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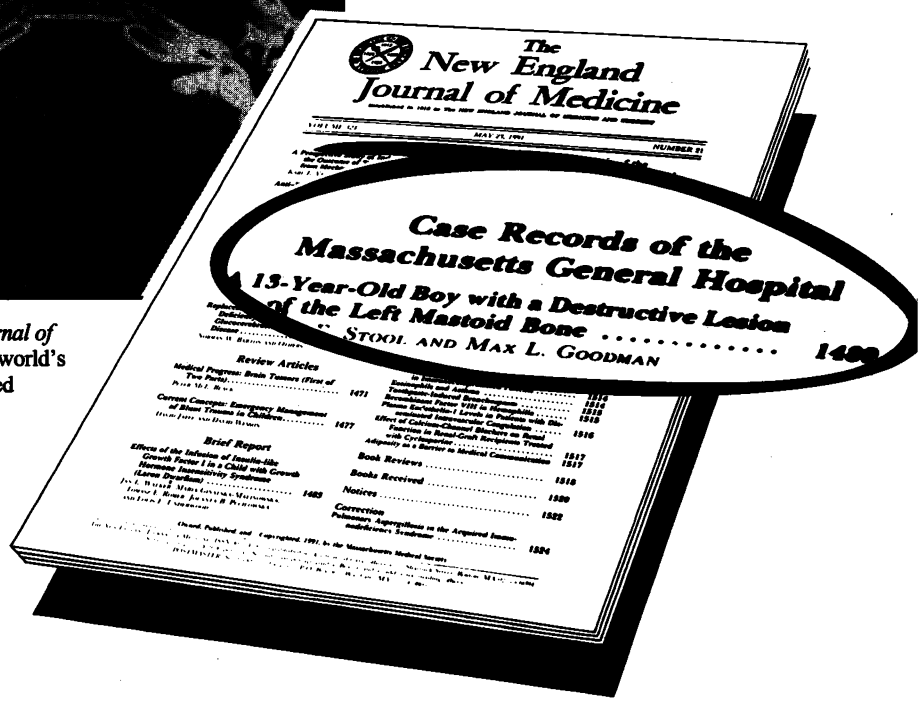

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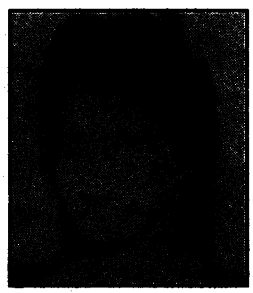

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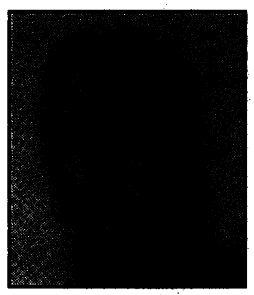

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The Ulster Medical Journal, Volume 62, No. 2, October 1993.

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1993

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The Ulster Medical Journal, Volume 62, No. 2, pp. 119 - 126, October 1993.

Familial subarachnoid haemorrhage

I C Bailey

Accepted 1 September 1993

SUMMARY.

Over the nineteen years 1974 to 1992 twenty-four families have been identified in whom more than one member have had a subarachnoid haemorrhage, usually due to rupture of an intracranial aneurysm. These cases usually occurred at an age younger than average, and multiple aneurysms were commonly found on investigation. This series strongly suggests that a congenital arterial defect may predispose to early rupture of these aneurysms.

INTRODUCTION.

It still remains uncertain whether intracranial aneurysms are congenital in origin, or are due to changes in the wall of the major arteries secondary to arteriosclerosis and hypertension. Chakravarty and Gleadhill[1] and Kak et al[2] reported from Northern Ireland five families in whom more than one member had developed subarachnoid haemorrhage due to rupture of an intracranial aneurysm. We present a further 24 families encountered between 1974 and 1992, where two or more members have had a subarachnoid haemorrhage, due to rupture of an aneurysm or an arteriovenous malformation.

MATERIALS AND METHODS.

The Royal Victoria Hospital Belfast has the only neurosurgical unit in Northern Ireland, so that all patients with a subarachnoid haemorrhage are referred to this department. Between 1974 and 1984, the average number of admissions was fifty to sixty per year, but over the past decade the number has nearly doubled, probably due to the policy of early referral and the availability of CT scanners in regional hospitals.

Table I. Relationships of the affected patients.

Brother - sister	11
Brother - brother	4
Sister - sister	2
Mother - daughter	5
Father - son	1
Cousin - cousin	1
	24

Department of Neurosurgery, Royal Victoria Hospital, Belfast BT12 6BA.
I C Bailey, MB BCh, FRCS, Consultant Neurosurgeon.

Table II. Details of siblings

Relationship	*Case No.*	*Age*	*Sex*	*Site*	*Blood Group*	*Number In Family*
Brothers	1 a	22	M	R.ICA	O+	4
	b	44	M	R.ICA: L.ICA	O+	
	c	44	M	L.ICA	–	
	5 a	40	M	ACoA; L.McA	A+	
	b	23	M	ACoA	A+	
	6 a	39	M	ACoA: L,MCA: R.MCA	O+	11
	b	46	M	L.ICA	O+	
	24 a	40	M	ACoA	O+	
	b	53	M	MCA (Giant)	O+	
Sisters	15 a	40	F	ACoA: R.MCA	A–	7
	b	22	F	ACoA	A–	
	21 a	50	F	R.ICA	B+	4
	b	36	F	ACoA	O+	
Brother/Sister	2 a	52	M	MCA	O–	5
	b	45	F	L.ICA	O+	
	4 a**	50	F			
	b	59	M	R.ICAx3: L.ICA		12
	c		F			
	d		F			
	e	48	F	R.ICA	A+	
	7 a	16	M	AVM		4
	b	28	F	R.ICA: Pulmonary AVM	O+	
	8 a	30	M			8
	b	31	F	R.MCA		
	c	40	M	ACoA: R.ICA.		
	d	27	M			
	e	29	M			
	10 a	40	M	ACoA	AB+	7
	b	42	F	ACoA	AB+	
	12 a	48	M	L.ICA; R.ICA; MCAx2: Basilar, AVM, L.Parietal	O+	2
	b	46	F	L.ICA; R.ICA; MCA; R.MCAx2,R. Sup.Cerebellar	O+	
	13 a	51	M	L.ICA: L.MCA	O–	9
	b	52	F	L.MCAx2: R.MCA	O–	
	14 a	61	M	L.MCA	A–	6
	b	49	F	Multiple (No details)		
	16 a	54	M	Basilar	B–	12
	b	46	F	Basilar	O–	
	18 a	16	M	L.ICA		4
	b	37	F	R.ICA	O+	
	22 a*	46	F	R.ICA	O+	2
	b	35	M	L.ICA	O–	
	c	39	F	Basilar	O–	4
	d	45	F	L.MCA	O–	

L=Left
R=Right
ICA=Internal CarotidArtery
MCA=Middle Cerebral Artery

ACoA=Anterior Communicating Artery
*=Mother
**=Twins

The relationship of the twenty-four cases are summarized in Table 1. Seventeen of the twenty-four (70%) were in siblings. In five instances, mother and daughter were affected. In another, father had an aneurysm, and his son an arteriovenous malformation. Two young cousins with similar aneurysms were also included. In five additional families, one member was known to have an aneurysmal haemorrhage, and their affected relative had a classical history of subarachnoid haemorrhage with blood-stained cerebrospinal fluid on lumbar puncture, but died before angiography could be carried out to establish the cause of the haemorrhage. Unfortunately, autopsy was performed in only one of these cases, the report stated "massive intraventricular haemorrhage".

Details of the age, sex and site of the aneurysm or arteriovenous malformation in those with an affected sibling are shown in Table 2. This sub-group was made up of twenty-three males and eighteen females, excluding the mother in Case 22. The average age of onset of the haemorrhage was 40.4 years and 40.7 years for brothers and sisters respectively.

Table III. Details of non-sibling relations

Relationship	*Case No.*		*Age*	*Sex*	*Aneurysm Site*	*Number In Family*	*Blood Group*
Cousins	17	a	17	M	L.ICA	–	A+
		b	21	F	L.ICA	–	A+
Father/son	19	a	39	M	L.ICA	4	B+
		b	10	M	L.Parietal AVM	3	B+
Mother/daughter	3	a	69	F	L.MCA	–	–
		b	44	F	R.ICA	–	–
	9	a	42	F	R.MCA, R.ICA, ACoA	–	–
		b	17	F	ACoA	4	B+
	11	a	47	F	R.PCoA	–	B+
		b	19	F	Cerebellar AVM	3	–
	20	a	52	F	R.ICA	–	–
		b	38	F	L.ICA	–	O+
	23	a	45	F	R.ICA, L.ICA	–	O+
		b	23	F	ACoA	6	A+

L=Left
R=Right
ICA=Internal carotid artery
MCA=Middle cerebral artery
ACoA=Anterior communicating artery
PCoA=Posterior communicating artery
AVM=Arteriovenous malformation

Table 3 shows the age and location of the bleeding site in the other cases. The offspring were significantly younger than their parents at the time of haemorrhage (average age of the parents 49 years, and of the children 25 years).

In total there were forty-one patients who had at least fifty-six aneurysms and two arteriovenous malformations. The number of lesions is an underestimate, as records of five patients were incomplete. In those cases with complete records, a single lesion was present in twenty-six instances, and multiple lesions were present in eleven (23%). Table 4 summarizes the sites of the aneurysms.

Table IV. Location of the aneurysms or malformations

SITE	*No.*	*%*
Internal carotid artery (Including posterior communicating)	22	35
Anterior communicating artery	10	16
Middle cerebral artery	18	30
Basilar artery	4	6
Superior cerebellar artery	1	1.5
Multiple (No details)	1	1.5
Unknown site	5	8
Arteriovenous malformation	2	3

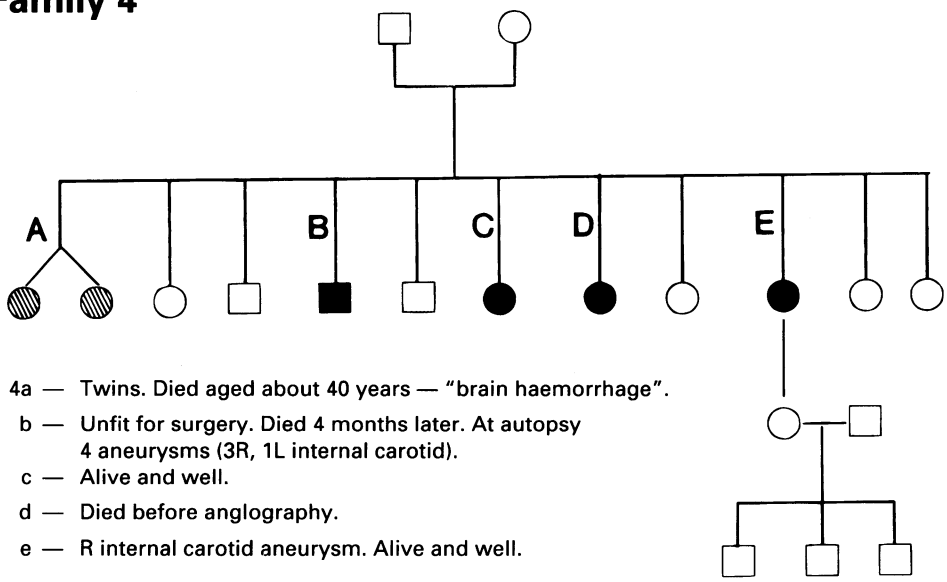
As expected, most of the siblings were found to have a similar ABO blood group, but there was no predominant group that appeared to be associated with subarachnoid haemorrhage. In three families more than two siblings had a subarachnoid haemorrhage, and in several other families it was also probable as sudden death occurred at a young age, due to some intracranial catastrophe. Two examples of the larger families are given in Figure 1.

DISCUSSION

There are two hypotheses to explain the development of intracranial aneurysms. The first, that there is a developmental weakness in the muscle coat of the arterial wall, and the second, that the aneurysm is the consequence of degenerative change secondary to arteriosclerosis and hypertension. Other aetiological factors may be important, such as the complete involution of fetal arteries, and the mechanical effects of streaming blood flow on an arterial bifurcation.

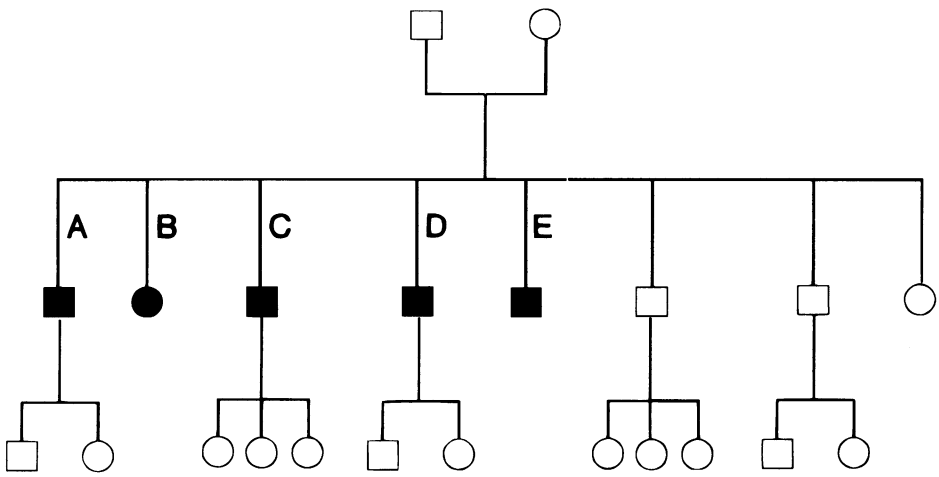
A possible hereditary basis for intracranial aneurysms was suggested in 1954 by Chambers et al[3], who reported occurrence in a father and son. Aneurysm formation has been reported in identical twins.[4, 5, 6, 7, 8] However, reports on the familial occurrence of subarachnoid haemorrhage have been relatively few, being confined usually to single case reports. In 1983 Fox[9] reviewed all familial cases in the world literature. The present series of 24 families represent the largest yet published. There are several explanations for this. Since our early interest in the familial aspect of subarachnoid haemorrhage, a detailed family

Family 4



4a — Twins. Died aged about 40 years — "brain haemorrhage".
b — Unfit for surgery. Died 4 months later. At autopsy 4 aneurysms (3R, 1L internal carotid).
c — Alive and well.
d — Died before anglography.
e — R internal carotid aneurysm. Alive and well.

Family 8



8a — Died aged 30 years.
b — Died after operation for right middle cerebral aneurysm, aged 31 years.
c — No symptoms. Anglography showed 2 aneurysms, L. anterior cerebral, R. internal carotid.
d — Died aged 27 years.
e — Died aged 25 years.

Fig. Two families with sibling subarachnoid haemorrhage.

history is always obtained, and as the population is relatively static, such information is usually known. Indeed, even when relatives have emigrated to other countries, even to the United States, this information is available. The fact that all patients with subarachnoid haemorrhage are referred to the Neurosurgical Unit means that records are complete and readily available.

The incidence of subarachnoid haemorrhage in the United Kingdom is estimated as 6/100,000 of the population,[10] which is an underestimate as about 50% of patients die before reaching hospital for investigation. This incidence concurs with the number of patients admitted to the Neurosurgical Unit. Our finding of 24 familial cases over 19 years suggests that one can expect to find one or two of these cases each year. It also suggests that as many as one in forty of all admissions could be familial.

Familial aneurysms tend to occur at an earlier age than non-familial cases. This observation supports the concept of some arterial developmental defect, rather than a degenerative process with increasing age. The peak incidence in familial cases is reported by Hashimoto[11] as 30-39 years, compared with 55-60 years for familial cases.[12] In the present study the average age of haemorrhage was just 40 years.

Siblings who have subarachnoid haemorrhage tend to have aneurysms at similar sites, which may also be a genetic aetiological factor. Andrews[13] commented that the incidence of intracranial aneurysms at identical sites in familial cases was more than twice the expected frequency in the general population. In many instances, the haemorrhage occurred at the same age in siblings. In this series, the sites of the aneurysms were not unusual, but the proportion arising from the anterior communicating artery complex (16%) was less than expected. This finding was also noted by Andrews. Neill-Dwyer et al[14] suggested that there may be a deficiency of Type III collagen in the arterial wall of patients who develop an aneurysm, but did not know how the deficiency led to aneurysm formation. Le Blanc et al[15] were unable to demonstrate any collagen deficiency in patients with multiple familial cerebral aneurysms. Ostergaard and Oxlund[16] sampled the middle cerebral artery and brachial artery post mortem in 14 patients who died following rupture of intracranial aneurysms, and from a control group of 14 age and sex matched patients who died of causes unrelated to aneurysm rupture. In 6 of the 14 patients deficiency of Type III collagen was demonstrated in specimens of the middle cerebral artery and this was accompanied by an increase in vascular extensibility of the affected blood vessels. Could it be that in the familial cases there is a gene mutation leading to defective collagen production and subsequent weakening of arterial walls at points of bifurcation, where pressure from streaming induces a saccular aneurysm?

Patients with a family history of aneurysm do not necessarily have other vascular anomalies. In this group, one family had polycystic kidneys, one had coarctation of the aorta, but none had Marfan's disease or other connective tissue disorders. The commonest congenital intracranial vascular anomaly in children is an arteriovenous malformation, and these tend to cause intracranial haemorrhage at a younger age than aneurysms. One of our cases, aged 16 years, bled from such a malformation. The only other arteriovenous malformation in the series was considered to be an incidental finding.

The identification of a large number of familial cases of subarachnoid haemorrhage provides support for the theory that aneurysms are developmental in origin. It also presents a problem as to how to advise other relatives in a family. This is even more difficult when they are prone to attacks of migraine, or have an intermittently high blood pressure. Our familial cases, however, did not have a high incidence of hypertension. At present there is no simple investigation to detect a relative with a quiescent aneurysm. CT scanning after the injection of intravenous contrast, or magnetic resonance angiography, will outline the major arteries of the circle of Willis, but may not display a small unruptured aneurysm. Intravenous digital arteriography does not give sufficient clarity of picture, and only intra-arterial angiography reliably demonstrates an aneurysm. Skin biopsy for collagen analysis is not an adequate screening test, and human leucocyte antigen (HLA) has not proved useful in identifying patients at risk of developing an intracranial aneurysm.[17] At the present time, our advice to relatives, especially siblings of affected patients, is that arteriography is the only reliable method of diagnosing an aneurysm. In healthy normotensive individuals this is a safe procedure, the risk of complications being less than 1%.

It is difficult to determine the risk of an incidental aneurysm rupturing. Wiebers et al[18] suggest that for aneurysms less than 1 cm in diameter the risk is less than 1%, but the risk is almost certainly higher with larger aneurysms. Although surgery for aneurysm carries a significant morbidity rate, in experienced hands this should be no greater than 1-2% when operating on anterior circulation lesions. The decision to recommend surgery in such instances deserves consideration but must be tailored to the fears and feelings of the family concerned. Angiography is not recommended for children, as an aneurysm is unlikely to be seen before 25 years of age. There is a need for further research for a simple test that would identify those at risk of having an aneurysm which could result in subarachnoid haemorrhage in later life.

I would like to acknowledge the help of my colleagues, Mr Derek S Gordon, Mr Dermot P Byrnes, Mr Thomas T Fannin and Mr W John Gray for allowing me to include some of the patients in this series. I thank Mrs Heather Selfridge for typing the manuscript.

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Are the birds feeding you *Campylobacter*?

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SUMMARY

During May and June 1992 there was a marked increase in reports of campylobacter *infections compared with other years. Several affected patients mentioned they had been drinking milk from bottles previously pecked by birds. A case control study was initiated to investigate whether there was any significant association. It was concluded that drinking milk pecked by birds was associated significantly with subsequent* campylobacter *infection.*

INTRODUCTION

During May and June 1992 the Department of Public Health Medicine received 58 reports of **campylobacter** infection, compared with 27 reports in the same months in 1991. Six of the cases, when first contacted by a local clinical medical officer or health visitor had consumed doorstep milk pecked by birds. An investigation was therefore initiated to test the hypothesis that consumption of doorstep milk was associated with subsequent *campylobacter* infection.

