepatic segmental anatomy,[5] and the introduction of low central venous pressure anaesthesia in the mid 1990s[6] also contributed to improving the safety of hepatic resection making zero perioperative mortality a realistic goal.[7]

In New Zealand, the performance of hepatic resection and liver surgery in general has been regarded with circumspection—partly because of uncertainty about its effectiveness in treating common conditions such as colorectal metastases and has been reinforced by the difficulty in obtaining formal training in liver surgery. However hepatic surgery has been undertaken in New Zealand in several centres over the last 30 years.[8–11] The first New Zealand series published in this area was the report of Sorrell in 1979 describing 11 resections carried out over a 10 year period.[9]

In 1995, Meyer and Christie reported 30 liver resections carried out by 8 surgeons over a 6-year period with a mortality rate of 13% and an average blood loss of 5.2 litres.[3] In contrast, Jourdan et al reported 70 liver resections carried out by a single surgeon over a 10-year period in a single institution with a mortality rate of 5% and a median blood loss of 1.5 litres.[11] This evolution of results mirrors the experience of surgical centres overseas.

This paper reports the first 100 parenchymal resections carried out by the author (JK) as a consultant surgeon. These resections coincided with the development of a dedicated hepatobiliary service at Auckland Hospital and the routine exposure of surgeons-in-training to surgery involving the liver. Its purpose is to highlight some of the pitfalls of liver resection, and to demonstrate that hepatic resection can be undertaken routinely and taught safely using a standardised operative technique.

In addition, statistical analysis was undertaken to define factors associated with perioperative morbidity, and to evaluate temporal trends in operative and perioperative variables.

Methods

A prospective computerised database of patients managed by the hepatobiliary service at Auckland Hospital was established in the year 2000. Demographic, clinical, pathological, management, and

follow-up data were recorded prospectively on the first 100 parenchymal resections performed by the author as a general surgical consultant between 3 October 2000 and 27 November 2002.

The general approach to patient evaluation and surgical technique is described elsewhere.[12] All patients underwent a thorough history and physical examination as well as cross-sectional imaging (either computed tomography or magnetic resonance imaging) of the chest, abdomen, and pelvis.

Cases were reviewed at a weekly multidisciplinary radiological conference attended by surgeons, radiologists, and gastroenterologists. Where appropriate, cases were also discussed with medical oncologists and hepatologists. Once the decision had been made to proceed with hepatic resection, informed consent was obtained by the operating surgeon. The resections were classified according to the nomenclature proposed by the International Hepato-Pancreatico-Biliary Association.[13]

Patients were explored under general anaesthesia after placement of central venous and peripheral venous lines as well as arterial catheters. An epidural catheter was placed in 94 of 100 patients, while intravenous patient-controlled analgesia (usually morphine or pethidine) was used in 6 patients in whom epidural catheters were contraindicated. A standard surgical technique was utilised—opening the abdomen through a right subcostal incision with a midline extension and occasional use of a left subcostal incision to facilitate access in patients with large right-sided tumours. A thoracoabdominal incision was not required in any case.

All patients underwent full abdominal exploration with bimanual palpation of the liver and intraoperative ultrasound. In-flow control of portal vein and hepatic artery branches was obtained by extra-hepatic dissection or by pedicle ligation[5,12] and the hepatic veins were controlled extra-hepatically.[5] Trans-section of the hepatic parenchyma was performed using the crushing technique under conditions of low central venous pressure (CVP of 2 mmHg or less). Intermittent inflow occlusion (Pringle manoeuvre) was used as necessary for periods of 5 minutes with 2–4 minute intervals of reperfusion.

At the completion of parenchymal division, a damp surgical pack was held against the cut surface of the liver to check for bile staining. Any bile leaks identified in this way were over-sewn. Total vascular isolation was not required in any case. Abdominal drains were not used for hepatic resections except those that included a biliary reconstruction. Postoperatively, all patients were extubated and transferred to a high dependency unit for overnight observation and thereafter transferred to a surgical ward.

For the purposes of this analysis hepatic failure was defined as a rise in plasma bilirubin post-operatively of ≥100 μmol/L. Hepatic insufficiency was defined as a rise in plasma bilirubin of <100 μmol/L postoperatively.[14]

Numerical data are presented as the mean ± the standard error unless otherwise indicated. Multiple clinical variables were analysed using the Cox proportional hazards model[15] to define prognostic factors.

Results

Demographics and diagnoses

100 parenchymal resections were undertaken in a 26-month period. Fifty-eight patients were male and the median age was 64 years (range 15–79 years). Fifty-two patients suffered from recognised comorbidities—the most common being essential hypertension (24 patients), ischaemic heart disease (18 patients), diabetes mellitus (15 patients), and chronic obstructive respiratory disease (14 patients). Twenty-four patients suffered from 2 or more comorbidities. The primary diagnoses are summarised in Table 1.

Table 1. Summary of the primary diagnoses in 100 patients undergoing hepatic resection

Malignant	**88**	**Benign**	**12**
Colorectal Cancer	40	Focal Nodular Hyperplasia	4
Cholangiocarcinoma	14	Biliary Stricture	4
Gallbladder Carcinoma	12	Hepatic Adenoma	2
Hepatocellular Carcinoma	8	Biliary Cystadenoma	2
Non-Colorectal Non-Neuroendocrine Carcinoma*	8		
Neuro-Endocrine Carcinoma	6		

*Breast cancer 2 patients, ovarian cancer 2 patients, soft tissue sarcoma 1 patient, adrenocortical cancer 1 patient, transitional cell carcinoma of the bladder 1 patient, adenocarcinoma of the small bowel 1 patient.

Procedures

Parenchymal resections were performed in all patients. The author was the primary surgeon in all cases. However significant parts of the procedures were performed by post fellowship surgical trainees in 19 cases. Fifty-six patients underwent a lobectomy (left lobectomy 18 patients, right lobectomy 38 patients); 13 patients underwent extended resections (12 extended right hepatectomies, 1 extended left hepatectomy); and 31 patients underwent resection of 1 (12 cases), 2 (13 cases), or 3 (6 cases) hepatic segments.

Overall, the median number of segments resected per patient was 3.5 (range 1–6 segments); 69 patients had 4 or more hepatic segments resected and 43 patients underwent bilateral hepatic resections. Abnormal hepatic parenchyma was present in 20 patients (cirrhosis 3 patients, fibrosis 1 patient, steatosis 16 patients).

The median operating time for all cases was 245 ± 7 minutes with a median Pringle time of 11 ± 1 minute. The median blood loss for all 100 cases was 375 ml (range 100–5800 ml). Forty-eight patients required transfusion of a median of 2 units (range 1–15 units) of packed red cells, while 12 patients required transfusion of fresh frozen plasma only in the postoperative period. The median postoperative hospital stay was 7 days (range 4–38 days).

Two patients required re-operation for bleeding. In both cases, the bleeding point was extra-hepatic. Bleeding was localised to the surface of the right adrenal gland in patient #14 following a right hepatectomy, while patient #69 developed a postoperative bleed from the stump of the right gastric artery following a portal lymphadenectomy for gallbladder carcinoma.

Morbidity and mortality

The 30-day and in-hospital mortality of this series was 3%. Patient #24 died from a variceal haemorrhage following a right hepatic lobectomy for an 8-cm diameter hepatocellular carcinoma. The patient was cirrhotic secondary to hepatitis B and preoperative left portal vein embolisation was undertaken with a 30% increase in

parenchymal volume of the left lobe. Resection was undertaken without complication. However a variceal haemorrhage occurred on day 6.

Endoscopic injection was undertaken acutely but the patient developed progressive hepatic failure and died on day 8. Patient #55 died from a respiratory arrest on day 3 following a right hepatectomy for a 6-cm hepatocellular carcinoma in a cirrhotic liver secondary to hemochromatosis. The cause of the respiratory arrest is unclear. A significant cerebral ischaemic insult was sustained by the patient and treatment was withdrawn on day 6 following resection. Patient #69 died from renal failure which developed after a significant haemorrhage from the right gastric artery stump. Dialysis was considered in this patient but not undertaken at the request of his next-of-kin.

Overall, 52 patients developed at least one complication postoperatively, and 22 patients developed 2 or more complications (Table 2). The risk of complications was related to the magnitude of the procedure, with 11 of the 31 patients undergoing resection of 1 or 2 hepatic segments developing complications. In comparison, 28 of 56 patients undergoing lobectomy developed complications, and all 13 patients undergoing extended resections developed complications.

Table 2. Postoperative complications in 100 hepatic resections

Major Complication	**Number**
Death	3
Hepatic Failure	2
Myocardial Infarction	1
Biliary Fistula	1
Minor Complication	**Number**
Wound Infection	18
Postoperative Biloma	10
Ascites Leak	8
Pneumonia	8
Hepatic Insufficiency	7
Cardiac Arrhythmia	4
Incisional Hernia	3
Chronic Wound Pain	1

Prognostic factors

The results of univariate and multivariate analysis undertaken to define adverse prognostic factors are outlined in Tables 3 and 4.

Temporal trends

Analysis was undertaken of the first and second 50 cases in this series to look for trends in operative variables and outcome. The results of this analysis are summarised in Table 5.

Table 3. Univariate analysis of adverse prognostic factors in 100 hepatic resections

Variable	Complications	P value
> 4 Segments Resected		
No	11/31	<0.05
Yes	41/69	
Comorbid Conditions		
Absent	17/48	<0.001
Present	35/52	
Perioperative Blood Loss		
<1000ml	38/88	<0.01
≥1000 ml	14/15	
Abnormal Parenchyma		
Present	11/20	<0.01
Absent	33/80	

Discussion

Historically, liver resection has been regarded as dangerous and complicated surgery that is often best avoided. However, over the last 30 years, hepatic surgery has been undertaken in New Zealand by several surgeons who often practise in difficult circumstances.[8–11] This series is presented as a continuation of their work. Most played a significant role in my surgical education and, by example, all were at least partly responsible for me deciding on a career in hepatic surgery.

The primary reason for presenting the current series is to demonstrate that liver resection can be undertaken routinely, it can be taught safely, and that learning and refinements in technique continue to occur as practice evolves. In all cases, the author was the primary surgeon however significant parts of the resections were carried out by general surgical fellows in training in 19 cases. While hepatic resections are relatively complex procedures, suitably prepared trainees can undertake significant parts including in-flow control, out-flow control, or parenchymal division.[16]

A 30-day mortality rate of 3% was achieved in this series. This is consistent with larger institutional series which indicate that mortality rates in elective hepatic resections of 5% or less are realistic and now represent the standard of care.[14,15,17,18] The patients treated in this series are typical of those patients managed by hepatobiliary units. Most patients were in their 7th decade of life, 52% had significant comorbidities and 88 patients had a malignant diagnosis. Sixty-nine patients underwent resection of a lobe or greater—emphasising that significant parenchymal resections were undertaken in two-thirds of patients and that the low mortality rate in this series is not due to the performance of small resections.

It is worth noting that all three deaths occurred in patients with abnormal parenchyma (2 cirrhotics and 1 patient with marked steatosis),[19] and, while only 2 deaths were directly attributable to parenchymal issues, patients with abnormal parenchyma are significantly more at risk of perioperative complications than those with normal parenchyma.[1,7,17]

Two patients were also returned to theatre emergently with bleeding. However, in both cases the bleeding was from a point outside the liver (right adrenal gland and

right gastric artery) indicating that, while the risk of bleeding is increased in hepatic resection, the surgeon's attention should not be entirely absorbed by the liver.[20]

It is clear that the improved safety of hepatic resection is directly attributable to the techniques employed to decrease intraoperative blood loss and to preserve a well perfused and drained hepatic remnant. The techniques utilised to decrease blood loss include division of vascular in-flow (portal vein and hepatic artery) structures and out-flow structures (hepatic vein) prior to the division of parenchyma as well as prompt attention to intraoperative bleeding. Intermittent in-flow occlusion was used extensively in the first 50 cases during parenchymal division. However, it was utilised less frequently in the second 50 cases with a decrease in transfusion requirement indicating that careful technique is probably just as important at maintaining haemostasis and does not subject the hepatic remnant to ischaemic insult with the greater risk of postoperative hepatic insufficiency.

Low central venous pressure anaesthesia[6] was also used in all cases and also decreases blood loss from hepatic veins during the phase of parenchymal division. However, it is interesting to note that Fan et al[7] were able to achieve a zero mortality rate for hepatic resection without utilising this technique.

In contrast to the mortality rate, which decreased over the series, the morbidity rate remained stable with 52% of the patients developing complications. The vast majority of these were minor and not life-threatening. However, this does emphasise that, when undertaking complex procedures, complications are frequent. In addition, the complexity of the procedure was directly proportional to the complication rate with all patients undergoing extended resections developing some form of postoperative complication. This is an important part of the information that patients require before giving consent for the procedure and, principally to ensure accurate transfer of information, all the consents in this series were taken by the surgeon rather than this being delegated to junior medical staff.

All resections in this series were anatomical and it is interesting to note that increasing use was made of extended resections and segmental resections rather than simple lobectomy in the second 50 cases in comparison with the first 50. In appropriate cases, segmental resections are parenchymal sparing but offer the same oncological benefits as classic lobar resections without the risks associated with the removal of large volumes of normal liver tissue. However, they are often technically challenging and more time-consuming for the surgeon. Conversely more use was also made of extended resections in the second 50 cases, which is probably indicative of a more complex caseload. Jarnagin et al[17] has already highlighted this trend in the development of a large high volume hepatobiliary unit.

An important reason for analysing this work is for the purposes of personal audit. It is clear that learning and development does not or should not stop with the confirmation of status as a consultant. Increasing experience as a hepatic resectionist is associated with increased use of extended resections and more technically challenging segmental resections with a decreasing need for red cell transfusion. However, perhaps concerningly, increasing experience did not decrease the overall complication rate and, while surgical folklore states that complications occur only when high volumes of complex cases are managed, this should not encourage nihilism.

It should be possible to reduce this complication rate further with careful case selection, preparation, operation, and postoperative care. In addition, it should be possible to undertake all major hepatic resections routinely without the need for red cell transfusion, which is currently required in half of the cases.

Finally, mortality rates of less than 5% now represent the gold standard of care, but Fan et al[7] and Jarnagin et al[17] have shown that zero mortality rates are achievable and this must be the long-term goal.