Throughout Northern Ireland the incidence of laboratory reported *campylobacter* infections has been increasing (Table 1). A seasonal increase is normally noted in spring and autumn; the incidence in Northern Ireland remains lower than that of the rest of the UK[1].

TABLE I

Laboratory reported cases of campylobacter infections throughout Northern Ireland 1985-1991.

Year	*No. of Notifications*
1985	90
1986	73
1987	122
1988	173
1989	192
1990	244
1991	306

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METHODS

Each case of reported *campylobacter* infection is investigated by a clinical medical officer or health visitor to ascertain risk factors and give advice on minimizing the impact of infection in the household and at work. Following comments that some people with *campylobacter* infection had been drinking milk previously pecked by birds 15 cases (22% of the total) were re-interviewed by telephone as part of a case/control study. A case was defined as someone with a laboratory confirmed *campylobacter* infection reported during May and June 1992, with no history of foreign travel within the previous three months, no pre-existing gastrointestinal pathology and who was easily contactable by telephone (maximum of two calls). Each case was asked to nominate one or two controls who were matched for age (within 5 years for children, 10 years for adults), sex and postcode area and who had not had any gastrointestinal symptoms in the preceding month.

Cases and controls were asked whether they received and consumed doorstep milk and whether this milk had been pecked by birds. They were also asked whether they had identified any particular species of birds pecking their milk. Households receiving two colours of milk top were noted and asked if the birds seemed to favour pecking one colour of top in preference to another. Enquiry was made about foodstuffs associated with *campylobacter* infection (poultry, raw milk, barbecued meat) (Table 3). They were also asked about farmyard visits and contact with gastroenteritis cases.

Local hospital laboratories routinely inform the NHSSB Department of Public Health Medicine of any confirmed cases of *campylobacter* infection. The laboratories do not routinely type *campylobacter* isolates and report that "*campylobacter species*" have been identified.

RESULTS

All cases were originally interviewed by a clinical medical officer or health visitor. Fifteen cases and 20 controls were re-interviewed. Two of the cases had been admitted to hospital. The most common symptoms were diarrhoea (100%), fever (93%) and abdominal pain (80%). Enquiry into perceived risk factors revealed that seven controls and eight cases had noted that their milk bottles had been pecked (p=0.285). Four of the seven controls discarded the entire contents of the bottle so that none was consumed. Consumption of the pecked milk was significantly associated with subsequent development of *campylobacter* infection (p=0.027). By the time the infection was reported, several days after milk consumption, samples of the pecked milk were no longer available.

TABLE II

Case/Control consumption of pecked milk.

	CASE		CONTROL		
	Yes	*No*	*Yes*	*No*	*Significance*
Noted pecked milk	8	7	7	13	N/S
Drank pecked milk	8	7	3	17	p=0.027

Farmyard visits, sick animals and contact with other gastroenteritis cases were not significantly associated with illness.

Enquiry into consumption of various foodstuffs demonstrated that none were significantly associated with *campylobacter* infection (Table 3).

TABLE III

Case/Control consumption of Foodstuffs.

	No. eating food		*No. NOT eating food*		*Unsure*		
Foodstuffs	*Case*	*Control*	*Case*	*Control*	*Case*	*Control*	*Significance*
Hamburgers	4	13	11	7	0	0	N/S*
Takeaways	5	12	10	8	0	0	N/S
Barbecued food	2	9	13	11	0	0	N/S
Soft cheese	0	9	15	11	0	0	N/S
Poultry/ poultry products	13	20	2	0	0	0	N/S
Raw milk	0	1	0	19	0	0	N/S
Ice lollies	8	9	7	11	0	0	N/S
Ice cream	13	13	2	7	0	0	N/S
Custard	3	2	12	17	0	1	N/S
Gateaux	2	6	13	14	0	0	N/S
Eggs	8	14	5	5	1	1	N/S
Yoghurt	7	10	7	10	1	0	N/S
Cold meats	12	18	2	2	1	0	N/S
Meat pies	1	8	12	1	2	11	N/S
Mayonnaise	7	15	4	5	4	0	N/S
Sandwich spread	5	7	8	13	2	0	N/S
Pate	0	3	14	17	1	0	N/S

* N/S denotes 'not significant'.

Six households (2 cases and 4 controls) received two colours of milk top — silver (fullcream milk) or silver/red (semi-skimmed milk). All six households reported the silver milk tops being pecked more frequently. Seven of those interviewed (20%) were able to name the species of birds pecking their milk — corvids (crow family, including magpies) were named as the culprits by four households. Many milk deliveries took place before the households had arisen and therefore pecking was unwitnessed. Several interviewees spontaneously mentioned that they had noticed an increase in the number of magpies in their area around this time.

DISCUSSION

Campylobacter is now the commonest bacterial cause of diarrhoea in Britain, the peak incidence being in spring and autumn. The epidemiology is not yet fully understood, most cases are isolated, and outbreaks, clusters and secondary cases are rare. One explanation suggested for this is that many of the population have immunity to *campylobacter* infection.[2] Several studies have linked *campylobacter* infection to consumption of milk by the crow (corvid) family[3,4,5], but none has so far confirmed this association in Northern Ireland. The present study is small, and the sample size was limited by unavailability of cases and contacts by telephone over the holiday period and by difficulty in nominating appropriate controls. The corvids are carrion eaters and are much more likely to transmit *campylobacter* infection than members of the seed eating tit family. Interestingly, six households reported the birds' apparent preference for silver top milk. In the past birds have been shown to favour pecking red colours[6]. Perhaps some birds have learned that the silver top milk is more nutritious?

One study[4] has mentioned the increase in this infection in new housing developments in the north of England which was an area of rapid population expansion. Many of these were in close proximity to the countryside and there was easy access for the local corvid population. The authors sampled the local bird population and corvids were found to be significant *campylobacter* carriers. Capture of local milk-pecking birds was not attempted in our study.

Many households in Northern Ireland still receive doorstep milk and sometimes milkmen cover bottles with upturned cartons to try and prevent pecking. Other households have made boxes for storage and protection of milk. The dairy industry in Northern Ireland has already recognized the potential dangers of milk pecking and in early 1992 one dairy supplied its customers with cartons printed with information about the dangers of drinking pecked milk. In January 1991 the Richmond Committee[9], in its report on the microbiological safety of food, recommended that the government and dairy industry prepare guidelines to minimize risk from doorstep deliveries of food and milk. The Ministry of Agriculture, Fisheries and Food, the Department of Health and the dairy industry established guidelines recommending that doorstep milk should be discarded if tampered with and it should be taken indoors and refrigerated as soon as possible. If this is impracticable householders should leave something out for their milkman to use to protect the bottle tops.[7]

In 1986 the overall cost of a single human case of *campylobacter* infection was estimated to be £587.[8] Allowing for inflation this will now have risen to well over £600. The cost, in financial terms alone, of the 58 cases in the Northern Board area during May and June would have been over £35,000.

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The artificial urinary sphincter. A new solution for incontinent patients

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SUMMARY

Treatment of urinary incontinence with the artificial urinary sphincter has been available in centres such as London and Liverpool for a number of years. This service is now available in the department of urology of the Belfast City Hospital. Twelve patients have had successful implantation of an artificial urinary sphincter for urinary incontinence, and ten are now fully continent. One patient with Wegener's granulomatosis developed active disease in his urethra which has precluded activation of the device. One patient has had the device removed because of erosion into the urethra.

INTRODUCTION

Urinary incontinence is a distressing condition which can have profound psychological effects on the patient, leading to social withdrawal and loss of self esteem. The financial consequences of conventional lifelong treatment of incontinence (pads and catheters) are enormous. The majority of patients suffering from urinary incontinence are female who usually respond to a bladder neck suspension procedure. Male patients and patients with neuropathic bladders need a more sophisticated approach to the problem [1,2].

In 1973 Scott [3] implanted the first artificial urinary sphincter and since then the device has undergone modifications to make it more reliable and easier to use. The advantage of the current model is that it can be left in a deactivated state until tissue healing is complete thus minimising the risk of device erosion. We describe our experience of 12 patients who had the American Medical Systems model 800™ (AMS 800) artificial sphincter inserted in a two year period.

PATIENTS AND METHODS

Twelve patients age range 19-76 (mean 48) have been treated. The clinical diagnosis, urodynamic findings and adjunctive surgical procedures for eleven are summarised in the table. All patients were assessed by clinical examination and endoscopy of the lower urinary tract. All patients had video urodynamics performed using the Aspen Medical, GaelTech GR 800 urodynamic system.

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Bladder capacity, intravesical pressure, and urethral pressure profiles were measured. The mechanics of the device were explained in detail to the patient, and those with neuropathic incontinence were shown how to perform clean intermittent self catheterisation.

The patients were admitted for preoperative bowel preparation. Triple antibiotic therapy (gentamicin, metronidazole and penicillin) is continued for five days postoperatively. In males the device can be inserted around the bulbar urethra, the membranous urethra or around the bladder neck. In the female it can only be placed around the bladder neck. The reservoir determines the pressure in the cuff and a variety of pressures (40-50,51-60, 61-70, 71-80 cm H_20) can be achieved using different reservoirs. (Fig 1).

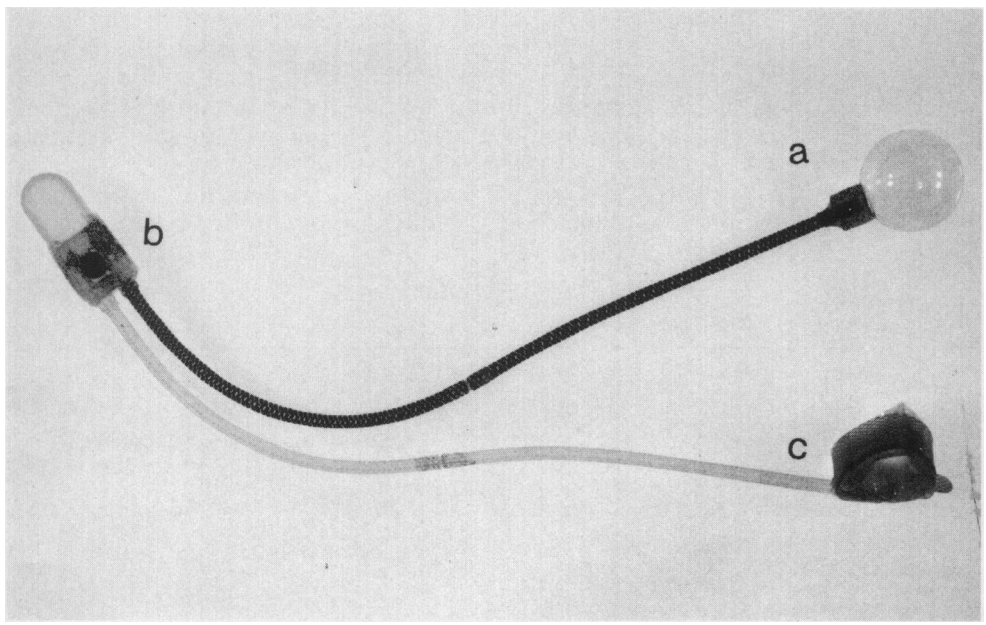

Fig 1. The artificial urinary sphincter. (a) The reservoir. (b) The pump. (c) The cuff which is inserted around the urethra or bladder neck.

To implant an artificial urinary sphincter around the bulbar urethra, an incision is made in the perineum and the bulbar urethra is mobilised with the bulbospongiosus muscle. A measuring device is used to select the correct size of cuff. A second incision is made in either iliac fossa, and the reservoir is placed deep to the rectus abdominis in an extraperitoneal position. A subcutaneous tunnel is made into the scrotum, and the pump mechanism placed in a subcutaneous position. In the female the pump mechanism is placed in the labium majus. The device is filled with an isotonic radio-opaque solution taking great care not to allow any contamination of the tubing with blood or air.

If the device is placed around the bladder neck a suprapubic approach is required (Fig 2). The procedure is technically difficult as there is a risk of entering the vagina in the female or the rectum in the male. If this complication occurs the procedure must be abandoned.

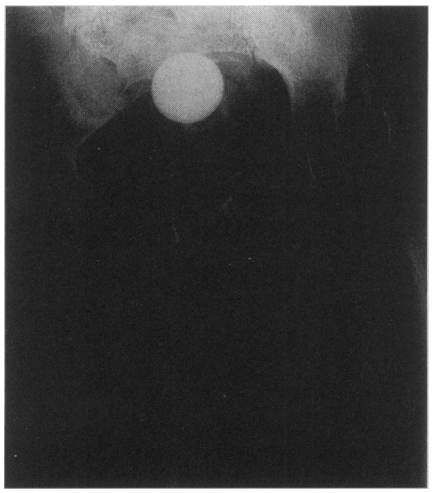

Fig 2. An artificial urinary sphincter **in situ** around the bladder neck of a patient with spina bifida.

RESULTS

Eleven patients have had successful insertion of the artificial sphincter. Ten are fully continent and using the device successfully. One patient's urethra was damaged during mobilisation, and the device subsequently eroded into the urethra and had to be removed. One patient who had Wegener's granulomatosis of the prostate and bladder neck developed a dense urethral stricture three months after insertion of the artificial sphincter. The stricture was biopsied which confirmed the presence of active Wegener's granulomatosis. He is currently undergoing treatment and the sphincter has been left deactivated. He will require a urethroplasty to maintain urethral patency. One patient with spina bifida who had mild stress incontinence postoperatively has had a further procedure to insert a higher pressure reservoir and is now dry.

Patient	Diagnosis	Cystometry	Sphincter	Adjunctive procedure
1	Post prostatectomy	Unstable	Weak	Cystoplasty
2	Post prostatectomy	Stable	Weak	
3	Post prostatectomy	Stable	Weak	
4	Post prostatectomy	Stable	Weak	
5	Post prostatectomy	Stable	Weak	
6	Post prostatectomy	Stable	Weak	
7	Carcinoma prostate	Stable Small capacity	Weak	Cystoplasty
8	Wegener's granulomatosis	Stable Small capacity	Weak	Cystoplasty Urethrotomy
9	Spina bifida	Stable	Weak Small capacity	Cystoplasty
10	Spina bifida	Stable	Weak	
11	Spina bifida	Stable	Weak	Urethrotomy

Table. Details of 11 patients who have had successful insertion of an artificial urinary sphincter.

DISCUSSION

Patients selected for implantation of an artificial urinary sphincter have one of the following conditions: post-prostatectomy incontinence, failed surgery for stress incontinence, neuropathic bladder, congenital abnormalities of the urinary tract or post-traumatic injury. Careful selection is essential if optimum results are to be obtained. The patients must be highly motivated and intelligent enough to understand the workings of the device, and be prepared to undergo more than one surgical procedure to attain continence.

The artificial sphincter is designed to produce a bladder outlet resistance in the range of pressures as described above. The design of the device allows rises in intra-abdominal pressure to be transmitted to the cuff. This usually occurs relatively slowly, but if intra-abdominal pressure rises very quickly, as when getting up from a low chair, slight stress incontinence may occur. This has an important bearing on patient selection, as patients with spina bifida in wheelchairs generate high intra-abdominal pressures when trying to move themselves in the wheelchair, as do those who walk with elbow crutches. Pre-operative assessment of the patient, treatment of any urinary tract infection, dermatitis or other foci of infection is essential before inserting the device.

Patients should be prepared to perform clean intermittent self-catheterisation if necessary. This is an important part of the management of the neuropathic bladder to eliminate residual urine consequent on inefficient bladder emptying. After insertion of an artificial urinary sphincter in patients with neuropathy, or in those who have had a cystoplasty, bladder emptying may be further impaired and some patients may need to perform self-catheterisation through the sphincter cuff to eliminate residual urine.

Video urodynamics are essential to accurately measure bladder pressure, capacity and sphincter function . The anatomy of the bladder and bladder neck can be visualised and vesicoureteric reflux identified [4]. Careful endoscopy is needed to ensure that the patient's urethra is normal and any stricture or urethral disease should be treated before inserting the device. The bladder must be of adequate capacity to allow the patient to hold urine for a socially acceptable time. The bladder must also be capable of storing urine at low pressure in order to protect the upper renal tracts. It is imperative to treat any detrusor instability with anticholinergics. If medical treatment of instability fails then the surgical procedure of choice is an ileocystoplasty (the "clam" procedure). The "clam" ileocystoplasty involves opening the bladder like an open clamshell and suturing in a patch of ileum, which has the combined effect of increasing bladder capacity and reducing bladder pressure [5].

Patients with post-prostatectomy injury, or following trauma, usually have pure sphincter weakness. Patients with neuropathic disorders, those following failed stress incontinence surgery, or those with congenital abnormalities of the urinary tract are more complex and may require a variety of adjunctive procedures.

The major complication following implantation is infection leading to erosion. If this occurs, the device must be removed, as healing will not occur in the presence

of a foreign body. Mundy[2] has identified patients who are at risk for this and quotes 15% infection erosion rate in patients with neuropathic bladders. In patients who have had a sling operation around the bladder neck or in any patient who has had pelvic radiotherapy the infection erosion rate is over 50%. Thus, previous sling surgery or radiotherapy is a contra-indication to insertion of an artificial urinary sphincter[6,7]. Erosion rates are higher in elderly patients or when the device is implanted around the bulbar urethra as opposed to the bladder neck. Although implantation around the bladder neck has a lower rate of erosion, the operative procedure is more difficult and is associated with greater morbidity. Patients with incontinence as a result of major trauma may have such extensive fibrosis at the bladder neck as to preclude implantation at this site. Erosion is also more frequent when higher pressure reservoirs are used and it is our practice to implant a low pressure reservoir initially, changing to a higher pressure if incontinence persists.

The major alternative to implantation of an artificial urinary sphincter is reconstruction of the bladder neck or a urinary diversion. Continent urinary diversions are associated with a high complication rate, with the obvious disadvantages of needing a stoma which has to be catheterised. Successful implantation of an artificial sphincter offers a better quality of life. This procedure does not have a place in the first line of treatment of stress incontinence in females and is only used for complex cases following failed anti-stress procedures.

The overall success rate of the artificial urinary sphincter is about 95%, with 5% being persistent failures. The major complications are infection and erosion, which occur in 10%-15% of patients. Two percent of the devices develop early mechanical failure and a further 2% develop late longterm failures usually due to leakage from the cuff.

Our experience indicates that with careful patient selection excellent results can be achieved with the artificial urinary sphincter. It is the procedure of choice for patients with post-prostatectomy incontinence. It is ideal for certain patients with neuropathic bladder dysfunction who are highly motivated and have normal hand function.

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Childhood accidental deaths on farms in Northern Ireland

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SUMMARY.

Deaths to children on farms in Northern Ireland over a five year period are reviewed. There were seventeen such deaths, the majority of which involved farm machinery. The circumstances of the accidents are described in order to highlight the preventable aspects of these accidents.

INTRODUCTION

The Regional Strategic Framework for Northern Ireland Health and Personal Services (1992-1997)[1] makes particular mention of accidents and sets a target of a reduction of 15% in the annual number of deaths by 1997. It further states that "special emphasis should be placed on preventing accidents to children".

Farms are particularly hazardous for children [2-7]. A recent review of deaths on farms in England, Wales and Scotland reported 26 deaths of children aged 0-14 years over a four year period[8]. Not all of these deaths were directly related to farming activity or were among children living on a farm. The most common accident was associated with farm machinery. In a study of farm accidents presenting to four hospitals in Ireland in 1986 four deaths occurred, three of them involving tractors and one a drowning on a farm[2]. The authors concluded that tractors and their equipment are the dominant cause of both fatal and non-fatal accidents on farms and stressed the need to educate families about these hazards. Tractors are also the most common piece of machinery involved in fatal injuries amongst children on farms in the United States[3-6]. All of the farm injuries described were potentially preventable by proper counselling on safety, supervision of children, and use of automatic safety devices[7].