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Elevation of serum liver enzymes after laparoscopic cholecystectomy

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Abstract

Background Laparoscopic cholecystectomy (LC) has been accepted as an alternative to laparotomy, and has become the standard treatment of benign gallbladder diseases. However, it has been noticed that (following LC) the serum level of certain liver enzymes raises markedly in patients who had preoperatively normal liver enzyme values.

Methods We measured serum values of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transferase, bilirubin, and international normalized ratio (INR) in 72 consecutive patients who underwent laparoscopic cholecystectomy and 36 consecutive patients who underwent open cholecystectomy (OC). During laparoscopic surgery, the intra-abdominal pressure was maintained at 14 mmHg of CO_2. To assess liver function, serum liver enzymes were measured before operations and at 1,3,7, and 10 days postoperation.

Results Mortality was nil. Twenty-four hours after the procedure, ALT and AST increased statistically significantly in the LC group (ALT_{LC24}: 87.1±24.2 U/L P<0.001; AST_{LC24}:82.8±19.1 U/L, p<0.001)—whereas in the OC group, 24 hours after the procedure, the serum value of ALT and AST was above the upper normal limits in only in one patient. A further increase in serum ALT and AST value was observed in the LC group (ALT_{LC72}: 99.3±19.5 U/L, p<0.001; AST_{LC72H}: 103.5±21.6 U/L, p<0.001) 72 hours after the operation. The mean value of ALT and AST in the OC group was within normal limits 72 hours after the procedure. Slow return to normality occurred 7-10 days after the procedure in the LC group.

Conclusion Alterations in hepatic function occur after laparoscopic cholecystectomy and appear to be clinically insignificant. CO_2 pneumoperitoneum seems to be the main reason for theses changes but other factors may also contribute. We also measured the values of ALP, GGT, INR and bilirubin. No statistically significant increase was noticed in any groups between the preoperative and postoperative values of these enzymes.

Laparoscopic cholecystectomy (LC) has been widely accepted as an alternative to laparotomy, and has become the standard treatment of benign gallbladder diseases such as cholecystitis and gallbladder stone.[1] Despite its numerous advantages (i.e. a shorter hospital stay, limited postoperative pain, quick recovery, fewer complications), this procedure may impair hepatic function. It has been noticed that following LC, the serum level of certain liver enzymes raises markedly in patients who had preoperatively normal liver enzyme values.[2]

We conducted a prospective clinical study to investigate the effect of laparoscopic cholecystectomy on liver function in humans, comparing changes in serum liver enzymes before and after laparoscopic and open cholecystectomy.

Materials and methods

A total of 72 patients (38 men and 34 women) with a mean age of 52 years (range, 31–88 years) were admitted to the Department of Surgery, Hellenic Air Force and Veterans General Hospital (in Athens, Greece) between May 2000 and January 2001 to undergo laparoscopic cholecystectomy (LC group). Thirty-six patients (19 men and 17 women) with a mean age of 58.3 years (Range, 51–89 years) were admitted in the same Department between May 2000 and July 2003 with symptomatic cholelithiasis or gallbladder polyps, and underwent open cholecystectomy (OC group). All patients selected for the study had normal serum transaminases values prior to the procedures.

The laboratory tests were carried out at the same laboratory using only one type of instrument. The normal range for the haematological parameters was ALT, 11–26 U/L; ALT, 8–31 U/L; ALP, 46–150 U/L; GGT, 8–35 U/L, and total bilirubin 0.3–1.2 mg/dL. The anaesthesiologic protocol was constant in all cases. Care was taken to select drugs that interfered as little as possible with the enzymatic activity of the liver.

The following patients were excluded from the study:

- Patients who had undergone endoscopic retrogade cholangiopancreatography and sphincterotomy within 10 days before the laparoscopic operation, and
- Patients who developed complications after the laparoscopic procedure (bile duct injury, bile duct leak, cholangitis).

The operations were performed by the same medical staff. All patients received general anaesthesia. During laparoscopic surgery, the intra-abdominal pressure was maintained at 14 mmHg of CO_2. Dissection of the gallbladder from the liver was performed with the use of monopolar diathermy. To avoid hepatic enzyme alterations of iatrogenic origin, intraoperative manipulation of the biliary tract (intraoperative cholangiography) was avoided in all patients.

Postoperatively, all patients were given the same intravenous glucose infusions and electrolytes plus antibiotics for 3–5 days (ceftazidime and metronidazole).

To assess liver function, serum values of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), bilirubin, and INR were measured before operations—and at 1,3,7, and 10 days postoperatively.

The mean and standard deviation of the collected data were calculated. Student t-test was used for statistical evaluation. Results were considered significant at $p<0.05$.

Results

Mortality was nil. All patients were haemodynamically stable during the postoperative period.

A statistically significant increase of ALT and AST was noticed 24–72 hours after the operation in the LC group. The mean preoperative ALT and AST values were 22.3±12.1 U/L and 21.6±13.4 U/L in the LC group, and 18.4±11.5 U/L and 19.9±11.6 U/L in the OC group, respectively (Table 1).

Twenty-four hours after the procedure, ALT and AST increased statistically significantly in the LC group (ALT_{LC24}: 87.1±24.2 U/L, $p<0.001$; AST_{LC24}: 82.8±19.1 U/L, $p<0.001$)—whereas in the OC group, the serum value of ALT and AST was above the upper normal limits in only in one patient 24 hours after the procedure (ALT_{OC24}: 23.8±10.9 U/L, $p>0.05$; AST_{OC24}: 25.5±7.7 U/L, $p>0.05$).

Seventy-two hours after the procedure, a further increase in serum ALT and AST value was observed in 43 (59.7%) and 39 (54.1%) patients in the LC group, respectively (ALT_{LC72}: 99.3±19.5 U/L, $p<0.001$; AST_{LC72H}: 103.5±21.6 U/L,

p<0.001)—whereas in the OC group, the mean value of ALT and AST was within normal limits (ALT_{OC72}: 21.6±13.4 U/L, p>0.05; AST_{OC72}: 20.9±10.4 U/L, p>0.05).

Seven days following the operations, the serum values of ALT and AST in the LC group, although lower than on day 2, remained above normal limits (ALT_{LC7D}: 45.6±13.4 U/L, p<0.05; AST_{LC7D}: 40.3±8.9 U/L, p<0.05)—10 days after the procedure, liver enzyme values have returned to normal values in the LC group.

We also measured the values of ALP, GGT, and bilirubin. No statistically significant increase was noticed in any groups between the preoperative and postoperative values of these enzymes.

Table 1. Preoperative and postoperative values of ALT and AST liver-enzyme levels in laparoscopic-cholecystectomy and open-cholecystectomy patients

Enzyme	Preop (U/L)	24 hr postop (U/L)	72 hr postop (U/L)	7 d postop (U/L)	10 d postop (U/L)
Laparoscopic cholecystectomy (LC) patients; n=72					
ALT	22.3±12.1	87.1±24.2	99.3±19.5	45.6±13.4	23.2±11.3
AST	21.6±13.4	82.8±19.1	103.5±21.6	40.3±8.9	21.3±12.4
Open cholecystectomy (OC) patients; n=36					
ALT	18.4±11.5	23.8±10.9	21.6±13.4	19.1±10.9	20.1±11.1
AST	19.9±11.6	25.5±7.7	20.9±10.4	20.2±10.2	19.5±8.4

ALT=alanine aminotransferase; AST=aspartate aminotransferase; hr=hours; d=days; preop=preoperative; postop=postoperative.

Discussion

In our study, we observed transient perioperative increases in ALT and AST in patients undergoing laparoscopic cholecystectomy, but no such changes were observed in the open cholecystectomy group. Ten days after the procedure, liver enzyme values had returned to normal in all our patients. Several factors could be responsible for the transient increase in aminotransferases values.

Despite the numerous clinical advantages, laparoscopy with pneumoperitoneum leads to complex haemodynamic, metabolic, neurologic, and humoral changes.[3–6] The pneumoperitoneum itself causes an increase in intra-abdominal pressure, which influences the cardiorespiratory system, thus reducing the venous return to the right atrium and (consequently) the cardiac flow.[6–7]

CO_2 has high haematic solubility and can cause hypercapnia and respiratory acidosis. Additionally, an intra-abdominal pressure of 12–14 mmHg of CO_2 is higher than the normal portal blood pressure of 7–10 mmHg, and is therefore capable of reducing portal blood flow and of causing alterations of the hepatic function.[8–18]

Giraudo et al[19] showed that a gasless technique causes smaller alterations in serological hepatic parameters than pneumoperitoneum at 14 mmHg, while Morino et al[20] reported that postoperative increase of liver enzymes was less when LC was performed with pneumoperitoneum at 10 mmHg. On the other hand, free radical-induced lipid peroxidation associated with a decrease in plasma antioxidant capacity, and altered hepatic function is observed after deflation of the pneumoperitoneum[16].

It seems that free radicals are generated at the end of a laparoscopic procedure, possibly as a result of an ischaemia-reperfusion phenomenon induced by the inflation and deflation of the pneumoperitoneum. Free radicals can damage tissues and organs, especially the Kupffer and the endothelial cells of the hepatic sinusoids.[16] Therefore, the elevated intra-abdominal pressure due to pneumoperitoneum may be responsible for the increase of liver enzymes after LC.

Another possible factor is the effect of patient position on blood flow. Sato et al[8] monitored hepatic blood flow during LC using transoesophageal echocardiography and concluded that the combination of pneumoperitoneum and head-up positioning resulted in decreased hepatic perfusion. Junghans et al[21] also reported that high intra-abdominal pressure combined with a head-up position resulted in the greatest disturbance in hepatic perfusion.

Several studies support the hypothesis that alterations in hepatic function after LC may be caused by the local effect of prolonged use of diathermy to the liver surface and subsequent spread to the hepatic parenchyma.[22–25] However, changes in the level of serum liver enzymes have been observed also after laparoscopic colectomy where the focus is far from the liver.

The effect of surgical manipulation on the liver, and the response to surgery-induced stress, may also lead to hepatocyte damage. Several factors such as vasopressin and norepinephrine play a critical role in the reduction of hepatic blood flow during LC.[26] However, Giraudo et al[19] studied laparoscopic surgical interventions performed without any manipulation the hepatobiliary structures. In this group of patients, the pneumoperitoneum of 14 mmHg provoked a statistically significant increase in cytosolic enzymes even in the absence of hepatobiliary manipulation.

The effect of general anaesthesia in liver function has been discussed in some studies.[27–30] It has been proposed that anaesthesia induces changes in splachnic blood flow and oxygen consumption. Yet, this theory does not explain why elevation of liver enzymes does not occur after OC, since the same anaesthesia protocols are used.

A last possible mechanism of alterations of serum liver enzymes after LC is the possible injury of the hepatic artery or any other arterial branch. More than 20 alternative pathways have been described for the hepatic artery. In 16% percent of people, it may run parallel to the cystic duct, while in 30% it is located anteriorly to the hepatic duct. Therefore, this vessel is frequently in the operative field and can easily be damaged. This, however, should be followed by a massive increase in liver enzymes, and usually has clinical implications difficult to predict in each patient.

Moreover, the fact that increase in liver enzyme values has been reported to occur after laparoscopic colectomy, where the chance to injure hepatic artery is minimal, suggests that arterial injury is not a possible mechanism for the elevation of liver enzymes after LC.

In conclusion, we showed that transient elevation of ALT and AST occurs after LC. CO_2 pneumoperitoneum seems to be the main reason for these changes, but other factors such as surgical manipulation, diathermy, general anaesthesia, patient position, and arterial injury may also contribute. These changes return to normal 7–10 days after the procedure and they have no clinical consequences in patients with normal hepatic function. However in patients with poor preoperative liver function, prolonged

laparoscopic procedures may not be the optimal choice for the treatment of several abdominal diseases.

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Suture material as a nidus for common bile duct stones: taking a closer look

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Abstract

A 72-year-old female with recurrent biliary colic and abnormal liver function 27 years after open cholecystectomy, was investigated by abdominal ultrasound, magnetic resonance pancreatocholangiogram (MRCP), and endoscopic retrograde cholangiopancreatography (ERCP). The ultrasound scan demonstrated a polypoid filling defect in the common bile duct (confirmed at ERCP), thus raising the possibility of a common bile duct tumour. The MRCP was normal. Visual examination of the duct with a choledochoscope revealed two stones attached to the wall by black suture material. The role of suture material in the formation of common bile duct stones, and direct choledochoscopy, is reviewed.

Stone formation around suture material or clips within the lumen or wall of the common bile duct (CBD) is an unusual but recognised late complication of cholecystectomy.

Case report

A 72-year-old female developed recurrent biliary colic 10 years after open cholecystectomy for gallstones. For 6 weeks prior to presentation she had experienced almost constant epigastric pain—with accompanying anorexia, nausea, and weight loss but no fever or rigors. Although the liver function tests and white cell count were normal, a previous episode of pain had been associated with elevation of liver enzymes; GGT to 199 (8—60 U/L), ALT to 124 (5–50 U/L), and AST to 60 (0–40 U/L).

An abdominal ultrasound scan suggested the presence of a fixed 8 mm filling defect (9.4 mm in diameter) in the mid portion of CBD (Figure 1). A subsequent magnetic resonance cholangiopancreatogram (MRCP) failed to confirm this finding.

Endoscopic retrograde cholangiopancreatography (ERCP) also showed a 6–8 mm polypoid filling defect in the mid CBD adjacent to the cystic duct opening and contiguous with the wall; probing with biopsy forceps indicated wall attachment. Brush cytology of the lesion and adjacent wall revealed normal ductal epithelium only.

Because of the difficulty in excluding a polypoid neoplasm, direct cholangioscopy using a 3.5mm diameter video-choledochoscope (Olympus, CHF-B160) through a large channel duodenoscope (TJF-160) was carried out. Visual examination of the dilated CBD revealed two, small, pale-coloured stones attached to the duct wall by black suture material (Figure 2). The decision to attempt removal of the stones or suture was deferred, and the patient subsequently decided against having choledochoscopic laser severing of the suture or surgical exploration of the duct.

Figure 1. Cholangiogram at ERCP showing filling defect (white arrow) in mid-common bile duct.

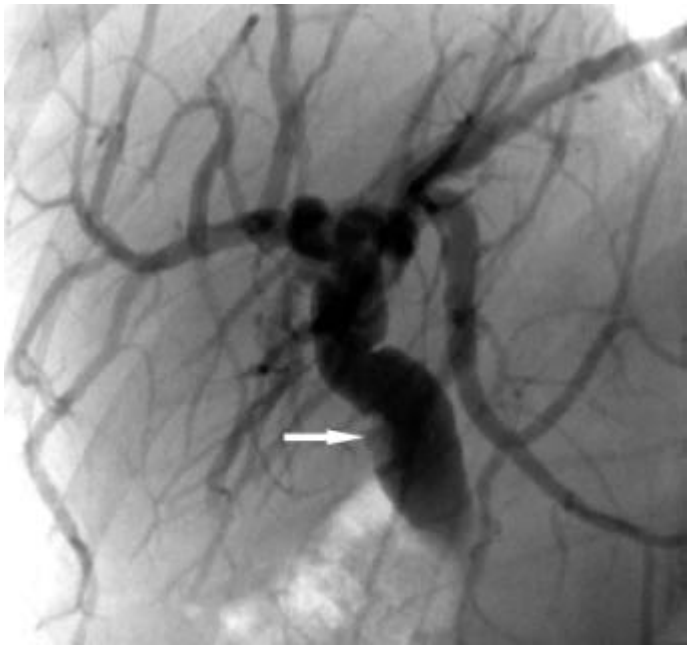
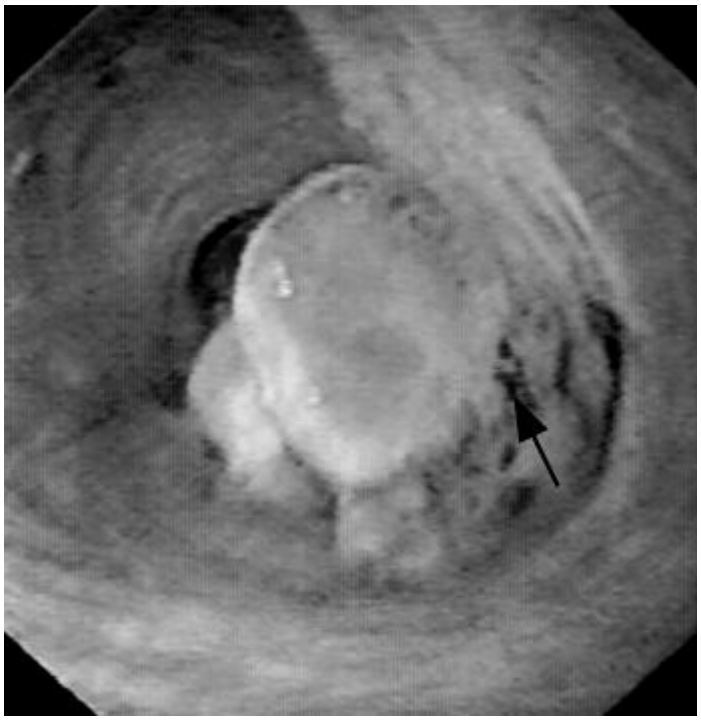


Figure 2. View with the choledochoscope showing at least two common bile duct calculi attached to the CBD wall, with black suture material forming the nidus for stone formation (black arrow)



Discussion

Suture material has been recognised as a focus for stone formation since the late nineteenth century,[1] with non-absorbable silk sutures regarded as being especially lithogenic in the common bile duct, postcholecystectomy.[2] Silk sutures have been implicated in 30% of all CBD stones,[3] and 40% of pigmented CBD stones.[4] Absorbable suture material is therefore recommended in surgery on the common bile duct, although other suture materials and clips have also been associated with stone formation.[5]

In our case, the choledochoscope was useful in providing assessment of the apparently polypoid lesion (US, ERCP) which was, in fact, two stones forming on suture material in the CBD wall.

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Metastatic colorectal carcinoma: clinicopathological downstaging following neoadjuvant chemotherapy

Simon Janes

Hepatic metastases develop in 20–30% of patients with colorectal carcinoma.[1] Untreated, the prognosis is poor, with a median survival of 6–12 months[2,3]—improving to 12–18 months with chemotherapy.[4,5] Hepatic resection is the only potentially curative intervention to date, with 5-year survival rates of 20–40%[6] and surgical mortality of less than 5%.[7]

Although hepatic resection has gained widespread acceptance, patient selection remains controversial. In particular, the presence of multinodularity, poor location, extrahepatic disease, or large-sized metastases is often considered a contraindication to surgery.[7,8] For 13.5% of these unresectable lesions, neoadjuvant chemotherapy downstages metastases to a resectable state, with 34% 5-year survival post-resection for multinodular disease.[8] However, recent reports have shown no survival disadvantage following resection of bilobar disease.[6,9,10]

Disagreement also exists regarding the number of lesions that should be resected. Having more than three lesions is regarded as a poor prognostic indicator, however recent evidence suggests up to seven lesions can be resected without affecting survival[6]—although there is consensus that peritoneal disease is a relative contraindication to surgery.

We present three cases of resected colorectal liver metastases that had an excellent response to chemotherapy prior to hepatectomy. Metastases were bilateral in two cases, and another case had multiple lesions within the right lobe. Postoperative histology showed complete resolution (CR) in all three cases. In each case, chemotherapy was associated with downstaging of disease to a more operable state.

Case reports

Case 1

A 63-year-old man developed bilateral hepatic metastasis 2 months after anterior resection for rectal carcinoma (Figure 1, Table 1). He had non-insulin dependent diabetes mellitus (NIDDM) with hypertension. Eight cycles of chemotherapy with oxaliplatin and modified de Gramont regime were well-tolerated, with carcino-embryonic antigen (CEA) falling from 30 µg/L to 1.8 µg/L (normal <10 µg/L). Post-chemotherapy computed tomography (CT) showed reduced tumour volume in the right lobe lesions, and apparent resolution of the left lobe metastasis (Figure 2).

A subsequent magnetic resonance image (MRI) scan confirmed the CT findings, and a right hepatectomy was performed. Intraoperative ultrasound (IOUS) demonstrated three subcapsular tumours in the right lobe, however segment IV and the left lateral segments appeared tumour-free.

Table 1. Characteristics of three patients with colorectal hepatic metastases

Age, gender	Primary site	Metastasis presentation	Number of metastases	Distribution	Chemotherapy	Chemotherapy response	Recurrence, months	Follow-up, months
63, m	Rectal	Metachronous	4	Bilobar	Oxaliplatin	Resolution	-	6
72, f	Rectal	Metachronous	3	Bilobar	5 FU	Resolution	11	13
47, m	Sigmoid	Synchronous	4	Right lobe	5 FU, folinic acid	Resolution	-	51

Figure 1. Pre-chemotherapy abdominal CT scan image (case 1). Two low attenuation lesions are seen in the right lobe and one in the left lobe

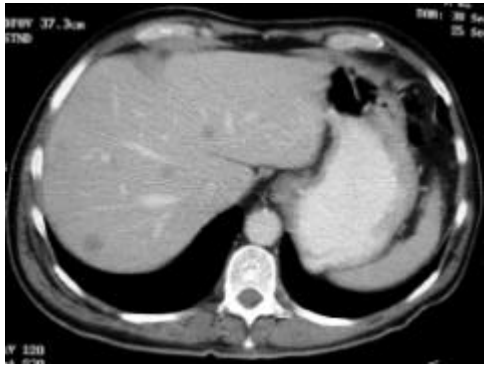


Figure 2. Post-treatment CT scan image (case 1). Only one right lobe lesion is seen

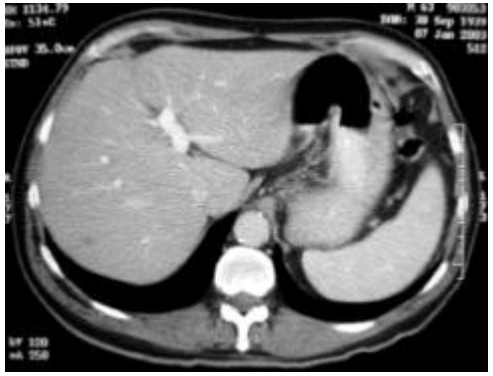


Figure 3. Liver resection macroscopy for case 1, showing a subcapsular tumour nodule

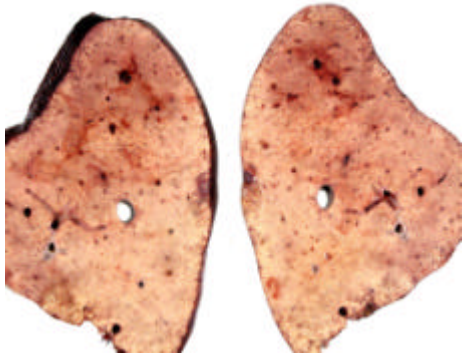
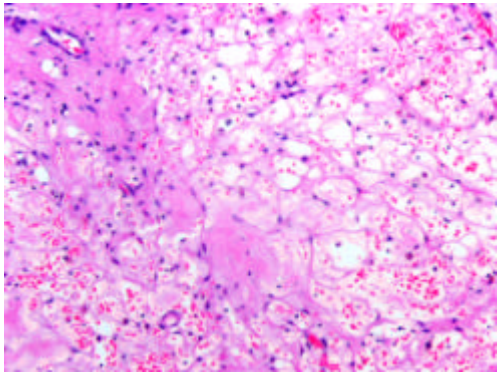


Figure 4. Microscopic appearance of the subcapsular nodule in Figure 3. Hyalanised fibrous tissue is present with no evidence of malignancy



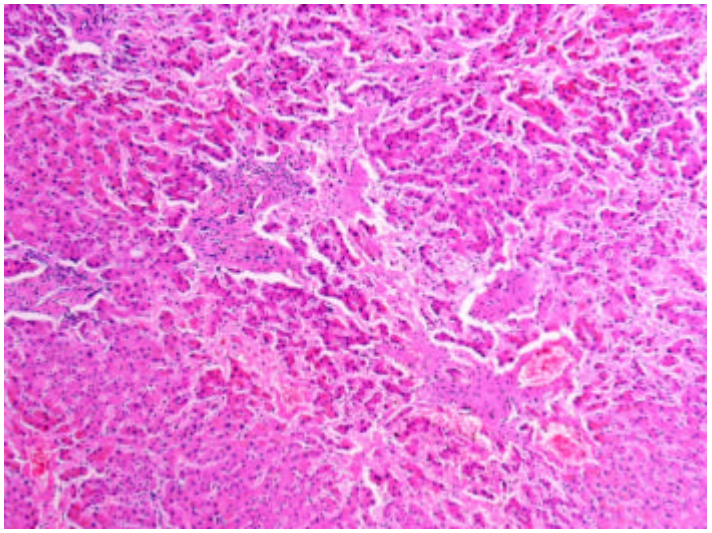
Macroscopically, there was a 2-cm tumour nodule in the subcapsular area (Figure 3). Microscopically, the tumour nodules contained hyalanised fibrous tissue, with no evidence of metastatic carcinoma (Figure 4). The patient made an uncomplicated recovery and has been free from recurrence after 6-months' follow-up.

Case 2

A 72-year old female underwent anterior resection for a Dukes C2 rectal tumour. En-bloc total abdominal hysterectomy and bilateral salpingoopherectomy was performed for locally advanced disease, however histology suggested complete resection; 8/17 lymph nodes were involved, including the highest. Fifteen years previously she had a mastectomy for breast cancer. Past medical history was otherwise unremarkable.

An abdominal CT scan after 1 month demonstrated metastasis in liver segments IV, VII, and VIII (Figure 5). CEA was 84 µg/L, falling to 2.5µg/L after 18-weeks of continuous 5-Flurouracil (5-FU) treatment. Treatment was restricted by the development of hand-foot syndrome. A mid-chemotherapy CT scan showed no change in the previously identified lesions but raised the possibility of a new lesion in segment III. A CT scan 2 months after chemotherapy demonstrated two metastatic deposits in the right lobe and one in the left, however their size had decreased dramatically.

Figure 5. Microscopic appearance of excised liver of case 2. Vascular congestion with atrophy of hepatocytes is present, but there is no evidence of malignancy



An extended right hepatectomy was performed. During the procedure there was no evidence of tumour either on palpation or with IOUS. Histological examination of the excised liver revealed no evidence of metastatic carcinoma. There was an area of vascular congestion with atrophic hepatocytes that probably represented the area where the tumour had been (Figure 5). Eleven months after the hepatectomy, she developed obstructive jaundice and abdominal pain. The CT scan demonstrated multiple hepatic and lung metastases.

Case 3

A 47-year-old man underwent sigmoid colectomy for a Duke's D sigmoid carcinoma. At operation, four metastases were found in the right lobe of the liver, confirmed on biopsy as metastatic adenocarcinoma. He had six cycles of 5 FU and folinic acid chemotherapy, complicated by stomatitis. MRI after three cycles demonstrated 3 right lobe lesions. A right hepatectomy was performed; and during the operation, one small lesion was palpable near the anterior surface of the right lobe. Histological analysis of the tumour nodule showed fibrotic tissue with no evidence of malignancy. There was no evidence of malignancy in the remaining excised liver. He has been recurrence-free after 4-years' follow-up.

Discussion

Surgical experience in hepatectomy has developed to the point that resection of 80% of the liver can be performed with mortality rates of less than 5%.[11] As a result, patient selection has become increasingly important. In the largest series to date, Fong et al showed that bilateral disease was not predictive of long-term outcome; however, multiple metastasis was an independent predictor of poor long-term survival.[7] Other reports indicate that, although bilateral disease does not affect long-term survival, surgical mortality is significantly higher if extended hepatectomy or concomitant colonic resection is performed.[10]

Our synchronous case would have been a difficult concomitant resection. The excellent chemotherapy response and long-term survival for this patient suggests synchronous lesions may benefit from delayed hepatic resection for at least 3 to 6 months, so that the effects of chemotherapy can be determined.