METHOD.

The information in this paper was obtained as part of a review of all accidental death in childhood in Northern Ireland over the five year period 1984-1988[9]. Sources included the Registrar General's Annual Reports and unpublished records held by the Registrar General, the Annual Reports of the Health and Safety Inspectorate of the Department of Agriculture, and information from the Coroner's reports for that period.

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The Department of Agriculture has a statutory duty to investigate all deaths which take place on a farm or in a location associated with agriculture. All accidental deaths must be reported to the Coroner for the district in which the death took place, who is responsible for investigating the circumstances and is charged specifically with the identification of the victims, deciding when they died and how the death came about[10].

RESULTS

There were 12 boys and 5 girls killed in farming accidents between 1984 and 1988 (Table).

TABLE

Age (years)	*Nos.*
0-4	9
5-9	4
10-14	4

Table. Ages of children killed in farming accidents 1984-1988.

All the children who died were related to the family who were living on the farm. Four deaths resulted from younger children falling into open pits containing semi-liquid agricultural products. The children were often at play close to the family home but unsupervised and with access to the typical structures of a farm environment.

Thirteen accidents involved either tractors or other farm machinery. These deaths can be broadly divided into three groups by age of victim: a group of very young infants, who were killed when a tractor reversed over them in the farmyard; an older age group who were involved in accidents while they were actually operating the tractor or other machinery; and an intermediate group who were killed after falling from a tractor which was being driven, in all cases, by an older relative.

Location and season of death.

Fifteen of the deaths occurred at the site of the accident, only two dying later in hospital. The highest number of deaths occurred in April and July, with no deaths occurring during the winter months (Fig).

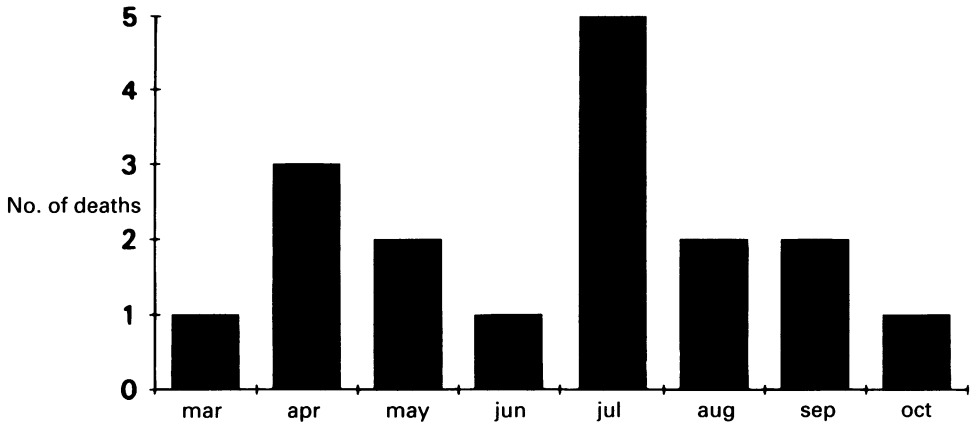

Figure. Farming related childhood accidental deaths 1984-1988 by month.

DISCUSSION.

This category of accidental death is not always included in statistics from other countries or areas, yet it is the third largest cause of accidental death in childhood in Northern Ireland, after road traffic accidents and fires which caused 125 and 25 childrens deaths respectively over the same period[9]. There are no figures available for the number of children who live in farming households in Northern Ireland so it is impossible to tell whether the rate of accidental death is higher among these families than those who live in urban areas. However it is likely to be those children who live on farms or who have regular access to them who will be at greater risk of accidental injury or death.

The types of accidental death at different age groups reflect the different sets of circumstances and risk factors which operate, at the same time, in an environment that is both home and a place of work. For the children of a farming family, the farmyard is their playground, but it is unfortunately filled with agents of injury that may not be compatible with their safety. Increased access to dangerous machinery is a part of their everyday life. The dangers of transporting children in the comparative safety of an enclosed car are well known and this risk exists also on tractors. Children of a farming family may also participate in the daily economic activity on the farm. As such they are then also exposed to the risks of a dangerous working environment. That most of the deaths occurred at the site of the accident reinforces both the serious nature of the accidents and the importance of primary prevention rather than concentration on secondary trauma care.

If these accidents are to be prevented farming parents of small children, like their counterparts in the town and city, should be conscious of the risk to the child at play.[4] Workers on farms must be aware of the changes they should make in their working practices to avoid injury to small children.

The seasonal incidence of the accidents reflects the increase in farming activity and the timing of the school holidays allowing children to be involved in this activity. It should be possible to concentrate preventive information and advice to highlight the need for caution at these times.

Health visitors, family doctors, childminders and teachers in contact with children in a rural environment must also be aware of the specific dangers to which these children are exposed. Local health promotion initiatives should aim to supply these educators with the appropriate information and training. Legislation concerning safe working practices already exists in the agricultural environment, and these regulations must be enforced more rigorously by the Health and Safety Inspectorate. Lay organisations, such as the Ulster Farmers Union and the Young Farmer's Association should also make child accident prevention part of their agenda.

Training courses at the local agricultural college could incorporate accident prevention into the curriculum and local radio and television programmes on farming could give time to highlight the dangers of the farm to young children.

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Huntington disease in County Donegal: epidemiological trends over four decades.

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SUMMARY

The prevalence rate of Huntington disease in County Donegal between 1961 and 1991 showed a decrease from 4.4 to 1.6 per 100,000 population. Emigration and reduction in family size probably account for the progressive decline in prevalence. Over the same time period in the rest of Europe, prevalence has declined only gradually, or has remained static.

INTRODUCTION

Huntington disease, due to an autosomal dominant gene, is characterised by cognitive dysfunction, psychiatric disturbance and movement disorder. (The term Huntington disease is now preferred to the possessive Huntington's disease). The gene has been localised on chromosome 4, and affected patients have a trinucleotide repeat expansion [1] of their IT15 gene [2]. The prevalence of Huntington disease has been extensively studied in the United Kingdom (Table I), and is between 4 and 10 per 100,000 [3]. In Northern Ireland the prevalence rate is 6.3 per 100,000 [4,5]. There is no prevalence data available for the Republic of Ireland. County Donegal was historically part of the province of Ulster, and, until the partition of Ireland, had closer population links with Northern Ireland than with the rest of Ireland [6,7]. We have investigated Huntington disease in County Donegal with the aims of ascertaining all living and deceased individuals with the disease, of estimating trends in prevalence rates, and of establishing a genetic register of affected and 'at risk' individuals to ensure that long term support and advice is available to families.

METHODS

The index Huntington disease patients were identified using multiple sources of ascertainment. Early in 1992, a circular was sent to all general practitioners, neurologists and psychiatrists, in the Republic of Ireland, requesting the name and address of known Huntington disease patients, living or deceased. Further contacts with the regional neurologist, regional psychiatrists, and general practitioners in County Donegal were made in person or by telephone or letter. The diagnostic records in the Department of Medical Genetics at the Queen's University of Belfast, which date from 1967, were examined. These are the

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clinical records of patients attending the genetic counselling clinics, including the satellite clinic in Altnagelvin hospital, County Londonderry, where patients from County Donegal may be seen. No genetic counselling service exists in the Republic of Ireland. In addition, from detailed examination of the pedigrees and by visiting affected patients and relatives in their homes, other affected and 'at risk' individuals were identified.

Estimates of prevalence rates per 100,000 population were made for 1961, 1971, 1981 and 1991, using the dates of the decennial census in Ireland. The prevalence rate was estimated using the formula

$$P = X/Y \times 100{,}000$$

where X = number of affected living Huntington disease patients,

and Y = the total population (obtained from the Central Statistics Office, Dublin).

TABLE I

Prevalence of Huntington disease per 100,000 population in County Donegal.

Year	Affected	Population	Prevalence
1926	7*	152508	4.6
1961	5	113842	4.4
1971	3	108344	2.8
1981	2	125112	2.0
1991	2	128117	1.6

* this older figure is most likely an underascertainment

RESULTS

All families ascertained have been domiciled in County Donegal for many decades. No patients were ascertained who had recently emigrated from other parts of Ireland or from the United Kingdom. The prevalence rates are shown in Table I. Reliable estimates are not available prior to 1955, but for comparison, a minimum historical estimate is shown for 1926. Twelve cases were identified over the period 1961-1991. One patient is still alive. For all patients, the mean age at onset was 40.7 years with a mean age of diagnosis of 44.4 years. For the 11 deceased patients, the mean age at death was 49.8 years. The mean duration of the disease was 12.3 years.

DISCUSSION

The survey is virtually a total ascertainment of Huntington disease patients in County Donegal. This was achieved because the area covered is small, personal contact with medical practitioners was feasible, and thorough primary and secondary family tracing was possible. Categories of Huntington disease patients liable to under-ascertainment in larger population studies such as new mutations, families with no current affected living members, or affected individuals from outside the area, are unlikely to have been excluded from this study.

All the patients appear to have a familial origin in County Donegal for at least five decades, and indeed some families can be traced back to the early 1800's. The prevalence rate has steadily declined as 'at risk' siblings and children have emigrated to other parts of Ireland, the United Kingdom or abroad. Several affected emigrant members have been traced to the United Kingdom [4]. County Donegal is mainly a farming community with no major industries. Over the last five decades, the population has decreased, mainly due to emigration of employable members of the population seeking employment outside the county. The birth rate also has decreased as younger people move away. The ages of onset and diagnosis are similar to other published studies [3, 4]. The age of death is slightly lower. Only one patient with juvenile Huntington disease has been identified, with an age of onset of 10 years, diagnosis at 14 years, and death at 21 years. Only one patient had an onset over 50 years of age.

TABLE II

Huntington disease: minimum prevalence per 100,000 population in the British Isles

Area	*Reference* *	*Year*	*Prevalence*
ENGLAND:			
Home Counties	Critchley	1934	0.2 - 1.3
London	Minski, Guttmann	1938	1.8
Cornwall	Bickford, Ellison	1953	5.6
Northamptonshire	Pleydell	1954	4.9
Northamptonshire	Pleydell	1955	6.0
Northamptonshire	Reid	1960	7.2
Northamptonshire	Oliver	1970	6.3
Carlisle (Cumberland)	Brewis	1966	2.8
N E London/Essex	Heathfield	1967	2.5
Bedfordshire	Heathfield, Mackenzie	1971	7.5
Somerset	Glendenning	1975	5.5
Leeds/Yorkshire	Stevens	1976	4.2
East Anglia	Caro	1977	9.2
SCOTLAND:			
Moray Firth	Lyon	1962	560.0
West Scotland	Bolt	1970	5.2
Edinburgh & Lothian	Venters	1970	6.5
Grampian	Simpson, Johnston	1989	9.9
WALES:			
South Wales	Harper	1979	7.5
South Wales	Walker	1981	7.6
South Wales	Quarrell	1988	8.5
North Wales	Quarrell	1988	5.5
IRELAND:			
Northern Ireland	Morrison	1991	6.3
Republic of Ireland (County Donegal)	Present study	1991	1.6

* These studies can be found in detail in references 3, 4, 5, 8, 9.

The trend for the Huntington disease prevalence rate to decline is likely to continue. In 1993, only one patient with the disease was living in County Donegal, and few 'at risk' patients remain. Population studies in Wales [8] over a 30 year period show a gradual downward trend in the prevalence of Huntington disease. The downward trend in our survey has been more rapid due to emigration of 'at risk' patients, and a reduction in size of the families compared to previous generations.

This study, involving a small area, illustrates how random genetic drift in more isolated populations has a more extreme effect on the prevalence of the disease than in a larger population area. The very high concentration of Huntington disease in the Moray Firth area in Scotland [9] shows the opposite effect, with genetic isolation causing a very high prevalence rate, (Table II).

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Historical Review

A memoir of Dr Norman Joseph Ainley (1924-1962), and a last look at smallpox and vaccination

J S Logan

"They are of laurel, such as are given to the brave" — Robert Koch, as he laid a wreath on the coffin of Louis Thuillier, who died of cholera, while investigating the disease in Alexandria.

Dr Norman Joseph Ainley 1924-1962

Norman Joseph Ainley was born in Belfast, the son of Joseph and Sarah Isabella Ainley. He went to school at the Royal Belfast Academical Institution, and studied medicine at the Queen's University of Belfast and the Royal Victoria Hospital. He graduated in 1946 and was a resident medical officer in the Royal Victoria Hospital 1946-47. After being house physician in the Leicester Royal Infirmary, he followed a career in pathology in Belfast at the University and in the Health Service laboratories. He received the degree of MD in 1950 and became a member of the Royal College of Physicians of Ireland in 1951. He married in 1952 Dr Margaret Wilkinson, and he had two sons. In 1956 he was appointed assistant pathologist in Bradford, and there tragically he came by his death, from smallpox, in the course of and because of his duty.

The course of events in Bradford in December 1961 and January 1962 can be followed in the excellent paper of Douglas and Edgar[1], extensively quoted in the following pages. Valuable details have been contributed by Dr Ruth Stuart, daughter of Dr Douglas.

A nine year old Pakistani girl arrived with her parents by air from Karachi on the 16 December 1961. She became ill, and was admitted on the 23 December, seven days later, to the Bradford Children's Hospital, Ward A1. She was thought

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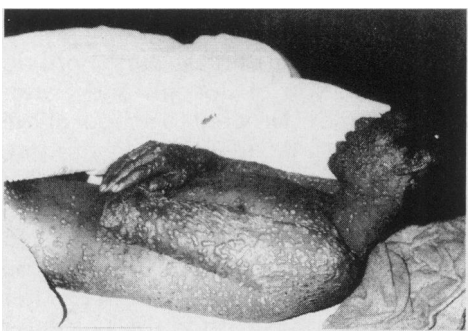
to be suffering from malaria, and indeed she was. A blood film showed numerous plasmodium vivax parasites, mostly in the ring stage. Antimalarial treatment reduced the temperature to normal, and it remained normal until December 29. On that day the temperature rose again, and the child died the next day, December 30. Dr Ainley made a post-mortem examination on January 1, 1962. Unfortunately the post-mortem report is no longer available, but from Osler's Canadian post-mortem reports[2] one knows that if the diagnosis was not plain clinically, it could not be made by the morbid anatomy at the autopsy. In the discussion of the cause of death, viral pneumonia, malaria and staphylococcal septicaemia were considered. Staphylococcus albus was later recovered from a blood culture. There had been no clinical features which suggested smallpox. That implies that there was no vesicular or pustular rash. Anecdote has said that there was a haemorrhagic rash, but that is not mentioned in the record available. The child's body was embalmed and sent back to Pakistan.



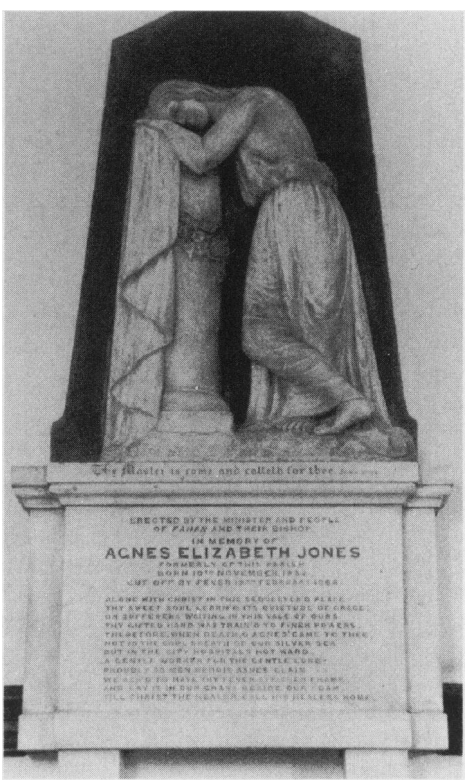
The rash of smallpox. Reproduced by kind permission of Dr J McA Taggart who took the photograph in India in 1968.

On January 10, 1962, a woman, a cook in the Bradford Children's Hospital, was under observation in the Leeds Road Fever Hospital as a probable case of haemorrhagic smallpox. This patient died. The next day, January 11, a man died in St. Luke's Hospital, Bradford. He had been admitted the day before with a provisional diagnosis of thrombocytopaenic purpura. Because the features of his illness closely resembled those of the cook in the Fever Hospital, it was realised that he had died from haemorrhagic smallpox. Indeed he had visited Ward A1 in the Children's Hospital on December 28. It was then plain too, that the five children, recently transferred from Ward A1 with "spots" to the Wharfedale Children's Hospital, were likely to be cases of smallpox. They had all been in the same Ward A1 at the Children's Hospital as the Pakistani child who had died. A full account of the epidemic in Bradford and the successful action to prevent spread can be found in the paper[1] by Dr Douglas and Dr Edgar, medical officer of health and deputy medical officer of health respectively, for the city of Bradford. Ultimately there were fourteen cases of smallpox in Bradford and neighbourhood, of whom six died from the disease. Nearly 900 contacts were identified and kept under surveillance by the medical staffs of the Health Department and the hospitals concerned. Between January 13 and 17, nearly 250,000 people were vaccinated in the city. No adverse effects are reported by Douglas and Edgar.

Dr Ainley had never been vaccinated, but even if he had been vaccinated in infancy, that would not have been protective in 1962. He was vaccinated on "the eleventh day after known contact", that is after the post mortem examination on January 1. "Assuming correct technique and a potent vaccine, a satisfactory take can be obtained in all non-immunes up to the first two to three days of *incubation* of an attack of smallpox".[3] The period of incubation averages eleven days. Dr Ainley was not immune, and the vaccination of January 11 was too late. He fell ill on January 12, was admitted to the Oakwell Isolation Hospital, Birstall,

and died on January 23 to the great distress of his colleagues and all who knew him. Unfortunately in the same year a similar fate overtook another doctor, engaged in obstetrics. Dr Robert Hodkinson died of smallpox in the Glamorgan epidemic. His patient had died inexplicably in her confinement and he had attended the post-mortem.[4] These are not the only examples of health workers dying of smallpox. In the Glasgow epidemic of 1950[5], initiated by the visit to Glasgow of a Laccadive Islands seaman who was only mildly ill, one woman doctor, two nurses and a laundry maid died. Others died in these epidemics, but one might have expected health workers in those days to have been protected by vaccination.

So far as one knows, Dr Ainley was the last, or latest, member of our medical school to die of an infection contracted in the course of his duty; though it may be that the terminal illness of Dr H G Calwell was due to a hepatitis virus infection acquired during his nineteen years of service in East Africa. In our profession they have had many predecessors. Ulster doctors remember Dr William Smyth of Donegal who perished from typhus.[6] His memorial window is in the Ulster Medical Society rooms. We also remember Mr George A Hicks[7], surgeon to the Samaritan Hospital, Belfast, who died in 1920 of haemolytic streptococcal septicaemia contracted in the practice of the hospital. Two weeks before his death a small wound in the thumb was infected during attendance on a septic case. The haemolytic streptococcus was isolated both from surgeon and patient. It is impossible to forget the nurses who died. Miss Agnes Jones, that devoted Ulster lady, matron of the Liverpool Workhouse Infirmary, who died in 1868, aged 35, of typhus contracted in the Infirmary, was only the most distinguished of the nurses who died of occupational infections[8]. There is a memorial to her in the parish church at Fahan, Co. Donegal. Craig[9] records the death of a nurse in the Belfast Infirmary from smallpox, and in 1860 five nurses dying of typhus. He also mentions some house physicians dying of typhus. Risks had to be run, and some paid with their lives. Miss Mewha, housekeeper in the Belfast General Hospital (now the Royal Victoria Hospital), died of "fever" "caught in the discharge of her duties" in 1865.[10] At various times two physicians, Dr Benjamin Thompson[11] and Dr McCabe[12], two house surgeons, Mr J C Bell[13] and Mr Alfred Anderson[14], and an assistant house surgeon Mr McMurray[14] of that hospital died of "fever".



The Memorial Tablet of Miss Agnes Elizabeth Jones in the parish church of Fahan, Co. Donegal. The photograph appears by the kind permission of the Rector and Select Vestry. Her grave is in the adjoining old graveyard.

In Belfast only sporadic cases of smallpox occurred after the end of the 19th century. In the city of Belfast in 1891 there were three deaths, in 1901 one, in 1902 one, in 1904 eight, and in 1905 one. There was a single death from smallpox in Northern Ireland in 1920, and none thereafter. In Belfast in 1921 there were three notifications, and one in 1942. The latter infection was contracted in Scotland. Vaccination was compulsory in Ireland and was enforced. In 1932 the Registrar General for Northern Ireland recorded that of 25,107 live births, 83 per cent had successful primary vaccination. All medical students in Belfast had to attend a class in vaccination, taught for many years in the Belfast Infirmary (Belfast City Hospital) by Dr S R Armstrong. The class certificate was necessary for admission to the Final MB examination, and for a practitioner to be a public vaccinator. The infection of vaccination was general, and not limited to the vaccinal lesion in the skin of the arm, but it was so mild in a healthy individual that it was hardly noticed. Very rarely a case of encephalitis followed vaccination. It may or may not have been vaccinial. The writer once attended a patient with what appeared to be vaccinial carditis. While vaccination was dangerous in those with impaired immunity, or with eczematous skin, or those generally ill, or frail and feeble, the worst was the deaths of infants and young children in the 19th century, when the practice was arm to arm vaccination, from bacterial infection of the primary take, and subsequent "erysipelas" and septicaemia.[15] This might be due, for instance, to contact with a case of scarlet fever, or bad home conditions, but some vaccinators had little or no regard for the sterility or cleanliness of the lancet used for "inserting" the lymph. The donor vaccination site must sometimes have been infected with pathogenic bacteria.

The haemorrhagic cases of the Bradford epidemic closely resemble those described by Osler[2] in the Montreal epidemic of the 1870's. Osler himself did "seven carefully performed autopsies". The findings were mainly haemorrhagic and non-specific. Osler could not have survived his duties in the smallpox department of the Montreal General Hospital, or the autopsies, if he had not been protected by vaccination and re-vaccination. Yet according to Cushing[16] he had never had a successful "take". Indeed he did have a very mild attack of smallpox, with only sixteen pustules. This must imply that a prolonged, severe exposure to a virulent strain of smallpox can in some degree overcome what must have been a high degree of protection. Presumably in the 1870s Osler's vaccinations were arm to arm, with human lymph. Osler and Douglas and Edgar draw attention to the "bright scarlatiniform redness" (Osler), "the colour like a cockscomb" (Douglas and Edgar) on the second day, or even on the evening of the first day — before the rash became haemorrhagic. Ramachandra Rao[17] states that haemorrhagic smallpox was fatal regardless of the vaccination status, but that, one hopes, refers to vaccinations which by the elapse of time had lost some or all protective power.

It is presumed that the Pakistani child was the origin of the Bradford epidemic. Smallpox was epidemic in Karachi.[18] In the last months of 1961 six hundred patients with smallpox had been admitted to the Epidemic Diseases Hospital there, and nearly a quarter of a million of the inhabitants had been vaccinated. The child had been vaccinated in infancy, and had been "re-vaccinated" along with her father and mother on December 5, 1961. The parents, when inspected in Bradford, had the scars of old successful vaccination, and, more important, scars consistent with recent successful re-vaccination. Why then was the child not protected? The father said that the child's arm was red after the attempted

re-vaccination, but no crust or scar developed although, as was evident in a few weeks, she was non-immune. If it was true that there was no primary take, and from the course of events it must have been true, that should have been evident at a routine inspection in eight days' time, and the vaccination should have been at once repeated. But when a quarter of a million vaccinations had to be done, probably inspection of each at eight days was impossible. Perhaps the child may have been vaccinated with an inactive batch of vaccine. Perhaps the co-existing malaria impaired the immune response. Failure of vaccination could also be due to "lack of cleanliness causing sepsis, the use of too strong an antiseptic for cleaning the skin, over-heating of the lancet needle or scarifier when sterilising it, drawing blood, exposure of the recently vaccinated area to the hot sun (a very important point in the tropics) or charring of the lymph in the capillary tube when sealed". [19] Or the lymph may be rubbed or washed off, or even licked off.

Baxby[20] assembles the evidence that the virus in the vaccine lymph in use in the United Kingdom (until vaccination against smallpox was no longer needed) was vaccinia and not the virus of cowpox. The origin of vaccinia virus seems undetermined. He reviews the 19th century debate about the identity of the virus in the vaccine, in the days before the orthopox viruses could be distinguished by modern virus laboratory methods.[21] It was an important question whether the vaccine was really an attenuated smallpox virus. Some thought it should be. For instance it was reported from East Africa[22] that "in Nairobi vaccine lymph was made from a strain of virus derived from a human case of smallpox, attenuated by calf passage and maintained by periodical rabbit passage. In Tanganyika likewise a human smallpox strain was passaged first through monkeys (Cercopithecus albogularis), then through a succession of calves and tested by titration in monkeys before release for human use". "This vaccine was used extensively", "without ill effect", and "gave a high degree of protection". It seems that in the practice of vaccination this vaccine behaved like vaccinia. One might speculate that smallpox virus may have been weeded out by attempted passage through insusceptible animals, and that vaccinia may have been contributed by laboratory animals already carriers of vaccinia. It is unnecessary to speculate. If the question arose again, it could be settled by the work of virus laboratories.

The history of the prevention of smallpox and of the development in England of the protective vaccine is described by Hutchinson[23] and by Dudgeon.[24] From the first decade of the 19th century, once vaccinal lesions had been established in humans, further vaccination was done with lymph from the vaccinal lesion on the human skin. It was transferred direct from arm to arm when the patient, vaccinated eight days before, attended for inspection, and also to provide lymph from his "take" for those waiting to be vaccinated. In an attempt to store it for transport to a distance some was taken on to ivory points, or quills, and allowed to dry. A lancet was used in those days to make the insertion into the epidermis. Children were preferred as the source of human lymph because they were much less likely to be infected with syphilis. By 1881 in England lymph from the skin lesions of vaccinated calves began to be available. After the report of the Royal Commission on Vaccination of the 1890's, the use of human lymph was abandoned, and glycerinated calf lymph became the standard preparation. In 1914-18 sheep began to take the place of calves and the change was complete in England in 1946. There may have been the possibility of transferring, to the human, calf or sheep viruses other than vaccinia.

It is interesting that in the days of arm to arm vaccination, a strain after many human passages sometimes became incapable of producing a vaccinal lesion in non-immune persons. What was the mechanism of this attenuation? It is difficult but not impossible to think that the genetic constitution of the virus had changed. One can also remember that in each vaccination of arm to arm type the virus met with an immune response in each new vaccinee. Presumably what was transferred arm to arm was not only the virus but antibody bound to it. One might think that after numerous passages there was so much antibody accumulated that the virus was inactive. This is an old thought. Simon[25] recorded the belief (of some) "that the original cowpox at each vaccination simply dilutes itself with certain passive juices of the vaccinated body, that it thus of course gets weaker at every stage, till at its thirty-fifth succession it is reduced . . . to a fraction of its original power". Whatever the explanation, it was usual then for vaccinators to look for a new strain, sometimes in Europe.

In Ireland the voluntary Cowpock Institution opened in Dublin in 1804[26]. It received an annual grant from the Government, at first of £100, increased in 1807 to £150. Its purpose was to vaccinate the poor without charge, and to provide lymph, human at that time, to all parts of Ireland by post. A "packet of infection" cost half-a-crown. By 1843-44 it was sending dry lymph to the Isle of Man, Jersey, Canada, Australia, Grenada, Demerara, and China, and this export continued for years. In Belfast, on the 13 April 1793, there had appeared in the Belfast Newsletter a prospectus of the proposed General Dispensary, the forerunner of what is now the Royal Victoria Hospital. One of its purposes was to prevent smallpox by "inoculation of the children of the poor". By inoculation the thirty-nine proposers meant inoculation with smallpox material. They did not mean vaccination, because Edward Jenner did not perform his first vaccination with cowpox until 14 May 1796, and he did not publish his monograph, An Inquiry, until June 1798. Inoculation had been carried on in the Poor House (now Clifton House) at least since 1777[27]. Vaccination became compulsory in Ireland in 1864. Inoculation was made illegal in Ireland by the Act of 1840 and the Vaccination Amendment (Ireland) Act of 1868. Inoculated persons were sources of infection for the non-immune, and there were some deaths of those inoculated. It survived in the hands of untrained primitive country people for some years. In Belfast in 1804 vaccination was being carried on in the General Dispensary, then in West Street, by Mr McCluney, Surgeon. In the Frederick Street Hospital vaccination began in 1828/29 in the hands of Dr McCormack. When a physician and surgeon were appointed in 1830 to attend daily at the Dispensary at the hospital, a day was set aside for vaccinations.

The Cowpock Institution was taken over by the new Local Government Board for Ireland in 1877. Its annual reports can be found in the sessional papers of the House of Commons. After 1877 there is a full report each year in the annual report of the Local Government Board. Eventually the vaccine department of the Board obtained the lymph, ultimately glycerinated calf lymph, from the National Calf Lymph Institute at Sandymount, Dublin, and it supervised the production there for safety and efficiency. It was many years later however, not till about 1900, that all lymph in Ireland was supplied only in capillary glass tubes.

The Therapeutic Substances Act of 1925 provided in the United Kingdom for the regulation of the preparation and standardising of, **inter alia**, vaccine lymph. The Regulations of 1927 made under the Act defined vaccine lymph as the substance

obtained from the vesicles produced on the skin of healthy animals by inoculation of vaccinia virus. The calves, or later sheep, were to be healthy animals, quarantined for five days, thoroughly cleaned and groomed. Several hundred animals were used each year in the Government Lymph Establishment. The skin surface was to be shaved, and cleaned to obtain, so far as possible, asepsis. A special room was to be provided for the inoculation and subsequent collection of the vaccine lymph. After the collection the animal was to be killed and a thorough postmortem examination done. Sterile methods were to be used for the processing of the vaccine lymph. It was to be treated with glycerol to bring its content of bacteria and other "microscopically visible micro-organisms" within prescribed limits. Then cultures were to be made to identify any gas-forming anaerobes or living streptococci. Treatment and examination of the lymph were to be continued until the total number of living bacteria had been reduced to not more than 5000 in 1ml of vaccine lymph. The potency of the lymph, ready for distribution, was tested in a dilution of one part of lymph in one thousand parts of physiological saline. This was applied to the skin of a rabbit or guinea-pig. Unless typical vaccinia virus lesions were produced, the batch of virus was not to be issued. The Act and the Regulations were doing for biological preparations what the British Pharmacopoeia did for drugs.

In May 1980 the World Health Assembly declared the world and its peoples free from smallpox. Its campaign to free the world was successful because, **inter alia**, of the world-wide search for cases, the fact that it was an acute readily diagnosable disease, there was no animal reservoir, and freeze-dried preparations of the vaccine, available in quantity, kept well in tropical heat and light[28]. Vaccination was no longer needed. Still, there are lessons to be learned from the history of smallpox, vaccination, and infectious diseases generally. One is that medicine and nursing are sacrificial professions. Another is that there is an extensive field, still to be explored, of infection as a cause of disease. With this in mind, the Royal Victoria Hospital has founded an annual prize to encourage the study of infectious diseases. It is to be called the Ainley Prize to commemorate our fallen colleague.

The careful typing of the manuscript by Mrs C McDonald is gratefully acknowledged.

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The Royal Group of Hospitals Arts and Environment Project

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INTRODUCTION

Artistic activity in hospitals throughout the United Kingdom has shown a remarkable increase over the last twenty years. In the mid 1970s the Arts Council, the Calouste Gulbenkian Foundation and the Carnegie (UK) trust funded a series of pilot projects. The most notable of these was at St Mary's Hospital in Manchester which expanded to encompass virtually all NHS facilities in the Manchester Area[1]. In 1990 Peter Senior, pioneer of the Manchester Project and now Director of Arts for Health, reported that 28 health authorities employed an arts co-ordinator and identified more than 300 individual projects [2]. A landmark in the development of the new hospital art movement is St Mary's Hospital in the Isle of Wight, where arts provision was integral to the original design of the building.

The arts have long had a significant place in hospitals. In sixteenth and seventeenth century Europe, hospital buildings were designed with aesthetic considerations in mind, and artists were frequently commissioned to paint pictures and murals which "prepared patients for the next world, gave consolation or extolled the virtues of Christian charity" [3]. The tradition of commissioning works of art and of buying completed paintings has continued down to the present day. Moreover, various kinds of art therapy have become an established part of hospital life, particularly in geriatric and psychiatric units.

The arts movement which has developed over the last twenty years is different in several respects. Unlike traditional commissioning schemes, it usually involves a professional artist or coordinator taking up "residence" in a hospital with the intention of promoting the arts and encouraging the active participation of patients and staff in the creative process. Rather than offer consolation or convey any uplifting spiritual message, the new hospital arts movement is primarily aimed at effecting an improvement in the hospital environment. People associated with the movement often claim that art can have a therapeutic effect — some

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even argue that it can contribute to healing[4] — but they are careful to differentiate hospital arts from art therapy by stressing that hospital art does not form part of clinical treatment [5].

THE ROYAL GROUP OF HOSPITALS ART AND ENVIRONMENT PROJECT

During 1989 discussions were initiated at the Royal Group of Hospitals with a view to appointing an artist in residence. The discussions involved management, medical and other staff, Mr Peter Senior and potential funding bodies. Funding was secured from a variety of sources with major support from the Gulbenkian Foundation and the Arts Council for Northern Ireland. Ruth Priestly was appointed as artist in residence in April 1990 on a part-time basis (3 days per week) for an initial period of three years.

Fig 1. Bronze statuette in the entrance hall at the Royal Belfast Hospital for Sick Children. *(Rosamund Praeger).*

The Royal Group of Hospitals was already rich in works of art. The present Royal Victoria Hospital was officially opened in 1903, replacing the building in Frederick Street to which the hospital (founded in 1789) had moved in 1817. These hospitals were supported largely by endowments and bequests. Among these bequests were a variety of art works, some of which can be seen in the present buildings. The famous bronze statue of Queen Victoria, for example, is attributed to J Wenlock Robins, and the stained glass window depicting the Good Samaritan, now situated at the end of the main corridor, was presented to the medical staff in 1887 by Sir William Whitla, a generous benefactor of Belfast medicine. Another fine piece of stained glass, depicting signs of the zodiac, can be seen in the vault of the ceiling in the Black and White Hall; the artist is unknown.

This tradition was continued in the other hospitals which now form part of the Royal Group. Rosamund Praeger, the Holywood artist, contributed the statuette in the entrance hall of the Royal Belfast Hospital for Sick Children (Fig 1), a mother and child bas-relief to the Royal Maternity Hospital and a plaque for the "Schubert bed", which was intended to be the first of a series of beds named after famous composers. The walls of old wards in the Royal Belfast Hospital for Sick Children are decorated with tiles depicting nursery rhymes made by McNaughtons, and in the entrance to the Eye and Ear Clinic at the Royal Victoria Hospital there is a remarkable mosaic symbolising the nose, ear and throat by the Belfast team Kinney-Dobson Design Associates.

Other forms of artistic activity were already well established at the Royal Group of Hospitals prior to the inception of the Arts and Environment Project. Notable amongst these is the work of Duncan Wallace, an Art Therapist who has been working in the geriatric medical unit for the past twelve years. Another example

is the musical performances by local school children and by a range of amateur and professional musicians. These were organised as a series of lunchtime concerts by Professor Philip Adams under the auspices of the Friends of the Royal, and included classical music, jazz and country and western.

Given the variety of artistic endeavour already on display at the Royal Group of Hospitals, one may question the need for an artist in residence. It was felt that such a person could do a number of things which had never been done before. Previous artistic activity did not form part of a coordinated policy and did not, with the exception of art therapy, involve patients or staff in the creative process. Individually, the various works of art donated to the hospitals in the past are decorative, but the buildings as a whole are showing the effects of time, and of their location in an area which has suffered more than most during the current troubles.

The terms of reference of the post of artist in residence were to work towards the improvement of the environment of the hospitals by the introduction of a comprehensive arts programme. The artist in residence was to use not only her own artistic skills to achieve this aim but also to commission and introduce other artists to work in the hospital, and to coordinate these activities. The performing arts as well as the visual arts were to be included in the programme. Patients, staff and the local community were to be involved wherever possible. The project was to be evaluated by an independent agency.

During the first 18 months of the project Ruth Priestly organised a programme of activities which included the painting of a mural in Block A of the Royal Victoria Hospital, a series of pilot workshops and the commissioning of two paintings — one for the waiting area at the delivery suite in the Royal Maternity Hospital and one for the Metabolic Unit. The pilot workshops provided the opportunity for six artists to explore a variety of art forms — painting and drawing, embroidery, music and creative writing with different patient groups, including those in a neurology unit, an acute medical unit, an ophthalmology ward, the ante-natal ward and the geriatric unit.

THE EVALUATION

The Centre for Health and Social Research at the University of Ulster was commissioned to evaluate this programme of activities in April 1991. Following discussions with the people involved in the project it was decided that the evaluation should have two main aims: to examine the processes involved in setting up and implementing the project and to monitor its environmental outcome (murals, paintings, performances, installations) and to examine the impact of the pilot art workshops on patients' experience of being in hospital and their interactions with staff. It was agreed that it was neither appropriate or feasible to test the hypothesis that artistic activity can contribute to the physical process of recovery amongst participating patients: therapy is not the primary aim of hospital arts, and testing such an hypothesis would have required quasi-experimental conditions which did not apply in the context of the project. The evaluation involved a variety of qualitative and quantitative research techniques which are documented in the report submitted to the project management committee[6].

To judge from the literature, the introduction of an arts programme in a hospital context may give rise to problems. A variety of difficulties are mentioned, but most devolve from what one author describes as the clash of "two cultures": that of the artist on the one hand and that of the hospital staff on the other. It can take some time for the artist to become accustomed to working within the complex hierarchical and administrative structures of the hospital. Conversely, hospital staff sometimes perceive the arts project as drawing on resources that might be better used elsewhere [3].

The artist in residence at the Royal Group of Hospitals adapted well to working in a hospital environment, but the project attracted a hostile response from a few staff. This hostility was expressed in the form of two anonymous letters published in the Belfast Telegraph shortly after the artist was appointed, but before she started work. One correspondent was worried that the project would turn the hospital into an art gallery! But the main concern of both correspondents was that the Eastern Health and Social Services Board was spending money on an arts project at a time when vacancies for physiotherapists, occupational therapists, and newly qualified nurses "cannot be advertised because the Eastern Health Board has insufficient funds to pay for their salaries" [7]. As the Chairman of the Advisory Committee of the Project pointed out in a subsequent letter to the Belfast Telegraph, the author of the letter quoted above had made a "false assumption": none of the funding provided for the Project could have been used "for any aspect of clinical services to patients".