Treating unresectable hepatic metastases with pre-operative chemotherapy renders 10–40% of lesions resectable after a median of 5–10 months treatment.[12] In this group, neoadjuvant chemotherapy with 5-FU and oxaliplatin is associated with 5-year and 10-year survival rates of 34% and 20% respectively,[13] similar to that of patients whose disease was operable at diagnosis. However, disease-free survival may be less due to the high incidence of hepatic recurrence.[10,12]

The chemotherapy response in three of our cases was dramatic, with no histological evidence of malignancy. According to World Health Organization (WHO) criteria,[14] CR can be objectively determined clinically, radiologically, biochemically, or via surgicopathologic restaging. Using the former three methods demonstrates CR in 1.2–7.7% of patients receiving hepatic arterial infusion chemotherapy (HAC).[15–18] However, these studies relied on CT evidence of resolution, hence it is unknown how many patients had undetected microscopic disease.

Histological evidence of CR is limited to case reports[19] and anecdotal evidence from series using HAC.[15] Randomised trials demonstrate significantly improved 2-year survival and disease-free survival using adjuvant HAC,[20] but no difference in 5-year survival rates.[20,21] Neoadjuvant HAC offers no clear advantage over systemic therapy and may even compromise surgery.[12] Further trials are required to evaluate the role of HAC for colorectal metastases.

Systemic therapy was used in preference to HAC in all our patients, and adjuvant chemotherapy was not routinely administered. Current systemic combination

regimens produce first-line responses in more than half of patients with colorectal metastases.[22] Using radiological criteria, peripheral 5-FU achieves CR rates of 6–8%.[23,34]

To the best of our knowledge, this is the second largest series with histologically proven CR of hepatic metastases following systemic chemotherapy.[8] Unfortunately, the small number of cases precludes determination of factors predictive of CR. Excision of the primary tumour may induce spontaneous CR of hepatic metastases without chemotherapy.[25] However, in this series, the temporal relationship between primary resection and metastatic presentation means spontaneous resolution was unlikely. These cases represent approximately 3% of hepatic resections performed at our institution during the past 4 years (92 cases). Hence the chemotherapy response, although important, may not be generalisable. The demonstrated survival benefit suggests that further prospective evaluation of neoadjuvant systemic chemotherapy may be warranted.

Conclusions

Systemic neoadjuvant chemotherapy for multiple colorectal hepatic metastases allows a subset of patients to undergo potentially curative resections. For some of these patients, chemotherapy causes complete histological resolution of metastases. A similar 5-year survival rate in patients whose disease was resectable at presentation suggests this approach should be used more widely.

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Informing consent in New Zealand research: researchers' conflict of interest and patient vulnerability

Martin Tolich, Kate Mary Baldwin

Abstract

The authors, members of two different regional health ethics committees, write about their observations evaluating ethics application where researchers' conflicts of interest go unacknowledged either when researching their own patients or when the research subjects experience a temporary vulnerability—i.e. they have learned they are to lose a body part such as a breast, bowel, or limb. Currently the operational standard code of ethics does not address either issue even when New Zealand health ethics had its origins at National Women's Hospital where a physician researched his own patients. Under this situation the researcher's conflict of role undermined informed consent. The paper ends rewriting Section 26 of the Operational Standard.

Recent debates about informed consent in the *New Zealand Medical Journal* (NZMJ)[1–3] focused on a narrow reading of the nature of informed consent. Their combined discussion was limited to the dynamics of informed consent within doctor and patient relationships. The Health and Disability Commissioner Ron Paterson[2] quotes the Medical Practitioners Disciplinary Tribunal's latest ruling that makes it clear informed consent is achievable and that the rationale for informed consent is to protect patient's, not doctors.

Paterson's comments follow arguments put forward by Frank Frizelle who outlines a defensive risk management rationale for securing the patient's informed consent. Paterson states that the reason informed consent matters (and is not an over-emphasis of the patient's autonomy), is, as explained by the Tribunal, an essential component to maintaining trust; a vital element in the doctor-patient relationship.[2] Furthermore, he dispels other common myths such as the obligation of the doctor to ensure the patient understands the information; when he states: *Doctors are required to facilitate understanding, but cannot be expected to guarantee patient understanding, and the law makes no such requirement.* Gillett[3] endorses this approach in his paper titled *At last some common sense*.

Promoted by a recent complaint about his practice, Frizelle[1] defends informed consent but argues that legislation of what should be a medical act has increased to such an extent that it is almost impossible to fulfil the requirements of informed consent. He cautions doctors to be realistic about the information they give to patients, and warns that even though retrospectively one may wish they had told the patient more about a particular complication, there is increasing evidence that the patient or family will not remember the information.

McKeague and Windsor[4] (see also Williams, French, et al;[5] Snowdon[6]) support this claim with their study on elective surgical patients—finding that a significant number of elective surgical patients were either dissatisfied with the information provided to them or had no memory of the consent process. Furthermore, McKeague and Windsor recommend that consent givers should understand that the information is neither supported by case law nor a requirement of the Operational Standard for Ethics Committees.[7]

The Commissioner[2] clarifies the legal requirement as follows:

- The patient has been given the information that a reasonable patient in that patients' circumstances, would expect to receive;
- The patient is competent to make a decision; and
- The patient, of his or her free will gives consent

Although it is a requirement that a patient is given the information as detailed in the first point above, the Commissioner, Paterson[2] states, *'…it does not follow that in giving my consent to proceed, I truly understand the information provided.'*

Situating a discussion of the nature of informed consent solely within doctor and patient discourse is problematic when unconnected to research-based informed consent or the web of ethical principles that underlie informed consent.

We 'problematise' the NZMJ debate by making three suggestions for *informing* consent in New Zealand, as follows:

- First, considering informed consent simultaneously in both research and ordinary medical care settings invigorates the informed consent debate. Rights that may satisfy the NZMJ debate for medical patients do not necessarily fulfil research requirements for informed consent when patients have a real choice about non/participation.
- Second, we underscore the centrality of informed consent to any ethical consideration but go one step further exploring its complexity as two distinct moments in time. 'Informed,' requires the risks and benefits, both direct as in physical side effects, and indirect, as in conflict of interest, to be identified. 'Consent' requires that the person is free (i.e. voluntary) and able to choose, both directly as in having options and indirectly as in freedom from coercion or feelings of obligation or personal vulnerability.
- Third, we elaborate this second point highlighting features of the Operational Standard for Ethics Committees, which supposedly guide researchers to act ethically.

  Two sub-principles concern us: first, the self-regulated option for researchers to declare their conflict of interest when researching their patients; second, the definition of who warrants vulnerable research subject status is too narrow; it is limited to certain statuses (such as children, elderly, or terminally ill) when vulnerability may be more pervasive.

To this vulnerable persons list we can add the term 'vulnerable times'[8] suggesting that all persons can be vulnerable when faced with the possibility of losing their bowel, breast, limb, or facing their imminent demise. Therefore, in failing to effectively address these two principles of conflict of interest and temporal/contextual vulnerability, the Operational Code undermines patient/subject's informed consent.

The authors' intention here is to revise these sub-principles. Our goal is to provide sufficient conditions to enable research subjects to truly make an *informed* consent to participate, thereby ensuring that health research in New Zealand is of a robust ethical standard. Therefore, we end this paper demonstrating how the revision of Section 26 of the Operational Code[7] advances this goal.

‘Informed’ consent

Beauchamp and Childress[9] provide a more stringent rationale for informed consent than offered in the recent NZMJ debates. Beauchamp and Childress’s justification for informed consent is that it respects the patient’s right to autonomous choice; they define an informed consent to be:

> ‘An informed consent in the first sense occurs if and only if a patient or subject, with substantial understanding and in substantial absence of control by others intentionally authorises a professional to do some thing’

According to this definition, sufficient information is given to the patient to enable them to evaluate the treatment. For the patient to have a substantial understanding, they need information on factors that concern (or are important to) them.[9] What is insignificant to the practitioner or most reasonable people may be the deciding factor to a patient. Indeed, the only way a clinician will know of the information needs of the patient is by a ‘mutual exchange of information.’[9]

For the patient to be able to freely consent, they must have information that is relevant to the treatment and in the context of the patient’s cultural and personal beliefs. Buchanan and Brock (in Wilkinson[10]) go further, stating it is an important mechanism to protect the patient’s well-being—as the patient is most likely to be best able to determine what makes their life good.

The partnership model of healthcare encourages clinicians to recognise the unique knowledge and perspective patients have on their treatment and care and to involve them in the decision-making. When time allows, the consent process takes place over time as the patient’s knowledge builds through ongoing information sharing between patient and clinician.[11]

The goal of healthcare, the betterment of the particular patient, directs the relationship and principles of health care providers and is described by various models: the agency model[12] whereby the professional carries out the wishes of the patient, and the contract model[13] whereby the patient’s expectations of the clinician and the clinician’s expectations of the patient are clearly defined by the contract.

Both agency and contract models are based on an egalitarian sense of power between the parties. Fiduciary relationships[12] however, are unequal; professional codes of practice recognise the inequalities of power between both parties and thus require the professional to act in the patient/client’s best interest. This is a primary expectation of the medical profession and is reflected in the acceptance by patients, society, the law, and the clinicians. Thus if a patient is incompetent and the situation is urgent then the clinicians should provide treatment that is (in the clinician’s considered opinion) in the patient’s best interests.

The moral authority of doctors to make decisions is reliant on the doctor being trustworthy. Kohen[14] (1994) identifies seven conditions a professional must meet to be considered trustworthy. These conditions are that the professional must have the client’s interests at heart and exhibit an open-ended willingness to act. This willingness must be sustained for as long as it takes to either render help or determine that nothing further can be done for the client. The professional must be competent and be able to demand from the client the degree of accountability and discipline necessary for the treatment to proceed. The professional is bound to monitor their own

behaviour and they must have freedom to serve each individual client's well-being with discretion.

The irony of this list of obligations is that if they worked in practice, written informed consent for the patient would not be necessary. Moreover, would this set of obligations change when the professional is a researcher or if the individual subject's risks and benefits are measured as an aggregate public good?

The primary guiding principle of health research, established by the Declaration of Helsinki[15] stated:

> Concern for the interests of the subject must always prevail over the interests of science and society.

The spirit of this declaration directs researchers to acknowledge the inherent risks of the researcher /subject relationship; the conflicting goals of personal health care and health research forces the researcher not only to develop strategies that protect the subject from these risks but that their patient's interests prevail.

New Zealand has its own Helsinki document. The Cartwright Commission *Inquiry into Allegations Concerning the Treatment of Cervical Cancer at National Women's Hospital and into Other Matters*[16] exposed a breakdown in the trustworthiness of the doctor/researcher in terms of the absence of informed consent confounded by unstated boundaries between treatment and research, and a failure to recognise the conflict of interest inherent in the role of clinician/researcher. Eight women died taking part in a research project conducted by Associate Professor Green. Most notable in this research project was the fact that these women took part in an experiment for which they knew nothing about.[18]

Research practice has changed in the post Cartwright era. No longer are researchers trusted to know what is in the patient's best interests and to act accordingly. Instead, an ethics committee (comprising of a balance of academics and laypeople) now approves all human-subject research. The new emphasis is on informed consent; providing the patient with sufficient information about the research to decide their participation; and recasting the fluidity in the doctor, researcher, and patient relationship. However, informed consent does not rely solely on information.

We now demonstrate that informed consent is not sufficiently robust and is undermined when a patient's vulnerability is not acknowledged, and/or when conflicts of interest between the clinician (as researcher) and the patient are not recognised and disclosed, as follows.

'Informing' consent

The *Operational Standard for Ethics Committees*, most recently published in 2002, guides the work of the ethics committees and promotes the highest standard of ethical behaviour among researchers and healthcare providers. However there are glaring omissions in the code. Specifically, there is no requirement in the Operational Code for a researcher (researching their own patients) to acknowledge and justify to any ethics committee that a conflict of interest exists. Although research committees are able to request clarification on any matter, the reality is that it is not only researchers that fail to recognise the risks of conflicting interests. Ethics committees follow

closely the Operational Code and weaknesses in the code results in weak examination in that particular aspect.

Failure to recognise the inherent conflict of interest is the fundamental problem and can be located within the Cartwright Commission findings. Professor Green's fundamental ethical issue is usually taken to be informed consent. He failed to inform his patients of the research and gain their consent. A more fundamental error was his failure to differentiate between the patients' individual needs and his research requirements and a failure to recognise his conflict of interest.

But for some unknown reason, this essential ethical condition was neither part of the Commission's final report nor has it become part of the Operational Code. Conflict of interest is mentioned in passing in the Health Ethics national application form in question 3.3.3.

> Is there any special relationship between the participants and the researchers? (e.g. doctor/patient, student/teacher)

There is no follow-up to question 3.3.3 in the application form. At a minimum, a researcher should be required to recognise their conflict of interest and describe how they plan to minimise and monitor the conflict of interest. In the guide to researchers for question 3.3.3, the instructions do not mention conflict of interest but are limited to information about researchers providing *copies of notices and/or advertisements for participants.* Thus the ethics committee's attention is directed to a very narrow view of conflict of interest.

The only reference to 'conflict of interest' in the Operational Code is in Section 26, but again it does not explicitly mention doctor and patient conflicts of interest. Section 26 reads:

> Respect for persons requires that greater protection be provided to those persons with diminished autonomy (such persons may include children, inmates, persons in dependent relationships, persons with an intellectual disability, and unconscious patients) to ensure that they are not subjected to abuse, exploitation or discrimination. Often, additional protection is provided to persons with diminished autonomy by requiring the input/advice of third-person representatives. Other classes of research participants that are sometimes considered to be more vulnerable include terminally ill patients, aged persons, and students and employees of the researcher.

There are two significant omissions in Section 26. First, a conflict of interest is established in two specific power relationships between students and their teachers and between employers and their staff. No power relationship is seen to exist between a doctor as researcher and their patients. An irony does exist however in the Question 3.3.3 above. There the doctor/patient relationship is clearly identified as being a conflict of interest. It would seem the national application form researchers fill out is not sufficiently connected to its Operational Code.

The second omission involves the limited reading for the protection of vulnerable persons. Section 26 fails to capture the everyday lived experience of normal patients coming to terms with what ails them during routine crisis of the human condition when learning for the first time they are to undergo surgery to lose a bowel, breast, or limb—or when they are in acute pain or in life threatening situations.

Under Section 26, these persons are not considered vulnerable. Yet we assert these persons are vulnerable by adding the notion of vulnerable times to the category of vulnerable persons. A patient learning that a bowel or a breast is to be removed may heighten their sense of vulnerability, albeit temporarily. We suggest that such vulnerable times weaken the person's capacity to give an informed consent and particular boundaries should be placed around such situations.

Section 26—revised

Respect for persons requires that greater protection be provided to those persons with diminished autonomy when gaining informed consent. Diminished autonomy status is afforded to three categories of persons and/or relationships:

- **Category 1—**Compromised persons who are limited in their ability to make an informed consent. These include children, inmates, persons with an intellectual disability, and unconscious patients. Protections are needed to ensure that they are not subjected to abuse, exploitation, or discrimination. A remedy to this situation is protection provided by requiring the input/advice of third-person representatives.
- **Category 2—**Persons whose vulnerability is temporary. For example, most patients are not routinely classed as vulnerable persons but they may experience diminished autonomy status at times during their illness such as when first learning of their illness or preparing for surgery. Equally, those patients in pain or emergency situations and the terminally ill need special protections.
- **Category 3—**Subjects in a dependent relationship with the researcher (such as teachers and their students, employers/managers and their employees or researchers, and their patients) need special protections. In each case, researchers are required to first recognise the dependent relationship before outlining how this subordinate relationship will be managed.

Category 1 involving compromised persons is virtually how it reads in the existing Operational Code. A notable omission from this list of compromised persons is Aged Persons who are no longer identified as in need of special protections (if ever they required any special protections). In Categories 2 and 3 above, our focus has been on re-informing informed consent by having researchers recognise the breadth of conflicts of interests and the contexts of patient vulnerability.

As members of regional ethics committees, the authors suggest that recognising and addressing conflict of interests in research is one way of beginning to shore up the inherent weaknesses of informed consent in research settings. Clinician/researchers, therefore, should be very specific in their research design on how they will counter the inherent conflict of interest. A second way is to re-contextualise the conditions under which a person can be classified (albeit temporarily) as a vulnerable person. Rewriting Section 26 of the Operational Code for Ethics Committees is a start to re-informing consent in New Zealand research.

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THE NEW ZEALAND MEDICAL JOURNAL
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The scope and limitations of balneological treatment: diabetes, chronic Bright's disease, renal calculus, dyspepsia, obesity, and cachexia

This extract comes from an article by Dr Arthur Wohlmann that was published in the New Zealand Medical Journal 1905, Volume 4 (14), p104–16.

Diabetes is frequently held to be relieved by a course of alkaline waters. I do not remember seeing particularly favourable results in cases of really severe diabetes, but in those mild cases of glycosuria occurring in elderly gouty subjects which are so common it is certain that the sugar disappears without the use of drugs and without strict dieting. For such cases Te Aroha is the spa specially to be recommended. .

Chronic Bright's disease should theoretically improve from the additional skin-excretion induced; but I am speaking from my own experience only, and it has been practically nil. Cases of slight albuminuria without evidence of further mischief certainly frequently clear up, but it is difficult to be sure that this is the result of treatment.

Renal calculus of uric-acid origin should also be mentioned on the list of suitable cases. My own experience has been entirely limited to a few cases in which symptoms of renal colic have disappeared after a course of alkaline waters, generally with the simultaneous passage for weeks together of large quantities of, urates. I only remember two cases in which a definite stone was passed under mineral-water treatment. A closely allied condition, and a very common one, is that of the man in the latter half of middle age, with a hard pulse, brain-fag, and perhaps *quasi*-hemiplegic attacks, who is passing very large quantities of urates or uric-acid crystals. He is frequently an able man who has fought his way to a high position, and maintained it by strenuous mental and physical toil— and suddenly broken down. For such a one spa treatment has generally most excellent results.

Dyspepsia.—For cases with hyperacidity as a prominent symptom I would recommend Te Aroha; the more common class of atonic and neurotic dyspeptics will do better with the douche- massage treatment available at Rotorua.

I would recommend the latter spa also for most hepatic cases, and especially for those with obstinate constipation and piles, which latter are treated with considerable success by the local application of the Scotch douche.

There is at present no facility for using purgative waters, as at some European spas; but this deficiency will, I expect, soon be remedied by the recent discovery of a purgative water at Banks Peninsula.

Obesity is treated with moderate success at both Rotorua and Te Aroha.

The *cachexia* induced by long residence in tropical climates, or by malaria and tropical diseases, can be treated with great success at the high-lying spas, Hanmer and Rotorua. In favour of the former resort is the more bracing climate, while the latter affords greater advantages in the way of douche-massage and electrical treatment.

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An early description of cancer-to-cancer metastasis in 1848

Wilson Onuigbo

It was stated by Leonard Weiss[1] that 'it is as well to remember that in routine autopsies, the pathologist examines selected areas of tissues by the eyes.' Such an examination led Mr H Smith[2] to present, in the first volume of the *Transactions of the Pathological Society of London*, a paper entitled *Malignant disease of the kidney, heart, and brain* on 17 January 1848.

On reading that paper, I discovered that it dealt with an important phenomenon in cancer metastasis, so I wrote a published review[3] in 1974, and stated 'organ selective metastasis is the formation of secondary tumour in an organ in such a manner that its location pattern is peculiar.' After drawing attention to its history, I demarcated 12 classes, the first being termed 'Oddity' whose 'most interesting group consist of tumours which are themselves selectively attacked by other tumours'. I added that 'what is particularly striking about tumour-to-tumour spread is that the recipient tumour has been found in the kidney in the vast majority of published cases.'

Therefore, let me reproduce an extract from the Smith's report because it was almost certainly, if not clearly, a case of melanoma of the eye progressing to carcinoma of the kidney:

> Taken from a patient, aged 35, who had suffered for some time past from a melanotic degeneration of the right eye ball: this was removed about six weeks before his death some improvement took place upon the removal of the tumour, but this was only temporary. He gradually relapsed, and suffered from severe pains in the head: coma slowly supervened, and he died in that condition. During the last year he had occasionally suffered from severe pain in the epigastric region, and had been at tacked with paroxysms not unlike those of angina pectoris.
>
> On post mortem examination, the brain was found very firm, and much congested. There was considerable effusion of fluid in the ventricles, but no abnormal deposit of any kind in the substance. Two round masses about the size of a garden pea was situated on the third nerves at their region; in fact the nerves appeared to have there origin from these masses .
>
> On looking at the heart, a black mass, about the size of a chestnut, was seen in the substance of the left ventricle. Several small tumours, the size of pears, were scattered about in the vicinity of the larger one.
>
> On opening the abdomen, several tumours were found connected with peritoneum; a black mass larger than that in the heart existed in the right lobe of the liver. Both kidneys were much diseased, but the right presented a rare and beautiful specimen of malignant disease. A large mass of the size of an orange involved more than one-third of the organ, situated chiefly towards its convexity. Two others of the size of pigeon' eggs were seen; one situated just

> below the first—the other at the concavity of the kidney where the vessels enter the organ.
>
> These deposits in the kidney differed much in their appearance and structure. The first was of a whitish colour, with dark matter in its centre; and hard in its consistency, presenting the appearance of cancer. The others were softer and black, presenting clearly the characters of true melanotic deposit. A large quantity of blood appeared to be mixed with the substance of that structure composing the blacker masses.

As fate would have it, in the above case, the observant pathologist noted differences, not only of colour but also of structures, in the two kidney tumours. It is noteworthy , therefore, in a modern case[4] reported from Thailand, lung cancer spread into renal cancer, the former being 'gray granular' while the later was 'bright yellow'. In fact, histological verification was confirmatory in the modern example, unlike the general run of cases published before the microscopical era of the 1850s. As I highlighted elsewhere,[5] humoral and cellular concepts were distinguished later.

Interest in tumour-to-tumour metastasis continues. In 2002, in the case reported by Shomaf in Jordan,[6] breast cancer spread to a thyroid adenoma, and the author's review showed that 'the most common host tumour was renal cell carcinoma.' Incidentally, in the American report,[7] the patient had both lung carcinoma and renal carcinoma (hypernephroma). Both carcinomas exhibited secondaries and it was extraordinary that there were 'secondary deposits within the sites of the metastatic hypernephroma.'

Next, what about management problems? In the 1980 Bowman Lecture of the Ophthalmological Society of the United Kingdom, Lorenz Zimmerman[8] concluded that 'uveal melanomas, though the subject of intensive clinicopathological investigation for well over a century, continue to present major problems in management because of incomplete knowledge of the natural history of these tumours and of how they metastasise.' Consequently it is worthwhile to add that the above 1848 account[2] indicates that the subject was known much earlier than currently held.

Certainly, long ago, cancer of the eyes was so important that Scarpa[9] (in 1811) devoted a whole treatise to it; and by 1846, the opinion from the London Ophthalmic Institution was that 'when fairly established, whether the primary tumour be extirpated or not, the patient dies, in the course of one or two years, of accumulation of similar character in all parts of the body.'[10]

Perhaps future researches will, as Zimmerman[8] hoped, 'pave the way towards more sensible management and improved survival as well as prolonged retention of eyes with useful function.'

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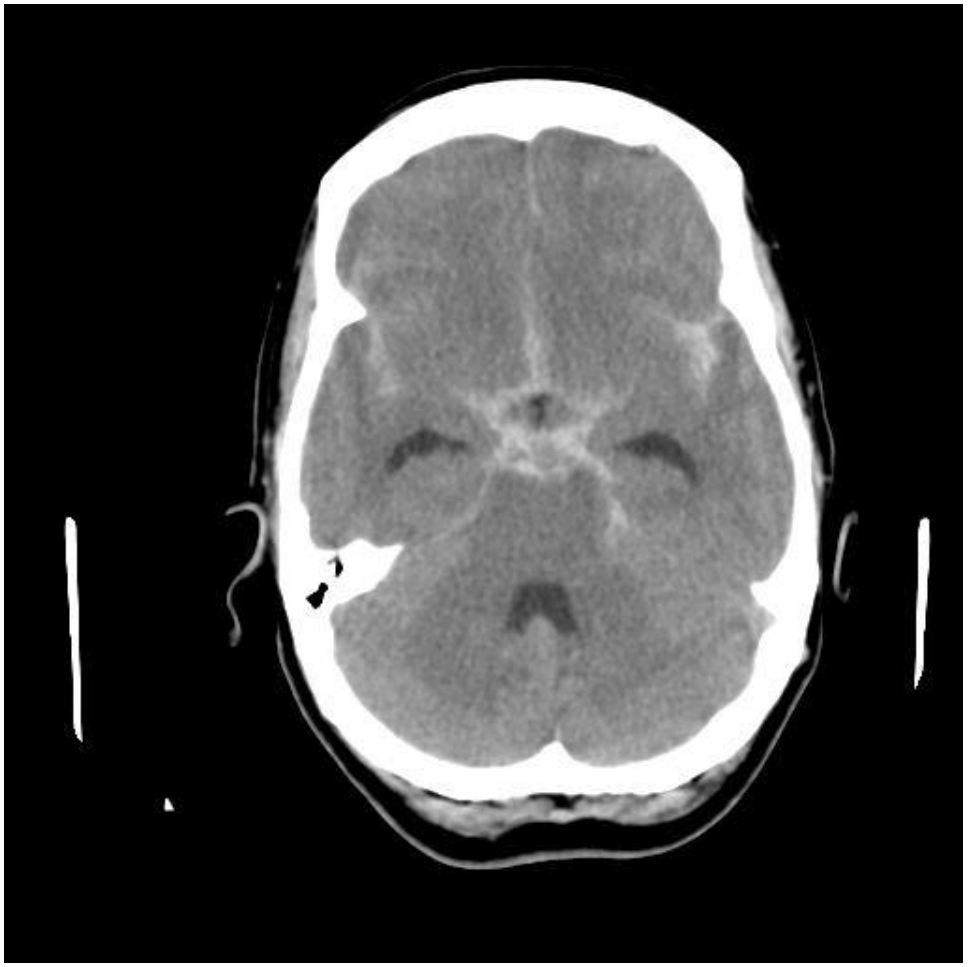
Thunderclap Headache

A 54-year-old woman presented with sudden onset of severe headache while pruning her privet hedge at home. An un-enhanced computed tomography (CT) scan was performed (Figure 1).

Figure 1. Un-enhanced CT scan of the brain



Questions:

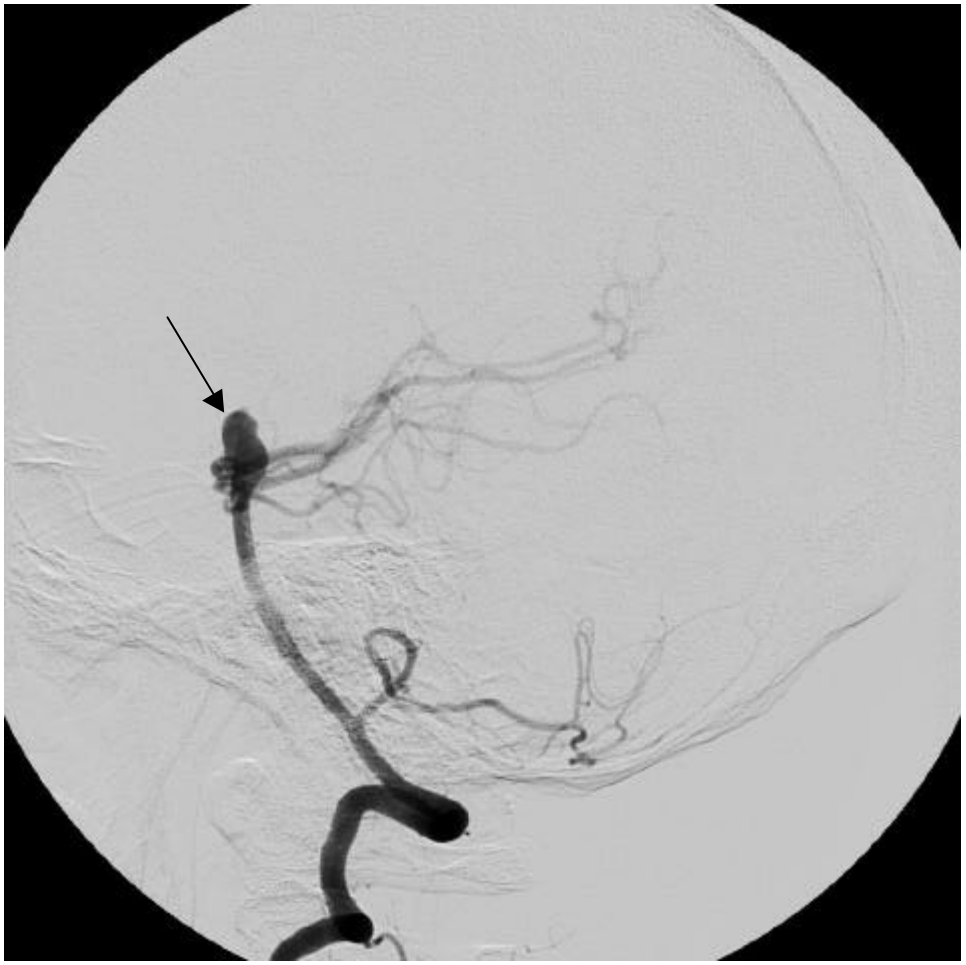
(1) What is the diagnosis and what is the underlying cause?