The most obvious impact of the artist in residence's work in the first 18 months of the project was the extensive mural work mentioned above (Fig 2). This highly colourful mural with its aquarium theme measures 7 x 3 metres and was completed with the help of four other artists. Designs for the frieze in the waiting area were also by Ruth Priestly and those for the mermaids on the central pillar were by Aileen Beattie. The approach corridor to the mural introduces a tropical theme, and a wave motif on one wall depicts the pounding of the sea. As the work on the mural progressed, passers-by made many comments and suggestions. The artists were able to respond to some of these as they worked, and the end result has met with almost universal approval. The Head Porter for Block A captured the general feeling well:

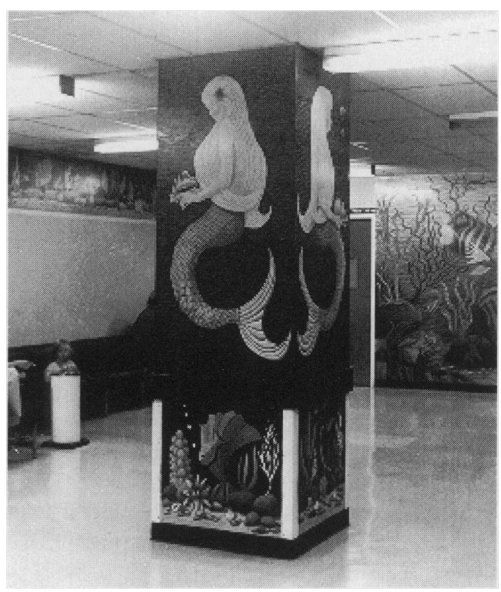

Fig 2. Mural in Block A, Royal Victoria Hospital, by Ruth Priestly, Artist in Residence.

"There's a lot of grief about this area. With intensive care next to us you're getting relatives coming to visit patients and they are distressed. But the fact

is, this place has brightened beyond all recognition from Ruth has appeared. I think it's great insight on someone's part, the management that proposed this. I think it's lovely, it has really lifted the spirits. People dread coming into hospital, you expect it to be drab and grey, but this is beautiful! The children enjoy it too".

One potential problem with murals relates to their long term upkeep: the works and maintenance department expressed concern about the susceptibility of the mural work to wear and tear, particularly as it is painted directly on to the wall. Only time will tell; however, it is noteworthy that, with one small exception, there has been no graffiti or wilful despoiling of the area since the art work was introduced.

The second aim of the evaluation was to examine the impact of the pilot art workshops on patients' experience of being in hospital and their interaction with staff. There is no doubt that the patients who participated in the workshops found them enjoyable and beneficial. The workshops provided a relief from hospital routine and facilitated mixing between patients. As a patient in the ante-natal ward told the researcher "it [the workshop] gives you someone to talk to, it's important to be occupied and you need someone else to take your mind off your condition". The patients' self-perception of the workshops as having been beneficial was largely confirmed by the ward staff. For example, one nurse remarked that the musical sessions in an acute medical ward eased tensions by providing an occasion for the expression of emotion: "sometimes tears, sometimes laughter".

It was not part of the evaluation to examine the effect of the workshops on the clinical condition of patients; however, two anecdotes were reported to us by staff which are worth recounting here. The first concerns a male patient in the neurology unit who had been suffering from post-operative urinary retention for a number of days. No treatment appeared to be of any help and the patient was becoming increasingly anxious. Nevertheless, the artist persuaded him to join one of the workshops and shortly after the workshop had ended the patient succeeded in passing urine for the first time since his operation. The second concerns an elderly female stroke patient who was present at a musical session held in an acute medical unit. After the session the patient told her relatives about the music and how much she had enjoyed it — it was the first time she had spoken for some weeks.

Although the workshops had a positive impact on patients who participated in them and on the ward environment at the time when the workshops were taking place, participation rates among patients were fairly low and the impact on the ward environment was not sustained. Participation rates were influenced by a variety of factors. Some were specific to particular wards, but there were two factors common to most of the workshops. The first was the high turn-over of patients; the second was the lack of continuity between workshops. The former was a consequence of choosing wards with short-stay acute or general patients. The latter was inherent in the way in which the workshops were planned; that is, to occur only once per week for a period of four or, at most, eight weeks. Together, these two factors meant that the facilitator often had to start each workshop afresh and build up a rapport with a new set of patients each week.

In looking at participation rates in the workshops, it should be borne in mind that these were pilot workshops designed, in part, to explore the feasibility of engaging short-stay patients in artistic activity. The conventional wisdom is that hospital arts are appropriate only for long-stay patients [5 8] and in the light of this the pilot workshops served their purpose well; they also demonstrated that it is possible to engage different categories of short-stay patients in a range of artistic activity from which they derive pleasure. This is an important lesson, particularly at a time when the trend in hospitals is towards the early discharge of patients and consideration is being given to the quality of care which patients receive in hospital.

A crucial factor in organising workshops or, indeed, any artistic activity is the involvement of hospital staff. One of the most successful workshops was that which took place in Ward 36 of the Geriatric Unit. The success of these workshops was not simply an expression of the fact that they took place in a ward with a lower turn-over of patients than the others, but that the facilitator, Sylvia Sands, had the help of a member of the nursing staff with special responsibility for patient activities. The nurse joined in the workshops and, in Sylvia's words, created a "safe atmosphere". The nurse also helped to maintain continuity, bringing the same core of people together each week. The facilitator attached considerable importance to this continuity: "as the sessions went on, the atmosphere grew more and more relaxed, and the people shared more freely and deeply".

THE CURRENT STATE OF THE PROJECT

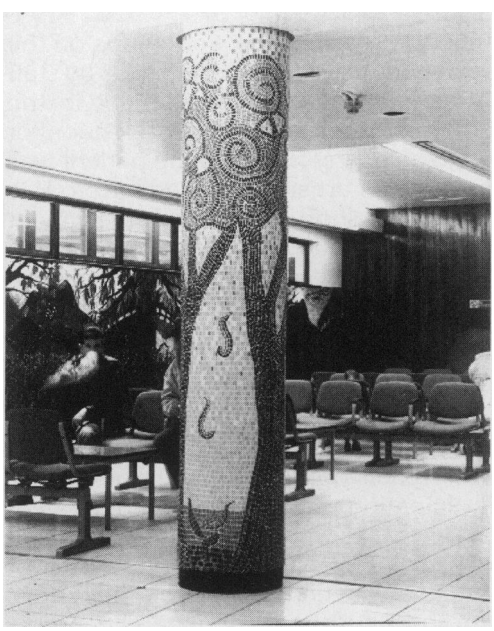

Fig 3. Entrance hall, Outpatient building, Royal Victoria Hospital. Mural of a County Down landscape by Brendan Ellis, and mosaic work on pillar by Ruth Priestly.

During the past year the project has been focused on the Falls Road entrance to the Royal Victoria Hospital, where the public receive their first impression on visiting the hospital. In consultation with the Patient Services Initiative Team it was agreed that a major arts input would improve the image of this area and a Four Seasons motif was suggested. A large mural in the cafe area was commissioned from Brendan Ellis, an artist in the medical illustration department of the hospital, which depicts a County Down landscape at various times of the year. (Fig 3). Another commission was given to Owen Crawford for a major piece of sculpture to form an arch over the entrance hall. This was carved mainly from sycamore and extends the hands of friendship and healing to all who pass beneath (Fig 4). Ruth Priestly herself has been engaged in beautiful and intricate mosaic work

which at present covers four of the pillars in the hall, each representing one of the seasons. Three more pillars will show doves of peace, again in mosaic. Some of this art work is being done on site, which generates interest and, indeed, participation from some of the many visitors who pass through each day. The mosaic work has also provided an opportunity for many local artists to come in and help with the project and to introduce them to the philosophy and potential of hospital arts.

Another area of attention has been the "Chatters" Restaurant in Bostock House, where artist Ben Allen has undertaken a major mural project. This was specially requested by the manageress and staff in the restaurant to try and brighten up, and stimulate interest in, a particularly drab and unwelcoming environment. The mural consists of a number of large panels of a humorous "pop" art kind which form a continuous frieze around the area and which have kindled a lot of interest and pleasure.

Fig 4. Wood carving by Owen Crawford in the outpatient entrance hall, Royal Victoria Hospital (detail).

Several more workshops have been held in wards during the past year. Of special interest has been the introduction of a creative writing session in the ophthalmology ward. This involves patients on the day before their eye operation; it has been a useful diversionary activity and has met with considerable enthusiasm from patients and staff.

Building on the links with the University of Ulster which were established in the course of the evaluation, a special relationship has developed between the project and the University's Faculty of Art and Design. During the summer of 1992 several groups of students engaged in work within the hospital. This included a photographic project documenting staff at work in the Caves Restaurant which subsequently formed the basis of a display in the restaurant. Several sculpture students explored preliminary ideas in relation to the grassed area behind the main corridor wards, and discussions were held with staff in the Institute of Pathology about the possibility of a mural in the area. The sculpture project will be further developed during the summer of 1993 when five students will compete for a £5,000 prize (won by the Royal Group of Hospitals project through the Allied Irish Bank Better Ireland Awards in 1992). The entries will be displayed throughout the hospital so that everyone will have an opportunity to register a preference and debate the merits of the designs.

A senior student from the University of Ulster has also been funded to take a year out to work in the hospital from September 1992. Eileen Bannon is also a qualified nurse and is at present working on a large mural depicting medicinal plants growing in their natural habitats (Fig 5). The mural will draw on information supplied by the Pharmacy Department to provide a description of the plants and their medicinal properties. Eileen will have opportunity to pursue her own work during this year and will also work alongside the Art Therapist in the

Geriatric Medical Unit with the aim of learning something of this particular discipline.

Fig 5. Miral of medicinal plants by Eileen Bannon in the link corridor/bridge between the Queen's University buildings and the Royal Victoria Hospital.

In addition to developing links with the University of Ulster, the project is also reaching out to the community. More than 20 local artists have been involved in the project in one way or another: facilitating workshops, working on commissions and assisting the artist in residence with particular pieces, notably the mosaic work in the entrance hall. Several local schools have presented musical programmes in the hospital, and children from St Peter's Primary School spent a day visiting various departments and talking to staff. Their teacher subsequently asked them to describe their impressions, and the resulting essays and drawings were displayed in the foyer of Level 3.

CONCLUSION

Judging from the evaluation report and subsequent feedback from other sources, the project is achieving its aims of improving the environment and helping to relieve some of the stresses associated with being a patient or, indeed, a member of staff in a busy hospital. The project has also been successful in other ways: developing links between the hospital and the community in which it is located, providing an outlet for local artistic talent and a learning experience for students.

The project was initially funded for a period of three years, up to April 1993, but its immediate future is secure: following the submission of a detailed business proposal, the Royal Trust Board has agreed to support the post of artist in residence for another three years and further project funding has been sought from the Arts Council and other funding voluntary organisations. Discussions have been held with management and the Department of Health and Social Security with the aim of ensuring that the project has an input to the planning process for any new developments on the site; indeed, advice has already been sought in relation to the new building for the Royal Belfast Hospital for Sick Children.

The Department has recently set up ARTSCARE, an organisation which will promote and support the arts in hospitals throughout Northern Ireland. Contact has been made with all the area boards and considerable interest generated. The appointment of an artist in residence at the Royal Groups of Hospitals has provided a model of one way in which an arts project may be developed in a hospital setting, and we hope that this article and the evaluation report may be of some help to other hospitals which are considering such an appointment.

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The Ulster Medical Journal, Volume 62, No. 2, p. 162, October 1993.

Historical note

Ode to Professor Walmsley

Oh, Walmsley was a Lecturer
Of fame and great renown,
He came with high credentials
To Queen's in Belfast town.

He came to the University
'Twas on a Saturday night,
The pubs weren't closed till half past ten
and most of the boys were tight.

It pained the great man sorely,
Our condition to behold;
So his term of office started,
and he began to get quite bold.

So he tried for to amend us
Like a decent person can:
Smoking while dissecting annoys
The poor dead man.

And now no Woodbines can be seen
Or Players No 3,
Within the precincts of the hall
Where we pelted old P.T.

No livers whistle through the air
Nor spleens gas mantles break.
With muffled steps we tread the floor
For fear the dead might wake.

(Anon) After $C_2 H_5 OH$

QUB 1922

Professor Thomas Walmsley was appointed to the chair of Anatomy at Queen's in 1919 and held the post until 1951. He graduated in Glasgow in 1912. While lecturing "he combined simplicity of presentation with impressiveness in delivery and held his class spellbound"[1]. It is said that he had great influence on staff and students alike and was respected by all who came in contact with him; in his time he trained many outstanding British anatomists. He encouraged students to have respect for the cadaver and so introduced in early student life an important element of medical ethics (attitude) which is continued to this day. This would explain very clearly why smoking was banned from the dissection room and why body parts no longer "whistled through the air". These bad habits most likely slipped in between the retirement of Professor Symington in 1917 and Walmsley's arrival in Belfast.

1. T.J. Harrison 1980 Inaugural lecture. New Lecture Series 120, printed Mayne, Boyd & Son Belfast.

This little poem was passed to the Ulster Medical Journal by Dr R L Carson of Limavady and Sir Ian Fraser. Dr D J Heylings of the Department of Anatomy, The Queen's University of Belfast has kindly provided the explanatory note.

The Ulster Medical Journal, Volume 63, No. 2, pp. 163 - 165, October 1993.

Case Report :

Peritoneal mesothelioma

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Primary mesotheliomas are rare tumours derived from the mesothelial cells of major serous cavities. They most commonly occur in the pleural cavity, but in recent years the incidence of peritoneal mesothelioma has been increasing. The prognosis for these tumours is generally poor, death normally occurring within one year of diagnosis, but can be improved by earlier diagnosis and aggressive management [1].

The non-specific presentation, and confusion with other more common intra-abdominal neoplasms make early diagnosis difficult. Appropriate investigations together with a high index of suspicion are therefore important if early diagnosis is to be made. We present a case which illustrates many features typical of this condition and which highlights important aspects of its management.

CASE HISTORY:

A 58 year old joiner presented with a history of abdominal pain, distension, weight loss and night sweats. He had a past history of asbestos exposure. On examination he was pale, with clinical signs of ascites. Haemoglobin was 10 g/dl, serum alkaline phosphatase 117 U/1 and ESR 90 mm/hr. Ultrasonography confirmed ascites. Barium enema showed no abnormality in the large bowel. Computed tomography of the abdomen demonstrated peritoneal thickening with metastatic deposits in the greater omentum, but diagnostic peritoneal aspiration was uninformative. Tumour markers CEA and CA19-9 were normal. Diagnostic laparoscopy revealed blood stained ascitic fluid with gross thickening of the peritoneum, biopsy of which showed mesothelial proliferation in a papillary configuration with nuclear atypia, consistent with malignant mesothelioma. It was decided that neither chemotherapy nor surgical intervention beyond repeated aspiration was appropriate. The patient remains well five months following diagnosis having had several admissions for peritoneal drainage to provide symptomatic relief.

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DISCUSSION

Primary peritoneal mesothelioma is a rare tumour. It accounts for approximately 10% of all malignant mesotheliomas although some sources quote figures as high as 40% [2]. There is an increasing incidence in the United Kingdom [3]. Males are more commonly affected than females, the male/female ratio in the United Kingdom being 10 : 1[4,5]. When the condition arises in childhood it tends to follow a similar clinical pattern to that in the adult [6]. Asbestos exposure has been cited as a major factor in the development of the disease[7], but a considerable period up to a mean of 44 years may elapse between exposure and diagnosis [8].

Peritoneal mesothelioma often presents at an advanced stage with non-specific symptoms such as abdominal pain, weight loss, anorexia and abdominal distension. Rarely it has presented with small bowel obstruction, an "acute abdomen" or symptoms suggestive of testicular torsion [9]. The most common finding on examination is ascites, present in more than 95% of cases. The patient may be anaemic or more rarely have a metabolic upset due to ectopic hormone production[10,11].

Most mesotheliomas have been diagnosed at autopsy, but increasing numbers are now diagnosed ante-mortem. A normal CEA level helps to exclude a diagnosis of intra-abdominal adenocarcinoma. Radiological abnormalities are non-specific; ultrasonography will reveal ascitic fluid and intra-abdominal masses, and computed tomography will demonstrate peritoneal thickening. Peritoneal fluid aspiration provides a cytological diagnosis but carries both a high false positive and false negative rate[13]. Until recently laparotomy offered the only sure method of diagnosis, but laparoscopy has now become invaluable and provides an opportunity for histological diagnosis and visual assessment of the extent of the disease process with relatively little patient upset.

Whitwell and Rawcliffe offered the first histological classification of mesotheliomas in 1971[14]. They described three histological subtypes, epithelial, diphasic, and fibrous. The majority of peritoneal mesotheliomas are of the epithelial form. Until recently the management of this tumour could do little to alter its bad prognosis. Surgical intervention may provide the diagnosis, but otherwise is limited to debulking the tumour and relieving bowel obstruction. Many chemotherapeutic regimes have been tried, the best results being from cisplatinum and doxorubicin compounds[15].

Peritoneal mesothelioma is a highly malignant condition. Its development is linked with asbestos exposure, which is relevant to the population of Northern Ireland with its high reliance on the shipbuilding industry in the past. Early diagnosis requires a high index of clinical suspicion and should be considered in patients presenting with ascites in whom serological and radiological investigations have proved uninformative.

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Case Report

Postsplenectomy sepsis: a lifelong risk

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Overwhelming postsplenectomy infection is a term used to describe the clinical syndrome of fulminant bacteraemia, disseminated intravascular coagulation, multi-organ failure, severe hypoglycaemia and rapid death which has been described in patients who have been splenectomised for a variety of reasons.[1,2] Whilst the highest mortality has been reported in the early post-operative period and in the immunosuppressed[3], the following cases illustrate the fact that splenectomy carried out at any age and for any reason increases the risk of overwhelming bacterial infection. Therefore vigilance and continuing education are always required on the part of patients and their physicians.

CASE 1

A 63 year old male had a splenectomy performed in childhood following a road traffic accident. He felt slightly unwell, developed a temperature and became confused and agitated. Some 12 hours after the onset of confusion he was admitted to hospital. He was not taking prophylactic antibiotics and there was no record of pneumococcal vaccination. He was allergic to penicillin.

On admission his temperature was 38°C. He was noted to be very confused and agitated. There were no localising signs. He was commenced on erythromycin, and cefotaxime was then added.

Coagulation screening tests on admission showed disseminated intravascular coagulation which progressed despite attempts at correction. Deteriorating blood gas measurements necessitated intubation and ventilation, but despite continued aggressive resuscitation he died within 24 hours. Blood cultures taken before commencement of antibiotics identified streptococcus pneumoniae.

CASE 2

A 37 year old male had had a splenectomy when aged 13 years following abdominal trauma. He presented to hospital with a three day history of feeling feverish and vaguely unwell. He was not taking antibiotics and there was no record of vaccination. On examination his temperature was 39°C, blood pressure

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was 105/65mmHg and there was a widespread purpuric rash. Coagulation screening tests showed disseminated intravascular coagulation. Therapy was instituted with benzylpenicillin, dobutamine and fresh frozen plasma. Pre-antibiotic blood cultures identified *streptococcus pneumoniae.* He gradually improved but developed gangrene of the feet and all fingers, necessitating bilateral below-knee amputations and amputation of all fingertips. On pathological examination of the amputated limbs occlusion of the small vessels was confirmed consistent with a diagnosis of disseminated intravascular coagulation.

CASE 3

A 62 year old male had had a splenectomy in 1977 at age 47 for an acute haemolytic crisis in association with hereditary spherocytosis. He was found at home confused and faecally incontinent. Relatives gave a history that he had been vaguely unwell for several days. There was no record of vaccination and the patient was not taking prophylactic penicillin. On admission to hospital he was confused and obviously unwell, temperature 38°C, blood pressure 80/50mmHg. There were no localising signs. Despite intensive resuscitation including intravenous penicillin, gentamicin, metronidazole and ciprofloxacin he deteriorated. Disseminated intravascular coagulation present on admission improved with intervention, but he remained hypotensive and developed anuria. Increasing hypoxia and acidosis necessitated intubation and ventilation but he continued to deteriorate and died within 15 hours of presentation. No organism was identified from pre-antibiotic blood cultures or from post-mortem bacteriological examination. Autopsy confirmed the presence of a consumptive coagulopathy with bilateral massive adrenal haemorrhage and it was concluded that septicaemia was the cause of death.