(2) What are the treatment options?

Answers:

The patient suffered a subarachnoid haemorrhage. There is extensive subarachnoid blood seen around the base of the brain. The cause was a ruptured basilar tip aneurysm—this was confirmed on arteriography (Figure 2).

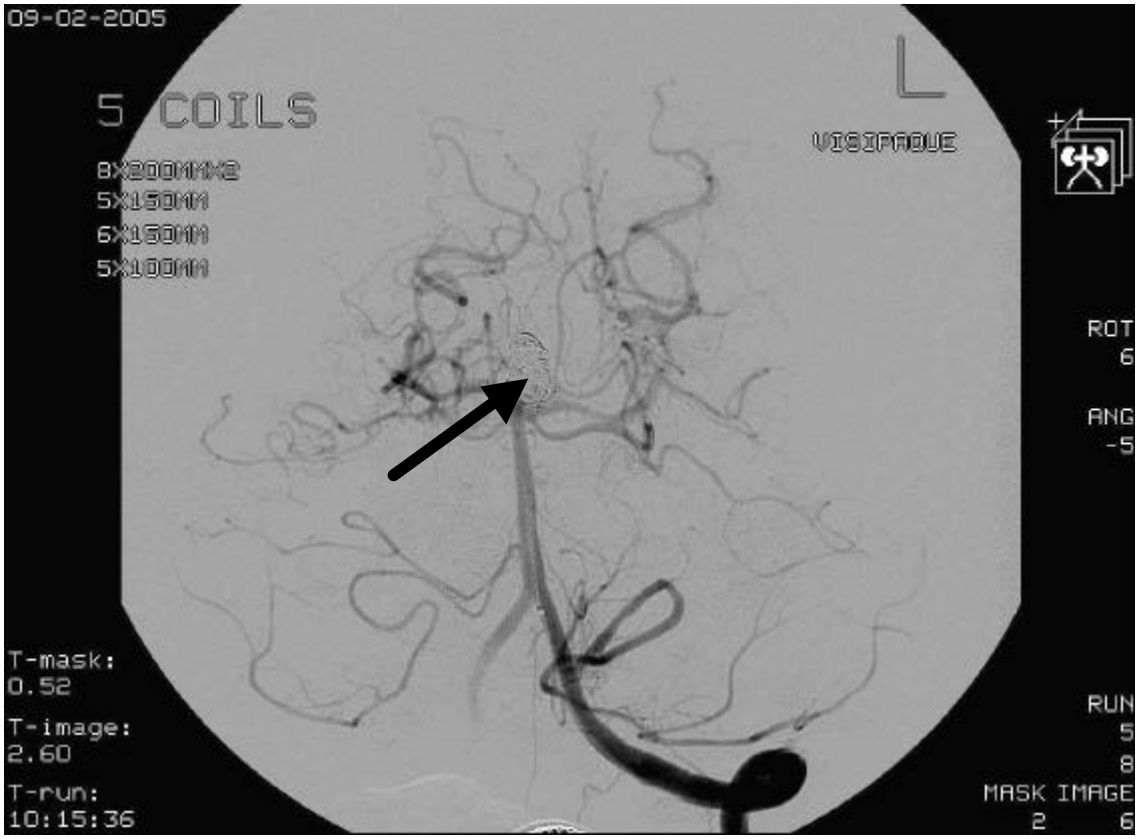
Figure 2. Lateral basilar artery digital subtraction arteriogram showing the basilar tip aneurysm (arrowed)



She was treated with endovascular placement of detachable coils (Figure 3). The aim of this treatment is to exclude the aneurysm from the circulation (if possible with preservation of the parent artery). This procedure is performed from the common femoral artery via a catheter placed in the aneurysm. The coils are detached from the delivery system by means of electrolysis, thus allowing accurate placement.

This is now the preferred treatment of basilar tip aneurysms and avoids the need for craniotomy and cerebral manipulation. An added advantage is that the medical condition of the patient does not affect the timing or performance of the procedure.

Figure 3 Frontal arteriogram of the basilar tip aneurysm showing coils *in situ* (arrowed)



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Trouble about COX 2 inhibitors

In the wake of the withdrawal of Vioxx, other COX 2 inhibitors are under fire.

Celecoxib (Celebrex) showed an increased risk of cardiovascular events in a long term study (sponsored by the US National Cancer Institute) that looked at use of the drug for prevention of colon cancer.

Furthermore, the British Committee on the Safety of Medicines has sent an urgent email to all doctors in the United Kingdom, saying that any patients with established ischaemic heart disease or cerebrovascular disease who are being treated with any COX 2 inhibitor should be switched to alternative (non-COX 2 selective) treatments as soon as is convenient.

Methinks a very good idea.

BMJ 2005;330:9

Healthy air?

Approximately 1.5 x 10^9 people undertake air travel annually. That's a lot of people! Methuselah along with others has wondered whether the confined space, limited ventilation, prolonged exposure times and recirculating air, all common to air travel, would create the potential for the spread of respiratory pathogens during flight.

In this interesting paper, the authors point out that the use of high-efficiency particulate air (HEPA)-type filters means that 99.9% of bacteria and viruses produced by aircraft passengers are removed from cabin air.

Furthermore, with modern cabin pressurization systems, the cabin air is completely exchanged at least 20 times per hour, compared with 12 air exchanges per hour in a typical office building and 5 exchanges per hour in most homes.

However, try not to sit next to a cougher and sneezer!

Intern Med J 2005;35:50–5

Once a Caesarean, always a Caesarean

Methuselah thought this was an immutable truth. But is it?

A commentary in a recent Lancet discusses this truism during an analysis of a 10-year US prospective study of 1913 women attempting vaginal birth after a previous Caesarean section (VCAC) in 41 birth centres.

The conclusion reached by the trialists was that VBAC should not be attempted in the non-hospital setting. The pros and cons were discussed further and inevitably the predictable (and bland) conclusion seems to be that "future research should examine strategies to combine the strengths of these apparently opposed philosophies of maternity service to provide safe intrapartum care with high levels of maternal

satisfaction and low intervention rates for women—whether or not they have had a previous Caesarean section."

Lancet 2005;365:106–7

UK Biobank

There is a plan to enrol 1% of the United Kingdom's population, or around 3% of people in the target age-group 45–69 years, into a massive cohort study in which genetic material is held for all participants. The driving force behind UK Biobank is a desire to have adequate statistical power to study gene-environment interactions for individual types of cancer—a daunting prospect.

With an estimated cohort of 500,000 this study will be 100 times larger than the famous Framingham Heart Study. The Wellcome Trust, the MRC, and the UK Department of Health have made £61 million available to UK Biobank.

However, 1000 days into the project, not a single participant had been enrolled. In commenting upon this, the reviewers state that the project "seems baffled by its own complexity, stranded in a bunkum of companies, contracts, and consortia that makes decoding the double helix look like child's play."

Med J Aust 2005;182:56–7

Non-ST-Segment Elevation Acute Coronary Syndromes (NSTE-ACS)

We used to call it unstable angina. In USA they now call it Syndromes NSTE-ACS. We now call it NSTEMI (NSTE myocardial infarction). But how do we treat it?

In a paper from John Hopkins University, it is claimed that treatment is sub-optimal. Their solution—an evidence based, easy to remember acronym—ABCDE—after those who require invasive treatment have had such.

The elements of ABCDE include "A" for antiplatelet therapy, anticoagulation, angiotensin-converting enzyme inhibition, and angiotensin receptor blockade; "B" for β-blockade and blood pressure control; "C" for cholesterol treatment and cigarette smoking cessation; "D" for diabetes management and diet; and "E" for exercise.

Hard to quibble.

JAMA 2005;293:349–57

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Regarding 'Prostate cancer screening—finding the middle road forward' editorial

The Editorial in the 11 February 2004 issue of this *Journal*[1] was written in response to my Viewpoint article in the same issue: *Prostate cancer screening: is it possible to explain diametrically opposed views?*[2] The authors of the Editorial, David Lamb and Brett Delahunt, found some difficulty with the answer to this question, which was provided in the Viewpoint article. To summarise, it is possible to explain diametrically opposed views by weighting the benefits and risks of screening differently. Those who support prostate cancer screening assign great weight to the benefits of screening (despite the lack of evidence), and little weight to the risks. Those who do not support screening acknowledge the risks and recognise that, given the lack of evidence of benefit, these risks could outweigh any benefits of screening.

Recognition of these risks has led to caution even from previous supporters such as Professor Thomas Stamey, one of the initial advocates for PSA screening for prostate cancer in the 1980s, who wrote last year:

> What is urgently needed is a serum marker for prostate cancer that is truly proportional to the volume and grade of this ubiquitous cancer, and solid observations on who should and should not be treated which will surely require randomized trials once such a marker is available. Since there is no such marker for any other organ confined cancer, little is likely to change the current state of overdiagnosis (and over-treatment) of prostate cancer, a cancer we all get if we live long enough. Finally, lowering the cutoff indication for prostate biopsy from 4.0 to 2.5 simply compounds the tragedy by adding millions of men to the biopsy list.[3]

In their Editorial, Lamb and Delahunt argued that "absence of evidence is not evidence of absence."[1] This argument could be a valid argument for screening only if there were no harm associated with screening. Then, even if PSA screening turned out not to be beneficial, at least no men would have been harmed. Unfortunately we know that there is harm associated with screening, so if PSA screening turns out not to be beneficial, the net effect of screening will be to have caused harm to thousands of men. Even if it transpires that there is a benefit from screening, the harm must still be considered.

The point is, at the moment we do not know:

- Whether there is any benefit from prostate cancer screening, and
- If there is, whether the benefit outweighs the harm.

This information can only be obtained from the randomised controlled trials that are currently in progress.

Finally, and most importantly, Lamb and Delahunt suggested that I regard "self-requested screening" as unethical. In fact, my Viewpoint article did not address self-requested screening at all, but discussed the ethical implications of *offering* prostate cancer screening to men. I addressed this issue specifically because many readers of this *Journal* are health professionals who need to decide whether to offer PSA screening to their patients. This issue is not confined to population screening, since

screening can also be offered opportunistically. It is the *offer* of prostate cancer screening that I believe to be unethical, because we do not know whether the harms of screening outweigh the benefits.

It would not (and should not) occur to most men that their doctor would offer them an unproven and possibly harmful screening test. Thus, men are likely to regard an offer of prostate cancer screening from a doctor as a recommendation to be screened, or at the very least an endorsement of screening. That is why I believe it is inappropriate for doctors to offer prostate cancer screening at present, especially because, as doctors, we should "first do no harm". The Editorial by Lamb and Delahunt, in focusing on *self-requested* screening, addressed a completely different issue.

The difference between offering screening and responding to a request for screening was recognised by the National Health Committee (which also recommended against *offering* screening), in its recommendation:

> "men who request a PSA test and/or DRE be provided with information which clearly explains the possible harms and benefits of screening and subsequent treatment. This is to ensure that men reach a fully informed decision"[4]

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THE NEW ZEALAND MEDICAL JOURNAL
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Regarding 'Prostate cancer screening—finding the middle road forward' editorial

I am sure that as Editor you see it as your role to encourage debate among readers of the Journal. The Viewpoint article on prostate cancer screening[1] (and the Editorial[2] responding to it) in the 11 February 2004 issue will undoubtedly provoke a response. Whether or not this represents truly informed debate is arguable.

The Editorial writers are clearly firmly convinced of the rightness of their position, and the error of the Viewpoint writers. So convinced, in fact, that they don't appear to have needed to read the Viewpoint to know just how wrong it is. Instead, they have created and knocked down a number of straw men that did not appear in the Viewpoint article. For example, Drs Lamb and Delahunt assert that *"Most clinicians do not believe that lead time bias can be the sole explanation for this difference (in survival from prostate cancer)."* [2].

Neither does Dr Richardson, as she includes at least three other possible reasons in Table 1 of her Viewpoint. The Editorial's authors also focus their attention on self-requested screening which Dr Richardson does not mention at any stage, or indeed dismiss as unethical or inappropriate. What she writes is *"screening should only be offered if the RCTs of prostate cancer screening that are currently underway demonstrate a benefit"* [1] and *"at present, it is unethical to offer prostate screening."* The offer of screening by a doctor is ethically different from a request for screening from a patient. Patients have a right to assume that if their doctor offers them an intervention (including screening), he or she does so based on evidence that it will do them more good than harm, not because their doctor holds a fervent belief (in the absence of evidence) that this is so. The assumption of benefit may seem reasonable, but it is not always subsequently proven to be correct (Dr Richardson gives some examples of this in her Viewpoint).

The Editorial writers also make some highly questionable assertions of a more general nature to support their position. For example, *"it is usually the majority opinion that determines what constitutes ethical behaviour."* Oh really? So if most doctors thought it was OK to sleep with their patients, that would make it ethical? *"The truth is that diametrically opposed views are rarely both right, and are often both wrong. The middle position, or moderate view, is usually shown to be the correct one."* Would they then argue that because some people think eating people is right and proper and others that cannibalism is abhorrent, both are likely to be wrong, and the moderate, and therefore correct view would be that it's OK to eat some people some of the time?

A debate is about the exchange of reasoned argument. Both these articles are contributions to the debate about the benefits of prostate cancer screening. Only one presents a reasoned argument and a genuine attempt to understand and engage with the other point of view.

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THE NEW ZEALAND MEDICAL JOURNAL
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Regarding 'Prostate cancer screening—finding the middle road forward' editorial

As a general practitioner who deals almost daily with men who ask about prostate cancer screening, I would like to reply to a few of the points raised in the Editorial by Lamb and Delahunt on prostate cancer screening (Prostate cancer screening—finding the middle road forward. N Z Med J 2005;118(1209). URL: http://www.nzma.org.nz/journal/118-1209/1306/).

I would first like to dispute their assertion that self-requested screening is very different from population-based screening. They say that in self-requested screening the "individual man is making a value judgement on whether or not they perceive there are advantages in being screened."

Men request this test because they assume that any cancer detection test offered is worthwhile. Few patients have any conception of the complexities or harms of cancer screening. Most men who discuss this with me are surprised to learn that there is no evidence that PSA screening will prolong their lives. To just offer this test without an explanation of the benefits (unknown) and harms (known and inevitable) is just as irresponsible as acquiescing to patients requests for whole body CT scans.

The authors' selective reporting on the Swedish reports of untreated prostate cancer is inaccurate. This study is of a cohort of men diagnosed before PSA testing was available based on clinical findings of prostate cancer or histological diagnosis following TURP for obstructive symptoms. The applicability of this study to men diagnosed with prostate cancer following PSA testing is therefore less than clear.

To correct just two of their statements, Lamb and Delahunt state that the "mortality rate (for prostate cancer) was particularly high in those aged 70 or less at the time of diagnosis" whereas Johansson et al state in their paper that "prostate cancer mortality was slightly higher among patients whose cancer was diagnosed at 70 years or younger than among those whose cancer was diagnosed at older ages." By twenty years follow-up, 91% of their cohort had died, and of these only 16% died from prostate cancer. As this group stated (in their earlier report of follow-up at 15 years of this cohort). "Patients with localized prostate cancer have a favorable outlook following watchful waiting, and the number of deaths potentially avoidable by radical initial treatment is limited. Without reliable prognostic indicators, an aggressive approach to all patients with early disease would entail substantial overtreatment. In contrast, patients with locally advanced or metastatic disease need trials of aggressive therapy to improve their poor prognosis."

I was surprised by the authors' statement that "it is usually the majority opinion that determines what constitutes ethical behaviour." Unfortunately the history of medicine is full of examples of unethical behaviour that has been embraced by majority opinion; the collusion in Nazi euthanasia programmes by German doctors being the most egregious example.

Finally, I was most surprised that the Lamb and Delahunt article appeared as an editorial. Editorials generally are a forum for expert opinion on a subject. I would be happy for their opinion on matters of pathology but I for one will rely on the advice of experts on screening to guide my patients and me regarding prostate cancer screening.

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What is the middle position on screening?

It would have been better to have published the piece by Lamb and Delahunt[1] (in response to Richardson's Viewpoint[2]) as another Viewpoint rather than as an Editorial—as it does not attempt to provide balanced comment. Their most tendentious claim is: "The truth is that diametrically opposed views are rarely both right, and often both wrong. The middle position, or moderate view, is usually shown in time to be the correct one."

It is tempting to mention a string of examples in medicine where the defenders of extreme positions (don't use hormone replacement therapy to prevent coronary heart disease, don't use stilboestrol in pregnancy, do lie babies on their backs etc etc) have proved to be right, and in which a middle position is worse than useless (give rubella vaccination only to children whose parents ask for it—leading to low vaccination rates, an increase in the average age of infection, and more cases of rubella in pregnant women than without a vaccination programme at all).[3]

More pertinently, it was exactly this attitude towards cervical screening: what Lamb and Delahunt call self-requested screening, which was responsible for the relative ineffectiveness of the first 20 years of cervical screening in New Zealand.[4] It wasn't until population-based screening was introduced that substantial reductions in incidence and mortality became evident.[5] If PSA screening really were judged to have benefits which exceeded harms, they should be recommending that all men deemed to be at sufficiently high risk be offered it, rather than leaving testing to a small self-selected group.

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Spending decisions for tobacco-related disease treatment and tobacco control: an example and a solution

The agency which pays for publicly subsidised pharmaceuticals, *Pharmac*, has recently announced that they will spend NZ$33 million over 5 years to subsidise the use of a treatment for chronic obstructive pulmonary disease (COPD). The use of tiotropium by about 16,000 people is expected by *Pharmac* to reduce hospital admissions for those people by 'nearly 40 per cent' .[1] The cost per person per year is approximately $NZ400, and is considered likely to provide significantly improved quality of life for these COPD sufferers, in addition to the potential savings of government health spending.

However, this type of spending to prevent harm in a largely ex-smoker population raises issues both in the specific New Zealand context, and, more generally, in many similar settings. This is because it may be far more cost-effective to increase government expenditure on both basic tobacco control, and on pharmacotherapy for smoking cessation. A focus on the treatment of tobacco-related disease, relative to prevention, is common in many countries. It is seen particularly with cardiovascular drug and surgical treatments for tobacco-related heart disease.

At $NZ27 million per year, basic tobacco control remains poorly funded in New Zealand relative to CDC guidelines.[2] Worldwide, there is evidence to show how cost-effective various population-level tobacco control interventions are.[3–5] Furthermore, tobacco tax increases have no net costs to government, are likely to have net population health benefits[6] but involve ethical issues unless the revenue gained is used for tobacco control.[7]

A crucial aspect of the effectiveness of smoking cessation pharmacotherapy is its promotion and availability to smokers. For instance, although the New Zealand government provides heavily subsidised nicotine replacement therapy (NRT) to smokers[8] (via the national Quitline and other health services), the funding of the *promotion* of this service is minimal. The NRT provision is relatively cost-effective compared to other pharmacotherapies used in New Zealand[9] (ie, the NRT programme costs between $NZ 5000 and $NZ 6800 per quality-adjusted life year – discounting benefits at 5% and using conservative quit assumptions[10]). Furthermore, the Government does not subsidise another proven pharmacotherapy for smoking cessation ie, bupropion (though nortriptyline does attract a subsidy and is a possible alternative). The government also fails to sufficiently subsidise and promote the consultations with medical practitioners that smokers need to access prescription-only therapies such as bupropion and nortriptyline.

However, even where the most cost-effective solutions for governments may be to focus additional resources on expanding tobacco control programmes and proven smoking cessation pharmacotherapies, there can be fundamental political and ethical policy constraints. In particular, there is a duty-of-care for governments to provide cost-effective disease treatments to all their citizens. Fortunately substantive investments in both disease treatment and prevention can be possible if an increasing

proportion of tobacco tax revenue is allocated to tobacco control. For instance, in New Zealand, the spending on tobacco control is less than three per cent of the tobacco tax revenue gained.[11]

Competing interests: George Thomson and Nick Wilson have done work for the New Zealand Ministry of Health and for non-government organisations on tobacco control.

Ethics approval: None needed.

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Food pricing favours saturated fat consumption: supermarket data

The *New Zealand Medical Journal* highlighted the threat posed by diabetes and obesity in its 17 December 2004 'theme' issue. A risk factor for diabetes is saturated fat (SF) intake.[1,2] Replacement of dietary SF with monounsaturated fat improves insulin sensitivity.[3] SF is also a risk factor for coronary heart disease based on epidemiological studies, metabolic studies and randomised trials.[1,4–8]

US Government nutrition guidelines for 2005 recommend decreasing SF intakes to less than 10 percent of calories.[9] One way to facilitate reducing SF intake is through food pricing. Food prices are a determinant of food purchasing,[10,11] and can favourably influence intake.[12] We therefore undertook a pilot investigation into the prices of selected New Zealand foods that were high in SF to see if pricing favours SF consumption.

Methods: A national nutrition survey has identified the food-types contributing the most fat to the New Zealand diet[13] (i.e. butter and margarine, beef and veal, milk, cakes and muffins, pies and pastries, bread-based dishes, sausages and processed meats, fats and oils, cheese, poultry, biscuits, dairy products, fish/seafood and sauces).

Out of these groups, we identified 9 food-types that:

- Had nutritional data on the label indicating at least one item with a composition of ≥20 g of SF per 100 g;
- Were in a ready-to-eat form (i.e. not needing to be cooked); and
- Were available in two large supermarket stores in Wellington (separate chains).

Within each of these food-types, we identified the particular items with the highest and lowest levels of SF and compared their prices (for 23 January 2005 prices and ignoring "specials").

Results: The highest SF food was cheaper than its low SF equivalent of the same food-type for 8 of the 9 comparisons, and in 6 of the 9 comparisons at supermarkets A and B, respectively (see Table 1). In the four comparisons where the low SF equivalent was cheaper, the difference was less than 10%. For the other comparisons, the low SF equivalent was at least 8% more expensive with the highest being 109% more expensive. Combining all 9 food-types, the high SF foods cost 49% and 22% more than their low SF equivalents at supermarkets A and B, respectively.

Discussion: This pilot study suggests that current pricing favours consumption of higher SF content foods. A more comprehensive and sophisticated analysis (eg, total energy and protein content and beneficial provision of healthier fats such as monounsaturates) may be appropriate. Nevertheless, this pricing gradient provides another explanation for inequalities in health in New Zealand. It also suggests the need for policy responses beyond existing approaches being considered by the Ministry of Health.[14]

Table 1. Levels of saturated fat (SF) and prices of ready-to-eat foods in product categories where at least some items exceed 20% SF by weight*

Category	Super-market	Highest level of SF / 100g	Lowest level of SF / 100g	Price of item with highest level of SF ($ per 100g)	Price of item with lowest level of SF ($ per 100g)	% lower SF of low fat item	% higher price of low fat item
Butter	A	54.7	41.0	0.52	0.63	25%	21%
	B	54.7	41.0	0.44	0.40	25%	-9%
Butter/vegetable oil blends	A	28.0	11.1	0.57	0.85	60%	48%
	B	28.0	22.0	0.50	0.49	21%	-2%
Margarine type spreads	A	29.3	9.0	0.35	0.74	69%	109%
	B	18.0	9.0	0.40	0.37	50%	-7%
Cream cheese	A	25.7	9.4	1.36	1.25	63%	-8%
	B	25.7	10.2	0.78	1.16	60%	49%
Hard cheese (blocks of mild, tasty, colby, edam)	A	25.4	15.2	0.96	1.86	40%	94%
	B	25.4	15.2	0.85	1.17	40%	37%
Grated cheese	A	25.2	15.2	1.05	1.78	40%	69%
	B	25.4	15.2	1.20	1.54	40%	28%
Cream**	A	28.5	8.0	0.43	0.57	72%	32%
	B	28.5	23.0	0.36	0.43	19%	20%
Biscuits & crackers	A	32.9	<1.0	1.06	1.78	97%	69%
	B	22.3	<1.0	0.96	1.59	96%	65%
Chocolate (250 g blocks)	A	32.6	10.7	1.52	1.64	67%	8%
	B	32.6	10.7	1.16	1.32	67%	14%
All above categories (means)	A	31.4	13.4	0.87	1.23	59%	49%
	B	29.0	16.4	0.74	0.94	46%	22%
	Both	30.2	14.9	0.80	1.09	53%	35%

Notes: *Some specialty cheeses also exceeded 20% SF but these were not included in the analysis due to the large range of different products involved. Where there were two different items with the same SF level, the lowest priced product (per 100 g) was used in the analysis; **Comparison in mls rather than grams.

The highest priority for analysis is probably deciding which one (or combination) of the following is most likely to make the lowest SF options the cheapest:

- Encouraging the food industry to do so;
- Regulation to require it; or
- Taxing the SF content.

The latter option has the advantage of generating revenue that could fund healthy school lunches and fruit and vegetable vouchers for low-income New Zealanders. Despite the expected resistance from commercial vested interests, the time is more

than ripe for substantive Government action to control the epidemics of diabetes and obesity.

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Failure to adequately investigate

Charge:

The Director of Proceedings charged the Doctor with professional misconduct. The particulars of the charge alleged:

(1) Between 27 March 1999 and 10 April 1999 in relation to the patient the Doctor failed to adequately investigate the cause or causes of the discharge of large volumes of fluid from the patient's perineum; and/or

(2) Between 27 March 1999 and 10 April 1999 in relation to the patient the Doctor failed to adequately investigate the cause or causes of swinging pyrexia.

Background:

The patient first underwent surgery for rectal cancer on 23 December 1996. Two years later the patient displayed symptoms of recurrent rectal cancer. He was referred to hospital on 3 March 1999 where the Doctor diagnosed recurrent rectal cancer. The patient was admitted into hospital on 24 March with the intention the Doctor would perform an abdominoperineal resection on 26 March.

The operation took longer than anticipated. Anaesthesia started at 9.15 am and the complex and difficult operation did not conclude until 4pm. There were adhesions from the patient's earlier surgery and an abscess was found in the left side of the pelvis. There were adhesions to the sides of the pelvis and there was a possible direct extension of the tumour which complicated dissection. There was also significant bleeding. During the surgery damage occurred to the posterial wall of the bladder. This was repaired. Following the operation the patient was transferred to the hospital's high dependency unit.

The Doctor regularly reviewed the patient's condition during the days following surgery. He saw the patient at least twice a day, and on one day he saw him four times.

The patient's temperature fluctuated significantly between 27 March 1999 and 10 April 1999. The Doctor did not consider that the patient's temperature fluctuations could be described as "swinging pyrexia". He did indicate that the patient's temperature readings might be described as "swinging temperature".

The patient's fluid loss was an important factor in the case. Of particular significance was the patient's loss of fluid from his perineal wound from 31 March to 4 April. From 29 March onwards nurses documented their concerns about the discharge of large volumes of fluid from the perineal wound. They described the volume of discharge in no uncertain terms. They used the adjectives "large" and "copious" to describe the volume of fluid they observed coming from the patient's perineal wound.

The Doctor told the Tribunal that on a number of occasions he wondered if the fluid that was draining from the perineum was due to ascites or if it contained urine. However, the Doctor said that the fluid he saw was not clear fluid and that it

contained blood and serum. He said he smelt the fluid on several occasions but it did not smell of urine. The Doctor said he asked his registrar to inquire with the laboratory to see if the perineal fluid could be tested for urine. The laboratory reported via the registrar that it would be difficult to determine whether or not the fluid from the perineum was urine.