DISCUSSION

The incidence of overwhelming postsplenectomy infection varies according to the study but has been reported as high as 6.9%,[4]. Although more common in the three years following surgery, sepsis can occur at any time. In case 1 more than 45 years had elapsed from the time of splenectomy until death, and the overall mortality is at least 50%[5]. There is still debate about whether there is any increased incidence of infection and death post-splenectomy[6].

The most common organism is *streptococcus pneumoniae* causing over 50% of infections[7]. Other organisms in decreasing frequency of infection include *haemophilus influenzae, neisseria meningitidis and e.coli.* No organism was isolated from case 3 although clinically and pathologically the diagnosis was not in doubt. Rarely in cases like this no organism is isolated, and the possibility of viral or other unidentified organism then arises.

Our case histories highlight several important points. All patients had a prodromal illness. If the patients and their families had understood the significance of urgent treatment of any prodromal symptoms, death might have been prevented. None were on prophylactic penicillin or had immediate access to antibiotics. They had not been vaccinated as splenectomy had been performed many years previously.

Opinion is divided over the use of prophylactic antibiotic therapy. Prophylactic penicillin does not always prevent overwhelming postsplenectomy infection as

sporadic case reports illustrate.[8,9] Zarrabi et al[10] reviewed all case-reports where patients were definitely stated to be receiving prophylactic penicillin. In only five out of fourteen did the patients have penicillin-sensitive pneumoccal infection. While the exact incidence of failure of penicillin prophylaxis cannot be calculated it would seem to be rare. Patient non-compliance must also be considered.

Traditionally penicillin has been used, but as up to 50% of infections are caused by non-pneumococcal organisms ampicillin has also been considered[3]. It would probably not be ethically acceptable to carry out a randomised long-term prospective study to decide the issue of prophylactic penicillin but retrospective data demands that the post splenectomy patient must be protected from overwhelming postsplenectomy infection as far as is possible.

The question of pneumococcal vaccination is also pertinent. Polyvalent pneumococcal vaccine is helpful in preventing pneumococcal infections in immunocompetent patients[11]. Post splenectomy the response to vaccination is impaired[12] but useful responses can be obtained[13]. Response to vaccination may also be impaired in the immunocompromised but some clinical effect is recognised.[14] Although the underlying disease and its treatment will affect the antibody response to vaccination these are not contra-indications. No vaccine is 100% effective. Pneumovax will not prevent infection with strains of pneumococci not represented therein.[12] Despite these reservations there are protective effects to be gained from vaccination. Current Department of Health guidelines recommend that pneumococcal vaccine is given, if possible, two weeks before splenectomy. Should vaccination prove impossible prior to surgery then it is recommended that it is carried out post splenectomy. Patients who have had a splenectomy and have never been vaccinated should be immunised at any opportunity that arises. In the splenectomised patient vaccination should be given every 5 to 10 years[14].

In cases of trauma, splenic salvage should be attempted where possible. Where operation is required, splenorrhaphy, partial splenectomy or heterotopic autotransplantation should be attempted[16].

Oral penicillin 250mg twice daily prophylactically for life is also advisable. In allergic patients erythromycin could replace penicillin. In these cases and those patients unlikely to comply with lifelong prophylaxis patient education is imperative. An informed discussion between patient, hospital doctor and general practitioner will help to ensure at least availability of an emergency antibiotic supply and awareness of the possible significance of prodromal symptoms. Wearing an engraved medic-alert bracelet may also be of value. In cases of trauma, conservation of any viable splenic tissue has a role. Increased awareness of the lifelong risk of splenectomy may help to avoid tragedies.

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Case Report

Acute thyroxine overdosage: two cases of parasuicide

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Factitious hyperthyroidism is a well documented clinical entity where the signs and symptoms of hyperthyroidism are self-induced by the chronic ingestion of excessive amounts of thyroxine [1, 2]. The acute ingestion of large amounts of thyroxine might be thought to carry a risk of acute thyrotoxicosis, but despite high plasma levels of thyroxine this may not be so. Previous reports suggest that such cases are largely asymptomatic [3], but the majority of these have been in children [4-7]. There are few guidelines available for the specific management of acute thyroxine overdose in adults, where the amount ingested is usually relatively larger and treatment is more likely to be delayed. Two cases are presented where large amounts of thyroxine were taken in attempted suicide.

CASE 1. An attention seeking 14 year old girl was admitted to the metabolic unit about 15 hours following an overdose of about 100 mixed tablets, including ferrous sulphate, multivitamins and 0.1mg tablets of thyroxine. Over 3mg of thyroxine had been taken. She had vomited once nine hours after ingestion, and on admission complained of dizziness. No formal gut decontamination (emetics and/or lavage) was performed. She did not exhibit flushing, sweating, tremor or agitation and her temperature was normal. Her pulse was 80/min regular, blood pressure 110/80 mmHg. Repeat measurements of pulse and blood pressure were made at two hourly intervals for the next three days. The maximum pulse rate was 92/min. An electrocardiogram showed sinus rhythm. Her initial dizziness settled within a few hours. Serum free thyroxine (FT_4), total triiodothyronine (TT_3), and TSH were measured as shown (figure 1). She was discharged after three days and followed up for blood monitoring as an outpatient.

CASE 2. A clinically depressed 40 year old woman had been taking 0.2mg thyroxine daily for one year for primary hypothyroidism. She was admitted four hours after taking approximately ninety-five 0.1mg thyroxine tablets and a considerable amount of alcohol. Initially she was drowsy but rousable. Ipecacuanha was given and induced vomiting successfully. She had a fine tremor but there was no flushing, sweating, agitation or pyrexia. A regular tachycardia of 100 beats per min. was recorded which fell to an average of 78 beats per min after 18 hours.

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The initial blood pressure was 150/90 mmHg and fell to 130/80 mmHg after four hours. Serum free thyroxine and TSH levels were measured as shown (figure 1). She remained asymptomatic and after six days was transferred to a psychiatric unit for treatment of her depression, where further serum free thyroxine and TSH measurements were made.

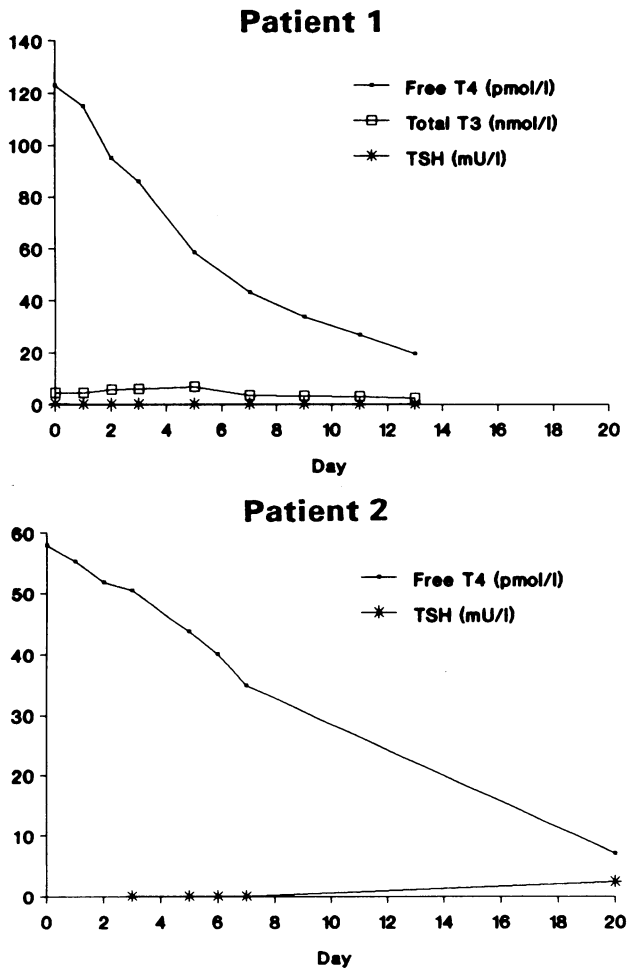

FIGURE 1. Serum free thyroxine (FT_4), total triiodothyronine (TT_3) and TSH levels in patients 1 & 2 following acute thyroxine overdose.

Laboratory reference ranges

Free T4:	10.5	– 25.5	pmol/l
Total T3:	0.3	– 1.5	nmol/l
TSH:	0.1	– 4.5	mU/l

DISCUSSION

Most of the reported cases of acute l-thyroxine ingestion have been in children. Although serious sequelae are generally rare, management is still justifiably aggressive when the child is even vaguely symptomatic. A combination of gut decontamination, antithyroid medication and beta blockade are standard measures [6,7,8]. There are no guidelines for the management of adult cases where the amount consumed is usually relatively larger, the presentation more likely to

be delayed, and the metabolism of the drug slower. Both of our patients had minimal intervention and yet, despite very high levels of serum thyroxine, they were essentially asymptomatic.

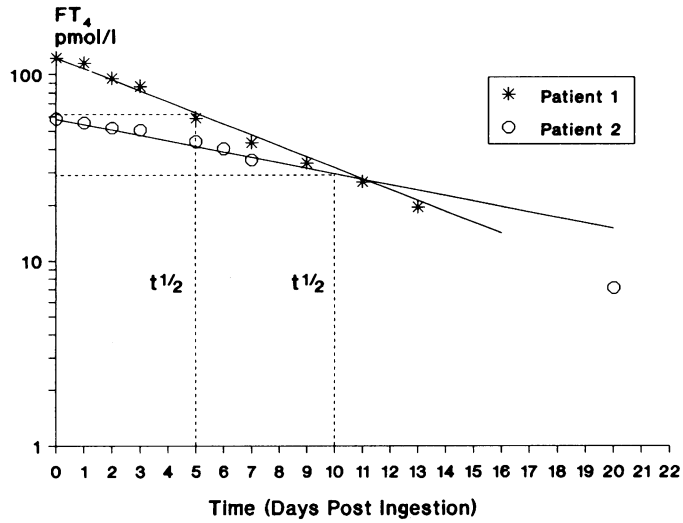

FIGURE 2. Decrease in serum free T4 following acute thyroxine overdose: (Log scale to allow calculation of T ½ (half life of thyroxine)

Estimated T ½ patient 1: 5 days
Estimated T ½ patient 2: 10 days

Calculation of the serum thyroxine half lives compared well with standard values of 6-7 days [9,10] (Fig 2). The longer estimate in case 2 may be explained in terms of age-related decreased tissue turnover. Serum total T_3 measurement in case 1 illustrates the slow conversion of T_4 to T_3 in the periphery, the peak level of T_3 being reached in five days. Serum TSH levels are predictably suppressed.

Paediatric **studies** suggest that when the body is presented with such large doses of T_4 there is greater production of the biologically inactive reverse T_3 (rT_3) which tends to maintain a euthyroid state. This pathway is enhanced by both exogenous and endogenous steroids and in any extrathyroid illness. This should decrease the risk of thyroid storm after T_4 overdose, [5,6,13,14,15] and down-regulation of the cell nuclear triiodothyronine receptors might also contribute [6].

Thyroid storm following a massive ingestion of the hormone in children is thought to reflect high serum free T_4, and free T_3 levels, combined with hepatic and renal impairment. Tissue levels of thyroid hormone would appear to be more significant in adults, as a storm or crisis may develop as late as five days after the insult when serum levels are much reduced [10]. A thyroid crisis is characterised by a rising temperature which may rapidly reach a lethal level, tachycardia progressing to atrial flutter or fibrillation, a widened pulse pressure, extreme agitation, flushing, sweating and diarrhoea. The patient can become comatose in under 36 hours if the cause is not identified at a very early stage [1,17,18].

Only four other cases of acute thyroxine ingestion in adults have been published [10,13,14,15]. All had formal gut decontam-ination and all required propranlol for the treatment of tachycardia. None developed a thyroid storm despite T_4 levels ranging from three to 16 times the average level. The cases presented here required no symptomatic treatment at all, despite levels that were seven times higher than normal. As thyroid storm carries a mortality of up to 75%, [1,18] prevention is the key to management: although we did not encounter any problems with an expectant approach, these cases would seem to be unusual.

In conclusion, the risk of acute thyroxine overdose in adults is slight, but the patient should be closely monitored for at least five days as an inpatient. Prophylactic propranolol may be of benefit if not otherwise contraindicated. Although the initial measurement of serum thyroxine levels may give a rough indication of the absolute quantity of hormone consumed, our results, and those in the literature suggest that further measurements in adults give a poor prediction of clinical outcome.

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Case Report

Myocardial infarction in association with misuse of anabolic steroids

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Abuse of androgenic and anabolic steroids is becoming both a medical and public health problem. It is generally underestimated just how prevalent steroid abuse is amongst young sports people. Vascular thrombosis (myocardial infarction,[1] stroke,[2] arterial thrombosis in a limb[3]) has been documented in the USA in steroid abusing athletes in the past decade. The problem is now appearing in Britain, and two cases of myocardial infarction and one of pulmonary embolus associated with steroid abuse have been documented since 1990.

CASE REPORT. A 24 year old competitive bodybuilder presented three days after development of recurrent, dull central chest pain radiating to his left arm. He had been aware of similar, less severe episodes over the previous six weeks, which he had attributed to muscular strain after heavy weight-training. He spontaneously admitted to use of anabolic steroids for two years — taking multiple steroid preparations in mixed dosage forms, both orally and by intramuscular injection, at high doses for a prolonged period — a process called "stacking and cycling" by those involved.[4]

Over the last six week cycle he had been taking oral stanozolol 40 mgs daily, nandrolone 200 mgs intramuscularly twice weekly, and Sustanon 250 (testosterone esters) 1 ml intramuscularly once a week. He also smoked 30 cigarettes daily — a 10 year habit. There was no family history of heart disease or lipid disorder.

Serial electrocardiographs and cardiac enzyme measurements confirmed lateral myocardial infarction. Serum creatine kinase (myocardial subfraction) rose from 42 to 68 units in 24 hours and fell to 33 by 48 hours. The percentage of this enzyme rise increased from 6 to 14%. (More than a 7% rise is diagnostic of myocardial necrosis). Fasting lipid measurements showed a raised serum total cholesterol (8.5 mmol/l) and low HDL cholesterol (0.7 mmol/l),giving a ratio of 12:1 (the normal ratio is less than 6:1). Fasting serum triglyceride was 1.65 mmol/l (normal range 1.2 — 3.0 mmol/l).

Echocardiogram showed a normal sized heart with good left ventricular function and a small area of apical infarction. Exercise stress testing under the modified Bruce protocol gave a total exercise time of 17 minutes, without chest pain and

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the test was terminated due to fatigue. Blood pressure and pulse rate rose with exercise as would occur in a normal healthy individual. At submaximal exercise he developed frequent ventricular ectopic beats with couplets and bigeminy. These ectopic beats decreased at peak exercise and recurred again in the early recovery period. He also developed ST segment elevation in standard lead 1 and the anterolateral chest leads, which reverted to normal after six minutes.

His blood pressure remained intermittently elevated (maximum 195/110 mmHq) and he was treated with atenolol 100 mg daily and aspirin. He was not started on a cholesterol-lowering agent as the lipid profile should improve once the anabolic steroids are discontinued. He was advised to stop all steroid abuse, to stop smoking, to avoid weight-training, and was encouraged to do moderate aerobic exercise. He is awaiting coronary angiography.

DISCUSSION

Although hypertension and adverse lipid profiles are well established side effects of anabolic steroid overdose, acute thrombosis has been linked only recently to androgen abuse. There is no direct evidence that these steroids are thrombogenic but experimental data suggests they probably facilitate thrombosis by an effect on platelet aggregation and on coagulation proteins.[5,6,7] In this case the aetiological factors favouring thrombosis would seem to be the adverse lipid profile and hypertension conferred by use of steroids; anabolic exercise (weight training in itself imparts a negative effect on lipids which is amplified when abusing steroids); cigarette smoking; and the possibility of steroids affecting platelet function and the clotting factors. At a molecular level steroid abuse produces mitochondrial and myofibrillar changes similar to those seen in early heart failure.[8] In athletes who die suddenly there is a higher incidence of right ventricular cardiomyopathy, although there is no direct evidence to link this to steroid abuse. Echocardiographic studies show concentric left ventricular hypertrophy and altered pressure-volume relationships within the heart, but in comparative studies between steroid-users and non steroid-users no statistically significant difference in left ventricular function could be found.[9]

It is well known that serious side-effects can be attributed to anabolic steroids. These may occur within weeks (decreased reproductive function, altered serum transaminases or deleterious lipid profile) or take years to develop, such as hepatocellular carcinoma. All the early side-effects are reversible provided the drug abuse is discontinued. Greater public awareness of the problem of steroid misuse is necessary. By and large, the medical community do not recognise the wide availability of the compounds or the prevalence of their misuse.

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Case Report

Odontoid peg metastasis from an oesophageal adenocarcinoma.

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Accepted 13 August 1993

Metastasis to the odontoid peg is a rare condition. We report a case where such a metastasis from an oesophageal adenocarcinoma caused problems in both diagnosis and management. This is the first case to our knowledge to originate from a primary oesophageal adenocarcinoma.

CASE REPORT. A 58 year old male was admitted with dysphagia and weight loss. Investigations revealed a lower oesophageal adenocarcinoma and he underwent oesophagogastrectomy. Histopathology of the resected specimen confirmed a poorly differentiated infiltrating adenocarcinoma extending through to the serosal fat. The resection limits were clear and there was no evidence of distant metastases.

On the thirteenth postoperative day he complained of neck pain and paraesthesiae in the C3 distribution bilaterally; he stated that he had experienced these symptoms before. Cervical spine X-rays showed only degenerative changes, although details of the odontoid area were partially obscured. He was treated with simple analgesics and a soft cervical collar followed by gentle mobilization. He was discharged well on the twenty-fifth postoperative day but still had some neck pain.

Three months later, he presented again with a three day exacerbation of neck pain, localised to the base of the skull posteriorly and with no associated neurological symptoms. Examination revealed cachexia, tenderness over C2/3, markedly reduced cervical spine movements but no abnormal neurological findings. X-rays now showed the odontoid peg to be very ill-defined with marked atlanto-axial subluxation.

Attempted per-oral fixation of the odontoid fracture in the Regional Neurosurgical Unit proved unsuccessful due to the degree of bony erosion, and bone biopsy only was performed, which showed adenocarcinoma consistent with gastrointestinal origin. His condition condition continued to deteriorate until his death ten days later from bronchopneumonia.

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DISCUSSION

Metastasis to the odontoid peg is uncommon[1] and metastasis to the C2 vertebra from a primary oesophageal neoplasm has not been reported previously. More usual primary sites for bony cervical metastasis reported include breast, lung, nasopharynx, tongue, stomach, colon, liver, urinary bladder and rhabdomyosarcoma[1-6]. The cervical spine is particularly vulnerable to the destructive effects of tumour invasion[7]. Odontoid peg involvement by metastatic tumour is usually caused by haematogenous dissemination, although direct extension of adjacent neoplasm may occasionally occur. The bone becomes distorted, fragile and more vascular; pathological fracture may occur [2,4].

The odontoid is an important component of the upper cervical spine, allowing free head motion, particularly rotation, and affording protection to the upper spinal cord. Most cervical metastases lie anteriorly to the cord, are small and involve more than one segment[1,4,5,7]. With progression, atlantoaxial instability results in subluxation and cord compression, although extradural tumour spread may also cause compression.

Odontoid metastases usually present around three years after the primary, and the symptoms commonly precede the diagnosis by several weeks to months. The lesion presents with a variety of features, many of which are common to nonpathological fracture. As in our patient, neck pain with suboccipital headache is virtually universal. Common presentations include symptoms of lower cranial or upper cervical cord compression and may include dysphagia from retropharyngeal haematoma. Markedly restricted rotation is an important clinical finding. Other clinical signs include those of cord compression, although lower limb weakness is not commonly found .

The only reliable means of diagnosis is by careful radiology [8,9], and our case demonstrates several of the pitfalls which may occur. Minimal X-ray studies of the odontoid peg and the body of the axis should include views through the open mouth as well as the lateral aspect. Common radiographic findings are of lytic destruction of the entire C2 vertebra, but this may remain unnoticed until the manifestation of clinical symptoms. Degenerative changes in the lower cervical spine, common in this age group, may distract from the odontoid lesion. Flexion and extension views of the cervical spine risk fatal displacement and must be avoided.

CT scanning, with or without myelography, delineates the extent of tumour invasion of bone and soft tissue, and provides additional information on the presence of epidural tumour and the available space for operative intervention [4,5]. The importance of obtaining a tissue biopsy to confirm the presence of metastatic carcinoma before embarking on any therapeutic regimen has been rightly stressed.

The management of metastatic fracture of the odontoid peg is both demanding and controversial [3,4]. Treatment options include initial immobilisation with high dose steroid therapy, bony fusion and radiotherapy, bony fusion alone, cord decompression with fusion, or stabilisation with bone cement, wires, plates or autografts with or without pre- or postoperative radiotherapy. The treatment goal is to alleviate pain, relieve spinal cord compression and stabilise the cervical spine. The treatment must consider the limited life expectancy of these patients

and the extent of their systemic disease. Even if curative action is unlikely, pain and threatening neurological deficit demand active intervention, and pain alone may be the main indication for surgery. Operative stabilisation should be considered in most patients, particularly if life expectancy is estimated as greater than one year. Aggressive treatment is becoming more common due to the longer survival resultant upon improved management of malignant disease. Stabilising surgery will improve the quality of life but may not improve survival time[2-7]. If the neoplastic disease process can be therapeutically altered, the value of cervical spine stabilisation in the cancer patient becomes even more marked. The survival time after the onset of neck pain ranges from one month to seven years and depends upon the type and site of the primary tumour. Reported postoperative survival times range between one and thirty months [1, 3, 5].

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Case Report

Intravenous mercury: a three year follow-up

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Accepted 20 August 1993

The clinical course following intravenous metallic mercury is unknown and ideal management has not been defined. The effects of a bolus dose seem to vary from the inconsequential to the rapidly fatal.

CASE REPORT. A previously healthy twenty-six year old woman presented to casualty about one hour after self - injection with metallic mercury using her boyfriend's insulin syringe. The mercury had been taken from an old thermometer in an attempt at suicide following an argument. She smoked 20 cigarettes a day; there was no previous medical history. On examination there was some localised inflammation in the right ante-cubital fossa and mercury was palpable subcutaneously. There were no other abnormal physical findings. Radiological examination of the chest and the ante-cubital fossa confirmed the presence of mercury in the forearm veins and in the pulmonary vasculature (Figs. 1 and 2).

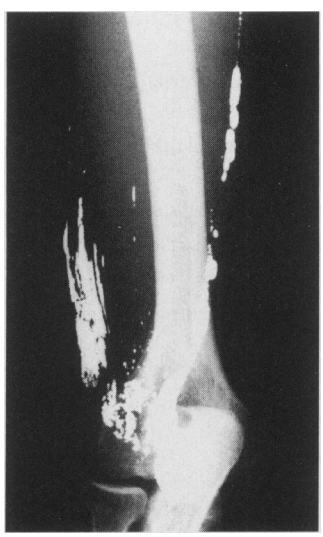

Fig 1. X-Ray of arm showing metallic mercury in the antecubital fossa and venous drainage.

Fig 2. Multiple metallic densities are seen in the distribution of the pulmonary vascular bed.

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She was commenced on intramuscular dimercaprol for 11 days followed by a two year course of its oral analogue dimercaptopropane-1-sulfonate (DMPS). During the second week she was treated with oral penicillamine. Ten days after admission much of the mercury remaining in her forearm was surgically removed. Two years after treatment with DMPS had been commenced, it was discontinued at her request as she found it inconvenient and was not convinced it was of any continuing benefit.

Throughout the three year follow-up she remained asymptomatic. Blood gases on admission showed a partial pressure of oxygen(PaO_2) of 104 mmHg, which deteriorated after four days to 85 mmHg but subsequently returned to normal. Pulmonary function tests were performed after 17 days: forced expiratory volume in one second was 122% predicted, forced vital capacity 122% predicted residual volume 51% predicted and total lung capacity 96% predicted. Transfer factor was 72% predicted by the single breath technique and when corrected for lung volume 94% predicted. These improved after one month when transfer factor was 81% predicted and 100% predicted when corrected for lung volume. Forty months after presentation transfer factor was 85% predicted and when corrected for lung volume 95% predicted. Chest x-ray remained unchanged throughout the clinical course.

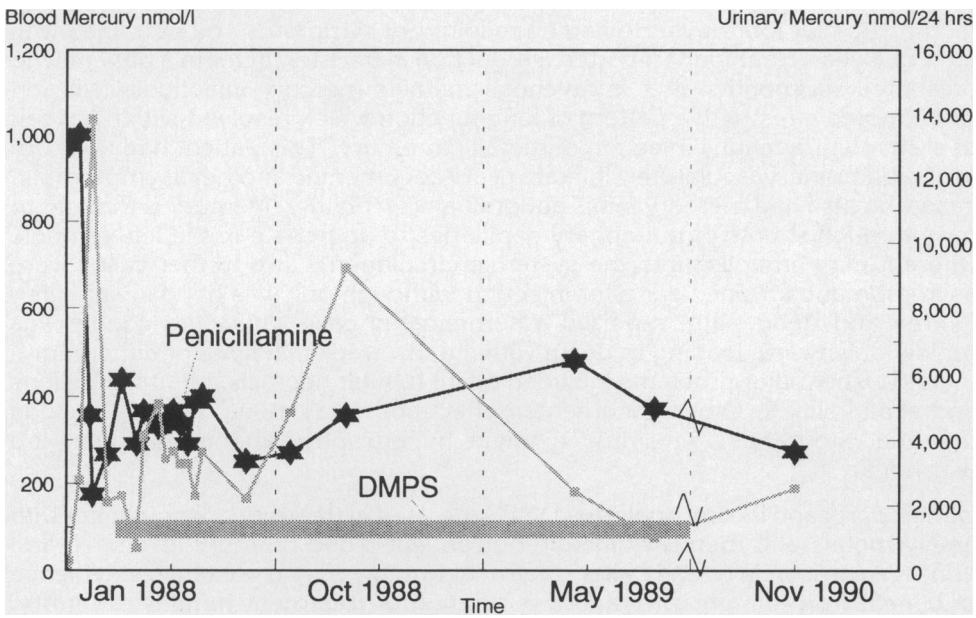

Fig 3. Graph to show changes in serum and urinary mercury levels. Serum mercury (black line) showed a rapid initial fall, urinary mercury (grey line) a transient rise on treatment. Both remain considerably elevated above normal after three years.

Full blood picture, liver, renal and thyroid function tests have remained within normal limits. Serum and urinary mercury levels have been monitored over the three year follow-up. Blood mercury levels which were initially 1000 nmol/l fell to 300-400 nmol/l [normal less than 25 nmol/l] after administration of DMPS and have remained at that level following the discontinuation of this treatment.

Urinary collections for mercury have been less consistent but rose from 300 nmol/day to nearly 13,000 nmol/day when DMPS was commenced. Urinary excretion fell to around 3,000 nmol/day within a few weeks and has remained fairly constant in spite of stopping the DMPS. Normal urinary mercury excretion is less than 100 nmol/day (Fig. 3).

DISCUSSION

Giobetti *et al.*[1] reviewed 24 previously published reports of intravenous injection of metallic mercury which included ten cardiac catheterisation accidents. At least 12 of the patients who were followed up remained asymptomatic throughout. Two cardiac catheter accidents were complicated by neurological signs and symptoms which were consistent with systemic emboli. Two further patients developed sepsis and one died. Seven patients reported pleuritic chest pain but only four complained of dyspnoea. Abnormal pulmonary function tests and blood gases were much more common than symptoms but most seemed to resolve. Five patients had evidence of renal disease, varying from proteinuria to a decline in the creatinine clearance and elevation of urea. Treatment of these patients for mercury toxicity was not documented.

Ambre *et* al.[2] reported the case of a 31 year old man who was noted to be hypoxic (PaO_2 77 mmHg) following 1ml intravenous metallic mercury. His PaO_2 was 92 mmHg after four days. He had no respiratory symptoms and remained well after one year. Hannigan[3] reported a reduction in transfer factor in a patient who presented six months after intravenous metallic mercury injection. Celli and Khan[4] noted a restrictive pattern of lung function which resolved within a week of a 20 ml intravenous injection of metallic mercury. This patient had mercury in his abdominal vasculature. Chitkara et al.[5] documented another asymptomatic case who also had mercury in his abdominal vasculature. Mercury is thought to pass through shunts or pulmonary capillaries to aggregate in the left ventricle where it may embolise into the systemic circulation[6]. Two further cases were asymptomatic for one year after injection, although one was hypoxic initially[7]. Murray and Hedgepath[8] reported a complicated case where the course was rapidly downward, leading to death within a few weeks, in spite of dimercaprol therapy. The major problems included acute tubular necrosis, pleural effusions and septic shock. Other documented effects of intravenous mercury include urticaria, stomatitis, gingivitis, gingival hypertrophy, abdominal pain and diarrhoea.

Dimercaprol and its oral analogue DMPS are used in treatment of poisoning with heavy metals and mercury salts. In our patient blood mercury levels fell and urinary excretion increased after treatment but there is no conclusive evidence of benefit from dimercaprol and the duration of treatment remains arbitrary. Known side-effects of dimercaprol therapy include hypertension, tachycardia, nausea, vomiting, lachrymation, sweating, burning sensations, constriction of the throat and chest, headache, muscle spasm, abdominal pains, tingling of the extremities and pyrexia in children.

Most reported cases of administration of intravenous metallic mercury have remained well. Some patients develop a reduction in transfer factor which is often asymptomatic and seems to recover. Variable renal and neurological sequelae have also been documented. Treatment with dimercaprol or another chelating agent may be of some benefit but the outcome remains variable.

I would like to thank David Bryce for producing the graph, and Dr R Lowry and Dr G Daly for reading early drafts of this report.

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MONICA/ECTIM Meeting Report: Heart attacks in France and Northern Ireland.

23-24 April 1993

INTRODUCTION

The MONICA centres in Belfast, Lille, Strasbourg and Toulouse have taken part in the WHO coordinated MONICA (MONItoring in CArdiovascular diseases) Project since the early 1980s. In order to test the Project's main objective to investigate the relationships between 10 year trends in the major CVD risk factors (serum cholesterol, blood pressure and cigarette consumption) and 10 year trends in incidence rates, the centres register coronary events and carry out risk factor surveys. The registration of events validates a four-fold greater incidence of ischaemic heart disease in Belfast than Toulouse, and the risk factor surveys show that the major risk factors are identical between these two centres. A dietary comparison also shows no important differences apart from a higher polyunsaturated fat, wine, cheese, fruit and vegetable intake in Toulouse (See Abstract 3).

Since 1988 a programme of studies has been mounted in the four centres. A large case-control study (ECTIM) completed its intake of 1,474 cases and controls in 1992 (See Abstract 4). In Belfast the ECTIM Study has been extended to women and into the families of the probands. PRIME, a cohort study began recruitment in 1991 (See Abstract 22). This recruitment will be concluded in the autumn of 1993 with a total intake of 11,000 middle-aged males in Northern Ireland and France; thereafter, there will be a 5 - 7 year follow-up. Intervention studies are also planned within this research programme.

This major collaboration, in addition to the four MONICA centres, involves several laboratories in Northern Ireland and France.

The two day meeting at Queen's University, held in conjunction with the Irish Hyperlipidaemia Association, was attended by 50 visitors from France, Switzerland, Spain, Scotland, England, Wales and the south of Ireland. It was opened by Dr Ivan Gyarfas, Chief of Cardiovascular Disease in WHO, Geneva. Key items presented and discussed were the deletion polymorphism of the ACE gene which has been identified as a risk factor for myocardial infarction in the ECTIM Study (See Abstract 9 and 19); the HVR48+ polymorphism of the apolipoprotein B gene which carries a high odds ratio for myocardial infarction in overweight subjects in Belfast and France (See Abstract 12); and polymorphisms of the lipoprotein lipase gene (See Abstract 15) which also appears to predispose to myocardial infarction. The major lipid difference between the French and Northern Irish populations is a lipid profile characterised by high levels of LpE:B and Lp(a)B and low levels of LpA1 in Belfast (See Abstract 7).

In conclusion, the contribution of molecular genetics to traditional epidemiology is immense as we are beginning to understand how environmental risk factors interact with the individual's genetic constitution.

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HEART ATTACKS IN NORTHERN IRELAND

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The Belfast MONICA Project has been registering coronary heart disease events as part of the WHO coordinated Project since 1983. The area covered is to the east of the Province (Belfast, Castlereagh, North Down and Ards Health Districts) with a total population of 510,000 persons. Despite its pre-eminence in ischaemic heart disease mortality during the 1980s when it vied with Scotland for the premier position in age-standardised rates for both men and women (40-69 years), over the decade 1980-90 statutory age-standardised IHD mortality data showed a 30% decline in men and a 25% decline in women (40-69 years). MONICA event registration data for males aged 25-64 years in Belfast showed a peak in 1984 of 431/100,000, with a decline to 272/100,000 in 1990: the corresponding rates in females were 137 and 100/100,000. Population surveys took place in 1983-4, 1986-7 and 1991-2 and risk factor data were assembled. Applying two multiple logistic function scoring systems (UK Heart Disease Prevention Project - age, cigs, chol, systolic BP and BMI and the British Regional Heart Study - age, cigs, chol, HDL-chol, mean BP and BMI), which estimate the chance of developing heart disease over the subsequent 4-5 years, resulted in trends which were broadly in agreement with the trends in incidence.

HEART ATTACKS IN FRANCE: CORONARY MORTALITY AND MORBIDITY, GEOGRAPHIC AND TEMPORAL TRENDS (1985-89)

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The three French MONICA centres are located in the areas of Toulouse (TOU), Strasbourg (STRA) and Lille (LIL), respectively in the south, east and north of the country. They cover similar sample size populations (about 500,000 inhabitants, aged 35-64 years). Acute coronary events are monitored and classified following the MONICA protocol but taking also into account medical diagnoses or death certification. There were 11,310 coronary acute events (ALL) with 57,331 definite acute myocardial infarctions (AMI) and 3,004 coronary deaths (CD) for the period 1985-89. Male cases made up 81% of ALL.

The first table gives age-standardized mean annual rates per 1000 for AMI, ALL and CD. Except for AMI, rates are slightly lower in TOU, particularly in females.

	MALES				FEMALES			
	TOU	STR	LIL	p	TOU	STR	LIL	p
AMI	1.82	2.13	1.73	≤0.001	0.22	0.43	0.28	≤0.001
ALL	3.53	4.10	3.91	≤0.001	0.56	0.98	0.85	≤0.001
CD	0.77	1.13	1.16	≤0.001	0.13	0.26	0.22	≤0.001

The second table gives age-standardized trends estimated from a logistic regression model and expressed as a relative percentage variation of rates during the period (men only).

	TOU	p	STR	p	LIL	p
AMI	–4	ns	–13	≤0.05	–25	≤0.001
ALL	+6	ns	–6	ns	–18	≤0.001
CD	–32	≤0.001	–21	≤0.02	–19	≤0.05

In general, all rates are decreasing in LIL, but attack rates for all events are stable in TOU and STR. CD are strongly decreasing in all centres in agreement with official death statistics. Coronary morbidity and mortality are not homogeneous in France. Such a geographic and temporal variability merits discussion and further research.

PREVIOUS NUTRITIONAL STUDIES

Ruidavets J-B[1], Evans A[2], Arveiler D[3], Nuttens M C[4], McCrum E E[2], Richard J L[5], Bingham A[5], Cambou J-P[1].

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Several hypotheses have been put forward to explain the differences in the incidence of CHD and mortality between France and North European countries. The incidence is fourfold higher in Belfast than in the 3 French registers. Conventional cardiovascular risk factors do not account for such differences. Population surveys carried out within the framework of MONICA registers and the ECTIM study reflect the absence of striking differences in conventional risk factors between France and Northern Ireland. Specific regional nutritional habits might account for the differences in the frequency of disease. The Belfast MONICA Centre and the 3 French registers participated in a nutritional survey (EURONUT) carried out in a representative population sample. The comparative analysis of the results of the initial nutritional survey, which was carried out in men aged 45-64 years in Belfast and in Toulouse, shows a higher consumption of polyunsaturated fatty-acids in the Haute-Garonne (7.1% vs 4.6% of total energy) with a higher P/S ratio (0.50 vs 0.30), a lower alcohol consumption in Belfast (3.6% vs 6.4% of total energy) and a higher intake of fruit and vegetables in the Haute-Garonne. The vitamin C serum level found in males is twofold higher in Haute-Garonne (Gey et al 1991) in accordance with the amount of vegetable intake. Nutritional behaviour differences seem to corroborate the hypothesis of the protective role of unsaturated fat and vitamins (E and C) against IHD. The predictive aspect of the different risk factors (lipoprotein profile, antioxidants) highlighted by the MONICA population surveys must be investigated in the framework of a prospective study (PRIME Study) now being carried out in Belfast and in the 3 French MONICA Centres.

GENERAL DESIGN OF THE ECTIM STUDY

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The ECTIM Study is a multicentre case-control study set up to investigate the large differences in ischaemic heart disease incidence and mortality between centres taking part in the WHO MONICA Project: the three French Centres (Strasbourg, Toulouse, Lille) and the Northern Ireland Centre in Belfast. The aim of the study is to compare the frequency of DNA polymorphisms in patients having suffered an acute myocardial infarction (MI) and in controls, and to study the association between these polymorphisms and various factors involved in the metabolism of lipids and of clotting factors: 662 cases and 812 controls were included between December 1988 and May 1992.

The cases and controls were men aged 25-64 years resident in the geographical areas covered by the MONICA registers. Their family had to have settled in the region for at least 2 generations. The cases were patients with a definite acute MI (MONICA Diagnostic Category 1), surviving 3 to 9 months after the acute event. The controls were age-matched men from the same population as the cases. The participation rates were 60% in Belfast, 68% in Toulouse, 56% in Strasbourg and 55% in Lille.

The cases and the controls were interviewed in a standardised way in the four centres, mostly by home visiting. The questionnaire for cases and controls concerned personal and familial histories as well as exposure to potential deleterious factors for the cardiovascular system (smoking habits, alcohol consumption, blood pressure measurement, anthropometric measurements etc). Furthermore, there was a specific questionnaire for controls, based on the ROSE questionnaire, and another for cases which collected clinical data concerning the acute event.

A blood sample was taken on fasting subjects for the setting up of a DNA bank, a plasma bank, the measurement of lipid parameters and clotting factors. The biological measurements were all centralised in specialised laboratories.

MEDICAL TREATMENT AFTER MYOCARDIAL INFARCTION: THE ECTIM STUDY

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The prescriptions six months after a myocardial infarction were compared between the different centres of the ECTIM Study (662 Patients). French patients took significantly more medicine than Northern Irish (4.65±1.57 vs 4.17±1.57 respectively, $p<0.001$). French patients had a higher frequency of hypolipidaemics, oral anticoagulants and ACE inhibitors (35% vs 5.5%, $p<0.001$; 23% vs 1.5%, $p<0.001$ and 18% vs 5%, $p<0.001$, respectively), while the Northern Irish had a higher frequency of beta-blockers and antiaggregating drugs (67% vs 54%, $p<0.01$ and 88% vs 67%, $p<0.001$, respectively). Three-quarters of the patients took anti-angina drugs (nitrates and non-nitrates), but the Northern Irish patients were almost exclusively on nitrates, while the French patients' nitrate and non-nitrate intakes were similar.

In France, a north-to-south gradient of the number of medicines prescribed was found (5.04±1.59 in Lille, 4.74±1.50 in Strasbourg and 4.27±1.57 in Toulouse, $p<0.001$). The frequency of the prescriptions of oral anticoagulants (38%, 5% and 15%, $p<0.001$), hypokalaemic diuretics (17%, 8% and 8%, $p<0.01$), and antiaggregating drugs (55%, 89% and 63%, $p<0.001$) were also different between Strasbourg, Lille and Toulouse, respectively.