A laboratory analysed blood samples taken from the patient on eight of the days he was in hospital. There were significant changes to the patient's white blood cell count. The nurses' notes contained a number of observations, the most pertinent of which related to the fluid loss from the patient's perineal wound.

On 4 April the Doctor arranged for swabs to be taken from the patient's anal cavity. A drain tip in the anal area was also sent to the laboratory for analysis. All the lab reports showed heavy growth of *Enterobacter cloacae* a potentially lethal bacteria that in all likelihood originated from the patient's bowel.

A chest x-ray report for 7 April indicated "*left lower lobe pneumonic consolidation and moderately small left pleural fluid collection… the left lung remains clear except for linear atelectatic streaks right lateral costophrenic angle"*.

The patient was transferred by helicopter to Wellington Hospital Intensive Care Unit on 10 April 1999.

Finding:

The Tribunal found the Doctor guilty of professional misconduct.

The Doctor was faced with a wide range of clinical data and observations, however the Tribunal was in no doubt that by at least 4 April the Doctor should have been very concerned about the discharge of large volumes of fluid from the patient's perineum and the swinging pyrexia. The Tribunal was also very satisfied the Doctor failed to adequately investigate the cause or causes of these conditions. Whilst the Doctor was undoubtedly concerned about the patient and very attentive, the Tribunal considered he nevertheless adopted a limited view of the patient's circumstances. He did not recognise that a ureteric injury may have occurred, nor did he properly investigate fluid leaking from the perineum or that fluid accumulating in the abdomen was contributing to sepsis.

When considering Particular 1, the Tribunal was satisfied the medical evidence clearly demonstrated that by 31 March the patient was discharging large volumes of fluid from the perineal wound.

The Doctor acknowledged being told on at least two occasions that the fluid smelt like urine, and he also told the Tribunal that the fluid was not always clear. The Tribunal observed there was no record in the notes of the Doctor considering transferring the patient to Wellington for a CT scan to determine the cause or causes of the discharge of the large volumes of fluid draining from the perineal wound. The Doctor said that referring a patient for a CT scan in the patient's circumstances needed to be balanced against the practicalities of transferring the patient by road to Wellington and whether a CT scan would provide a diagnosis. The Doctor acknowledged he did not consider transferring the patient to Wellington on 4 April.

The Doctor's failure to take any steps to arrange for the patient's transfer to Wellington on 4 April was a significant breach of the duty he owed his patient and was not the conduct which the Tribunal would expect of a surgeon of the Doctor's position.

In relation to the first particular of the charge, all five members of the Tribunal found the first limb of the test of professional misconduct is established. The Tribunal was not unanimous in its assessment of the second limb of the test of professional misconduct. Three members of the Tribunal believed the Doctor's omissions were so serious that a disciplinary finding was warranted in relation to the first particular of the charge in order to maintain professional standards and to emphasise that the public's safety should not be compromised.

When considering Particular 2, the Tribunal was satisfied the patient experienced swinging pyrexia from 27 March to 10 April. On occasions there were very profound fluctuations in the patient's temperature.

It was apparent that the Doctor did consider the patient's temperature variations might be due to a pelvic infection. He sent swabs and the tip of a catheter to the hospital laboratory for analysis. Two days later the laboratory confirmed the presence of *Enterobacter cloacae*. The Doctor's explanation for not further investigating the cause or causes of the patient's swinging pyrexia was his belief that in general, the patient's condition improved after 5 April.

The Tribunal was satisfied the Doctor did what he could reasonably do with the resources then available at the hospital. However, he should have realised that the patient required services that were not available at the hospital and that it was reasonable to have taken steps to arrange for his transfer to Wellington no later than 4 April.

The Tribunal concluded the Doctor's failure to arrange for the patient's transfer to Wellington Hospital on 4 April was a significant breach of the duty he owed his patient.

In relation to the second particular of the charge, the Tribunal was satisfied the first limb of the test of professional misconduct was established. As with the first particular, the Tribunal was not unanimous in its conclusion in relation to the second limb of the test of professional misconduct. Three members of the Tribunal were satisfied that the Doctor's omissions were so serious in relation to the second particular of the charge that a disciplinary finding was justified in order to maintain professional standards and uphold public safety.

Two members of the Tribunal were of the opinion that the breaches described in the first and second particular of the charge did not separately justify a finding of professional misconduct. However, they considered that when the established breaches were viewed cumulatively, a finding of professional misconduct was required in order to maintain professional standards and to protect public safety.

The Tribunal was unanimous that the charge of professional misconduct was established.

Penalty:

In this case the Tribunal believed there were extenuating circumstances which justified the Tribunal imposing only an order for costs. The factors which have influenced the Tribunal in reaching this conclusion were:

- The Doctor has not previously appeared before any disciplinary body in this country. He deserves credit for his long and unblemished career.
- Aside from the two matters focused upon during the hearing the Doctor appeared to have managed the patient in a caring and professional manner. Aspects of the Doctor's management of his patient were described as exemplary by the expert witnesses.
- There was a very unsatisfactory delay in investigating the complaint and laying of the charge. The Health and Disability Commissioner received the complaint on 20 August 1999. The Tribunal believed that delay can be fairly regarded as a punishment in this instance.
- The Doctor was practising under oversight when he was treating the patient. The Tribunal believed that in the circumstances of this case proactive steps could have been taken by others at the hospital which may have resulted in a more timely transfer of the patient to Wellington Hospital.

The Tribunal ordered the Doctor to pay $16,349.41 being 50% of the costs and expenses of the hearing by the Tribunal; and pay $10,643.28 being 40% of the costs and expenses of and incidental to the investigation and prosecution of the charge by the Director of Proceedings. It further ordered a summary of the hearing be published in the New Zealand Medical Journal.

Appeal:

The Tribunal Decision was appealed to the District Court. The Court upheld the Tribunal's finding in respect of both particulars of the charge. However, the Court allowed the appeal to the extent that the Tribunal finding of professional misconduct was replaced with a finding of conduct unbecoming. The penalty and costs ordered by the Tribunal were unaltered.

The full decisions relating to the case can be found on the Tribunal web site at www.mpdt.org.nz Reference No: 03/100D.

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Computerworld Excellence Awards 2005 (Excellence in the Use of IT in Health): entries invited

The annual Computerworld Excellence Awards are approaching. For the first time, we have a category for Excellence in the Use of IT in Health. This award is for those who have improved the delivery of healthcare in New Zealand through the implementation of IT.

We are now calling for entries from teams and individuals doing great things with IT in New Zealand. The Excellence Awards has established itself as the leading recognition programme within the New Zealand IT industry, with many IT professionals striving to achieve the accolade of excellence.

Now in their 8th year, the awards honour outstanding achievement by users of information technology in New Zealand. In the 2004 year, the event attracted over 300 entries with an equally large turnout at the gala presentation dinner. There are 14 separate categories for 2005, covering an individual award (CIO of the Year) and group awards in areas such as Small to Medium Enterprises, Education, and Government.

An exciting new development for 2005 sees the launch of 3 new categories—Excellence in the Use of IT in for Export, Excellence in the Use of IT in Health, and Excellence in the Use of IT for a Community Project. Each represents the changing face and the social impact of information technology in New Zealand.

For the second year, the Awards will not only recognise, but reward, innovative IT applications and solutions implemented within Not for Profit Organisations. Often these groups work with extremely limited budgets and resources, however, what they achieve with IT can have a huge positive impact on the wider community. Proudly sponsored by Westpac, the category winner will be rewarded with a NZ$10,000 cash prize donation.

Each category is judged by an independent panel of three. Among the 42 Judges involved in the awards are some of New Zealand's most prominent IT and business leaders.

For full category, eligibility and entry form please go to www.idg.net.nz/cwea – or contact Darrell Denney on (09) 302 5727, or email: events@idg.co.nz

Entries will close on 18 March 2005, so be sure to act quickly to register your entry for the event.

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The Hawke's Bay Medical Research Foundation: funding applications invited

Applications for funding for Research Projects are now being accepted by the Foundation.

A Studentship Grant up to $NZ2,600 based on a 10-week course is also available.

Applications can obtain an Application Form together with the guidelines of assessment by phoning the Secretary on:

(06) 879 9190

or writing to:

The Secretary, P O Box 596, Napier

or email:

jmbax@xtra.co.nz
(website: www.hawkesbaymedicalresearch.org.nz)

Applications close March 31, 2005

(Priority will be given to applications from appropriate persons employed in Hawke's Bay or having an association with the region.)

JM Baxter
Secretary

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World Atlas of Epidemic Diseases

Andrew Cliff, Peter Haggett, Matthew Smallman-Raynor. Published by Hodder Arnold, 2004. ISBN 0340761717. Contains 212 pages. Price $462.00

This beautifully produced atlas, written by three geographers, provides an illuminating overview of the global epidemiology of 50 of the great infectious diseases. The introductory chapter deals with the global burden of infectious diseases, the nature of epidemics, mapping of epidemic diseases and, finally, the organisation of this atlas. The authors provide an authorative and thought-provoking historical overview of global epidemiology, and a particularly interesting section on the development of mapping of epidemic diseases. Throughout there are numerous illustrative maps, illustrations, and photographs (many of historical importance), which blend superbly with the text.

From the many hundreds of infectious diseases which could be considered for such a tome, the authors have selected 50 on the basis of diverse criteria, including global or historical importance, the illumination of disease process, or simply the availability of epidemiological data. This selection process has resulted in an eclectic collection which includes a number of the “Classic Plagues” [Plague, Cholera, Leprosy, Small Pox, Measles, Rabies], Tuberculosis, Typhoid, Diphtheria and several Tropical Diseases, and on to vaccine-preventable diseases and newly emergent diseases—including HIV, Legionnaires Disease, the viral haemorrhagic fevers, and a scattering of other “new” diseases. Several notable diseases [pneumococcus, viral hepatitis] are conspicuously absent].

Each chapter is organised similarly with a brief summary of the clinical aspects followed by an entertaining discussion of disease history and lastly a succinct current geography. Throughout the book, reference is made to important historical events and the key individuals, with wide use of documents and photographs from the relevant period.

This book is crammed with fascinating historical facts that illuminate how the current global pattern of many diseases has evolved. It is a pleasure to read and, although essentially aimed at epidemiologists, should be of interest to anyone broadly involved with infectious diseases, or medical historians.

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Move More Eat Less: Putting the squeeze on lifestyle disease

Elaine Rush. Published by the Body Composition and Metabolism Research Centre at Auckland University of Technology (AUT), 2003. ISBN 1877314218. Contains 77 pages. Price $35 ($70 with pedometer), plus $10 postage and handling

Most books we receive for review at the *Journal* are sent to us by publishers and we then send them out to appropriate persons (usually experts in the book's subject) to read. In this case, however, I asked to see the book after following a link (http://www.my-lifestyle.com/) in one of Elaine's emails. Being a bit overweight myself, and becoming increasingly health-conscious after reading numerous manuscripts extolling the virtues of exercise and the prevention of heart disease and type 2 diabetes by being within a healthy weight range (see the 17 December 2004 issue of the *Journal*), I also thought it might contain some useful information for myself.

Although healthcare professionals may wish to recommend it to their patients, this unique publication, a collaborative effort by staff and students at AUT, is not really aimed at healthcare professionals as it mostly contains facts and advice that they already should know. Instead it is a good self-help guide for less well-informed overweight and obese people and/or their concerned friends or relatives (such as those buying the food and preparing the meals). It reaches its target audience successfully with key facts, messages, and tips written in easy-to-read, plain English separated with plenty of white space and charming, thought-provoking graphics created by Graphic Arts students at AUT. Particularly powerful examples include white sugar pouring out a soft drink can under the heading *What are you really drinking?*, and a photo of a fish and chip shop's deep fryer with the heading *Would you take a dip in this? so why dip your food in it?*

Many of the tips are already well known such as cutting off visible fat from meat, taking the skin off chicken, and taking the stairs instead of the lift—but the book also contains lesser-known ones such as 'asking for salad dressing to be served on the side of your plate at restaurants (so you can choose how much to add),' and 'using a thin scraping of low-fat cream cheese on bread instead of butter or margarine.'

In Rush's authoritative and chatty style, and unlike some publications, it not only explains *what* not to eat but also *why* not to eat it (backed up with facts and figures)—e.g. *one meat pie contains 32g of fat, 40% of the average daily fat requirement.* Messages such as these are also reinforced with numerous photographs of healthy (low-fat) and unhealthy (high fat) food choices; blocks of butter are particularly useful at representing the amount of fat in food items placed nearby. (I have also seen similarly effective representations in posters elsewhere showing the huge amount of sugar in commonly eaten foods/drinks.)

Other strengths of the book include explanations of medical terms, diseases, and concepts (such as body mass index [BMI]), a page refererring readers to other resources (recommended websites), and the inclusion of a large 'glossary of terms

related to nutrition and activity' at the end. Another nice touch is the author's invitation to write to her at AUT with questions, feedback, or suggestions.

Criticisms are relatively minor and relate to its production. It is not a particularly robust book as, being spiral-bound, it could soon fall apart if handled roughly and only right-hand pages are printed (and on one side only). Therefore, a protective plastic cover and stiffer pages could enhance as well as printing it out using a photocopier that prints on both sides of the page to keep the conservationists among us happy! On the plus side, however, it provides plenty of blank space for readers to write notes such as recipes and action plans. Also I found one inconsistency; page 27 saying there are 9 teaspoons of sugar in a can of soft drink while page 30 said 8 teaspoons—but this is a minor gripe.

In defence of the publisher, I am sure the budget printing was utilised to keep costs down so that the book's important messages could reach as many people as possible without cost being an major obstacle. (If cost is an issue, then perhaps health-related companies could sponsor the book in return for being acknowledged or letting them put in a few discreet advertisements?)

Actually, unlike most other books that are published for profit, all proceeds from this book will go towards further lifestyle intervention research at AUT. It is a worthwhile initiative to combat obesity and sedentary living (and their associated health effects)—a huge and increasing problem nowadays in New Zealand and other developed/developing countries—and Elaine Rush and her team at AUT can be congratulated for this contribution.

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