In conclusion, there is a lack of consensus as regards the therapy after a myocardial infarction. A follow-up study is currently under way to assess the outcome of the patients from each ECTIM centre.

CARDIOVASCULAR RISK FACTORS IN THE ECTIM STUDY

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The aim of this study is to compare patients with myocardial infarction (category 1 MONICA) and controls. Cases and controls were born in the area of the four MONICA centres (Belfast, Lille, Strasbourg and Toulouse).

	FRANCE			BELFAST		
	Cases (n=460)	Controls (n=609)		Cases (n=202)	Controls (N=202)	
Previous history (%)			OR*			OR
- Diabetes	13.7	7.4	1.9	6.4	3.0	2.2
- High blood pressure	33.0	19.7	2.1	17.3	14.3	1.3
- Hyperlipidaemia	37.3	21.1	2.4	11.4	4.4	3.2
Tobacco						
- Number of cigs	8.6	5.7	p<0.001	15.9	5.1	p<0.001
-Smokers(%)	41.5	31.0	p<0.001	55.9	25.2	p<0.001
Alcohol (ml/day)						
- Wine	23.9	29.5	p<0.05	0.5	1.7	p<0.05
- Beer	6.9	8.6	NS	16.4	18.2	NS
- Spirits	2.0	3.7	p<0.001	17.2	17.1	NS
- Total Alcohol	32.0	41.0	p<0.001	34.2	37.2	NS

* OR = Odds ratio

This study confirms the role of the four risk factors in the incidence of myocardial infarction. Alcohol and alcohol type also seems to play a part. The part that alcohol plays in protection from atherosclerosis is clearly different in France than in Belfast.

LIPID AND LIPOPROTEIN PARAMETERS IN THE ECTIM STUDY

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The incidence of coronary heart disease (CHD) in middle-aged men is more prevalent in Northern Ireland than in France. The ECTIM Study was undertaken to investigate the differences in CHD incidence and mortality between the French populations of Strasbourg, Toulouse and Lille and the Northern Irish people in Belfast. In the present study, an investigation of lipid parameters was performed in normocholesterolaemic patients with myocardial infarction and controls, with a particular emphasis on lipoprotein particles defined by their apolipoprotein composition.

In Belfast and France, cases had lower levels of HDL-cholesterol, Apo A-I, Apo A-II, LpA-I and LpA:AI and higher levels of LpE:B and Lp(a):B than controls. Triglycerides, VLDL-cholesterol, Apo B and LpCIII:B were higher in cases than in controls only in Belfast. In controls, the levels of cholesterol fractions and apolipoproteins were similar in the two countries; however, the level of LpA-I was lower and the levels of LpE:B and Lp(a):B were higher in Belfast than in France.

A high-risk profile, characterized by a low LpAI level and by high levels of LpE:B and Lp(a):B, was thus more frequent in the population of Northern Ireland.

The data indicate that measurement of lipoprotein particles defined by their apolipoprotein composition may be useful indicators of CHD risk. However, this profile must be assessed in prospective studies to estimate its predictive value.

THROMBOTIC FACTORS IN THE ECTIM STUDY: A MINI-REVIEW

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Plasma levels of fibrinogen, factor VII coagulant activity (fVIIc) and plasminogen activator inhibitor type-1 (PAI-1) were measured on participants in the ECTIM study. Mean plasma fibrinogen levels were consistently and markedly higher in cases than in controls, even after adjustment for smoking and other confounding factors. There was significant variation in mean fibrinogen levels between centres in the controls, with Belfast being highest (314 mg/dl) and Toulouse lowest (291 mg/dl), with Lille and Strasbourg (both 305 mg/dl) intermediate. This geographical variation may go some way towards explaining the differences in incidence of coronary heart disease (CHD) between Northern Ireland and France. Mean fVIIc was, in all centres, higher in controls than in cases, which does not support previous observations from prospective studies, although different fVIIc assays have been used in different studies. In all regions except for Belfast, PAI-1 levels were higher in controls than in patients, raising questions as to the role of PAI-1 in CHD. Among the controls, PAI-1 levels were significantly higher in the French centres than in Belfast, an unexpected and currently inexplicable finding. In conclusion, the results of the ECTIM study strengthen the epidemiological evidence for a possible role for fibrinogen in the pathogenesis of CHD but do not confirm previous studies which implicated plasma fVIIc and PAI-1 levels as risk factors for CHD.

PARENTAL HISTORY OF MYOCARDIAL INFARCTION IN FRANCE AND NORTHERN IRELAND

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The objectives of the present study were to compare the prevalence of parental history of coronary heart disease and its impact on individual risk of myocardial infarction (MI) in Northern Ireland and France, and to identify which factors could partly explain the familial concentration of disease. Parental history was investigated at interview by specially trained staff. In Belfast, data were validated from General Practitioner or hospital records or death certificates, and those for whom this validation was not possible (15%) were excluded. In France, confidentiality legislation does not permit such validation, and self-reported history was used. Positive parental history was more frequent in Northern Ireland than in France (24% vs 10% in controls' fathers, 14% vs 3% in controls' mothers). In both countries, prevalence of MI was higher, and mean age of onset was lower, in cases' than in controls' parents. The odds ratios for disease associated with a premature parental MI (≤60 yrs for fathers/≤65 yrs for mothers) were 2.3 ($p<0.001$) in France and 2.8 ($p<0.01$) in Northern Ireland respectively, whereas those associated with a late parental MI were 2.0 ($p<0.001$) and 1.4 ($p=0.09$), respectively.

In the control populations, lipid and lipoprotein levels were compared between individuals with and without parental history. LpAI, ApoAII, triglyceride and Lp(a) levels did not differ between the two groups, whereas total cholesterol and ApoB levels were significantly raised among those with a positive parental history. The difference was even more marked when the parental history was restricted to premature MI (ApoB level: 1.44 vs 1.30; $p<0.01$). Comparison of genetic polymorphisms between the two groups indicated a higher frequency of ApoE (44+43) phenotypes among those with premature history (OR=2.4; $p=0.02$). There was also an excess of angiotensin-converting enzyme DD and ID genotypes among those having a parental history, which was even more marked when parental history was restricted to fatal MI (OR=2.8, $p<0.01$ for DD; OR=2.0, $p=0.06$ for ID).

HOW RELIABLE IS A FAMILY HISTORY OF MYOCARDIAL INFARCTION?

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Previous studies have shown that a positive family history of myocardial infarction (MI) contributes significantly and independently to individual risk. Less frequently has the reliability of self-reported family histories been assessed. Our objective was to assess the reliability of reports of MI in first degree relatives of Belfast ECTIM recruits.

Of the original 400 cases and controls in Belfast, 349 were interviewed approximately 18 months to 2 years after their initial recruitment. Demographic and clinical histories were obtained in respect of 2812 first degree relatives. Death certificates were retrieved for 753 of 783 deceased relatives. The medical history of 93% of living first degree relatives (1893/2029) was verified primarily through correspondence with family doctors and retrieval of hospital records.

The sensitivity of reports of MI in living first degree relatives was 72% (58/81). The positive predictive value of such reports was 64% (58/90). For deceased relatives reported as dying of MI the sensitivity was 66% (121/183) and the positive predictive value was 76% (121/159). There were no differences in these proportions between cases and controls. The overall kappa scores were modest, 0.73 for cases and 0.65 for controls.

Whereas the odds ratio (OR) for a reported history of MI in at least 1 parent was 1.58 (95% Confidence Intervals (CI), 1.02 to 2.45), the OR for a validated history of MI in at least 1 parent was 1.64 (95% CI, 1.05 to 2.54). However, the OR for a reported history of MI among siblings was 1.75 (95% CI, 1.02 to 2.94), slightly greater than the OR for a validated history of MI in these kin (1.59; 95% CI, 0.93 to 2.72).

These results suggest that there may be some recall bias affecting self-reported family histories of MI among siblings in this Belfast ECTIM sample. The relatively modest sensitivity and positive predictive value may limit the overall effectiveness of a targeted screening programme for risk factors for myocardial infarction

THE IMPACT OF APOLIPOPROTEIN E POLYMORPHISM ON LIPOPROTEINS AND RISK OF MYOCARDIAL INFARCTION; THE ECTIM STUDY

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In the ECTIM Study, 574 male patients aged 25-64 years were examined 3-9 months after myocardial infarction in 4 regions participating in the WHO-MONICA Project. Controls (n=722) were randomly selected from the background population. Results were adjusted for age, centre, body mass index and alcohol consumption reported using a standardized questionnaire. The distribution of Apo E phenotype was significantly different across the 4 control samples ($p=0.04$) with a higher frequency of epsilon 4 allele in Belfast than Toulouse. The association of Apo E polymorphism with biological measurements was studied in the control groups (n=644). Allelic effects were estimated from a codominant genetic model. Individuals carrying the epsilon 2 allele had lower levels of plasma chol, LDL-chol and Apo B. TG, VLDL-chol, Apo CIII, Apo E, LpCIII:B and LpE:B levels were higher. The epsilon 4 allele was associated with increased Apo B level and decreased LpAI level. Subjects with the epsilon 4 allele had higher TG, VLDL-chol, LpCIII:B levels than those having the Apo E3/3 phenotype. Relative risk (RR) for MI associated with Apo E phenotypes in comparison with Apo E3/3 were found to increase in the following order: E2/2<E3/2<E3/3(RR=1)<E4/3=E4/2<E4/4($p<0.05$). The presence of the epsilon 2 and epsilon 4 alleles carried a respective relative risk of 0.73 ($p=0.05$) and 1.33 ($p=0.02$) in a codominant model logistic model. In conclusion, Apo E polymorphisms explain a modest proportion of myocardial infarction in the ECTIM Study.

APOLIPOPROTEIN B POLYMORPHISMS IN THE ECTIM STUDY

Visvikis S, for the ECTIM group.

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The aim of the ECTIM study is to identify genetic factors involved in the development of myocardial infarction (MI). More than 600 patients with MI and 700 controls were recruited from 4 populations, in France (Lille, Strasbourg, Toulouse) and Northern Ireland (Belfast). Several lipid variables including LDL-cholesterol, Apo B and polymorphisms of the Apo B gene including the EcoRI, MspI, XbaI, signal peptide (SIPE) and 3'HVR were investigated in all participants.

Homozygotes and heterozygotes for the 48 repeats allele (HVR48+) were more frequent in cases (21.8%) than in controls (15.0%) ($p<0.003$ after adjustment on population). No statistically significant heterogeneity of this association could be detected across populations. The population adjusted odds-ratio (95% confidence interval) for MI was 1.55 (1.15-2.07) and the fraction of cases attributable to the HVR48+ genotype was 0.074. Body mass index (BMI) was positively associated with MI in HVR48+ individuals ($p<0.004$) but not in HVR48- individuals. In HVR48+ individuals, the mean excess weight (standardized to a height of 1.75 m) in cases relative to controls was: 6.6 kg in Belfast, 6.3 kg in Lille, 2.5 kg in Strasbourg and 2.3 kg in Toulouse. In individuals with a BMI>26 kg/m^2 (the median of BMI in controls), the population adjusted odds-ratio for MI associated with the HVR48+ genotype was 2.21 (1.47-3.31) ($p<0.0001$) and the fraction of cases attributable to the HVR48+ genotype was 0.14. In contrast, in individuals with a BMI<=26 kg/m2, the HVR48+ genotype was unrelated to MI.

In Belfast, in addition to the HVR48 polymorphism the SIPE polymorphism was also associated with MI. Significant associations were also observed between the Apo B signal peptide polymorphism and mean levels of total cholesterol, LDL cholesterol, ApoB and Lp(a) in the Strasbourg control population. Individuals homozygous for the rare allele had higher levels of these lipid parameters. In Belfast, although not statistically significant, the Apo B signal peptide polymorphism had a similar effect on Apo-B-related parameters as seen in Strasbourg. No significant associations were observed in the Toulouse population where the risk of MI is three times lower than in Belfast.

Finally, the polymorphisms investigated in the ECTIM study were in strong linkage disequilibrium and these disequilibria were of similar magnitude in the four populations. These last results suggest that in the presence of one of several variants of the Apo B gene carried by the HVR48 allele, overweight has a deleterious impact on lipid metabolism and raises the risk of MI.

(CA)n REPEAT POLYMORPHISM OF THE APOLIPOPROTEIN AII GENE: RESEARCH OF ASSOCIATION WITH MYOCARDIAL INFARCTION AND LIPOPROTEIN LEVELS: THE ECTIM STUDY

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Apolipoprotein AII (ApoAII) is the second major High Density Lipoprotein (HDL) component with apolipoprotein AI. In a multicentre retrospective study of myocardial infarction, the ECTIM study, we explored the association of an ApoAII gene polymorphism with coronary heart disease and with lipid and lipoprotein plasma levels. We studied a (CA)n repeat length polymorphism located in intron 2 of the gene. The ECTIM study was carried out in four regions: Belfast area, Toulouse area, Strasbourg area and Lille area. A sample of men aged between 25 and 64 was recruited: cases of myocardial infarction were included and controls were selected from the general population as age matched controls for myocardial infarction cases. The (CA)n repeat genotypes were detected with PCR amplification technique in 1358 subjects (595 cases and 763 controls). We identified 10 different alleles. The effect of this polymorphism on lipids and lipoproteins was analysed in the control group for subjects without any hypolipidaemic drugs.

	22	2X	XX	p
ApoAII(mg/dl)	33 (8)	35 (8)	37 (8)	0.0001
HDL Chol.(mg/dl)	52 (15)	51(15)	52 (15)	NS
LDL Chol. (mg/dl)	146 (33)	150 (39)	159 (42)	0.007

Allele 2 thus appeared to be associated with ApoAII plasma levels and influenced the levels of LDL-Cholesterol plasma levels, but not HDL-Cholesterol plasma levels. However, no association of this allele 2 with the disease was observed.

(TTA)n REPEAT POLYMORPHISM OF THE HMG CoA REDUCTASE GENE: RESEARCH OF ASSOCIATION WITH MYOCARDIAL INFARCTION AND LIPOPROTEIN LEVELS: THE ECTIM STUDY

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HMG CoA reductase is a key enzyme in the initial steps of cholesterol metabolism. Regulation of the rate of cholesterol biosynthesis is, in general, mediated by regulation of HMG CoA reductase activity. In a multicentre retrospective study of myocardial infarction, The ECTIM study, we explored the association of a HMG CoA reductase gene polymorphism with coronary heart disease and with lipid and lipoprotein plasma levels. We studied a (TTA)n repeat length polymorphism located 10 kbp 3' of exon 2 of the gene. The ECTIM study was carried out between 1988 and 1992 in four regions: Belfast (Northern Ireland), Toulouse (South of France), Strasbourg (North-East of France) and Lille (North of France). A sample of men aged between 25 and 64 was recruited: cases of myocardial infarction were included and controls were selected from the general population as age matched controls for myocardial infarction cases. The (TTA)n repeat genotypes were detected with PCR amplification technique in 1297 subjects (558 cases and 739 controls). We identified eight different alleles ranging from 10 to 17 repeats. The presence of at least one 15 repeat allele was significantly less frequent ($p<0.008$) in cases (14.7%) than in controls (20.4%). The effect of this polymorphism on lipid and lipoprotein levels was analysed in the control group for subjects without any hypolipidaemic drugs. The presence of at least one 15 repeat allele was associated with high levels of low density lipoprotein cholesterol ($p<0.003$). HMG CoA reductase gene polymorphism thus appears to be associated with the atherosclerotic process and coronary heart disease.

LIPOPROTEIN LIPASE GENE POLYMORPHISMS: ASSOCIATIONS WITH MYOCARDIAL INFARCTION AND LIPOPROTEIN LEVELS IN THE ECTIM STUDY

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Lipoprotein lipase (LPL) is a major determinant of the hydrolysis of triglyceride rich lipoproteins. Four DNA polymorphisms of the LPL gene were examined (PvuII, HindIII, Asn291 —>Ser and Ser447—>stop) to detect associations with lipid and lipoprotein levels and with the occurrence of myocardial infarction in the ECTIM study.

Significant pairwise linkage disequilibria were found between PvuII, HindIII and Ser447—>stop polymorphisms. Asn291—>Ser was in linkage disequilibrium with PvuII only.

Lipid related variables were analysed in the control group to avoid the bias resulting from lifestyle (treatment) changes after myocardial infarction. HindIII polymorphism was associated with apolipoprotein (Apo) C-III levels ($p=0.04$). Triglyceride, Apo B, Apo CIII and LpE-B levels were weakly associated with PvuII polymorphism ($0.05 < p < 0.10$). Ser447—>stop polymorphism was associated with triglyceride and Apo C-III levels ($p=0.04$ and $p=0.02$ respectively). No association between Asn291—>Ser polymorphism and lipid related variables was detected.

HindIII and PvuII polymorphisms were significantly associated with the occurrence of myocardial infarction, independently from their effects on triglycerides ($p=0.015$ and $p=0.006$ respectively, after adjustment on centre and triglyceride levels by multiple logistic regression). The relative risk of myocardial infarction (estimated by the odds ratio) for H2H2 subjects was 1.8 when compared to H1H1 (homozygotes for HindIII polymorphism). The relative risk for P2P2 was 1.4 when compared to P1P1 subjects (homozygotes for PvuII polymorphism). Moreover there was an interaction effect between PvuII polymorphism and triglyceride levels on myocardial infarction: triglycerides were associated with myocardial infarction only in P1P1 group ($p=0.006$).

These results indicate an effect of the genetic variation(s) of LPL on myocardial infarction. This could be due to the central role of LPL in lipoprotein metabolism, including the post-prandial phase, and not only to an effect on fasting lipoproteins.

GENETIC VARIATION AT THE B FIBRINOGEN LOCUS IN RELATION TO PLASMA FIBRINOGEN CONCENTRATIONS AND RISK OF MYOCARDIAL INFARCTION

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Increased plasma fibrinogen concentration is a major cardiovascular risk factor. Conflicting results on genetic variations in plasma fibrinogen levels have been reported. Furthermore, whether fibrinogen genotype is associated with the risk of ischaemic heart disease has not been studied so far. An HaeIII restriction fragment length polymorphism (RFLP) of the ß-fibrinogen gene was used in a case-control study to investigate the genetic variation at this locus in relation to plasma fibrinogen concentrations and the risk of myocardial infarction (MI). Five hundred and thirty-three male patients and 648 control subjects were recruited from 4 WHO MONICA centres in Northern Ireland and in France. The absence of HaeIII cutting site (H2 allele) was associated with a significant rise in fibrinogen concentrations in both patients and controls. The effect of the HaeIII polymorphism on plasma fibrinogen levels did not significantly differ between centres. Fibrinogen levels were higher in smokers than in non-smokers. The difference between the two groups was larger in subjects with the genotype H2H2 than in those with the genotype H1H1 or H1H2, regardless of the case-control status. However, there was no significant interaction between smoking status and genotype in its effects on fibrinogen levels. HaeIII genotype accounted for about 1% of the total variance in fibrinogen levels, whereas smoking and age together explained 7% and 5% in controls and patients, respectively. The frequency of the H2 allele was 0.21 in controls and 0.19 in patients. The estimate of relative risk for MI associated with the presence of the H2 allele was 0.89 (95% confidence interval: 0.69 - 1.13). The results were consistent with respect to the centres. Multiple regression analysis showed that smoking and raised plasma fibrinogen made independent contributions to the increase in MI risk. There was no significant interaction between HaeIII genotype and the effect of smoking on MI risk. These data provide further evidence for a role of the genetic variation at the ß-fibrinogen locus in the determination of plasma fibrinogen concentrations. However, this study failed to detect an association between this genetic variation and the MI risk. Further investigations are needed to assess the relative contribution of genetic and environmental determinants of plasma fibrinogen to the prediction of atherothrombotic diseases.

FACTOR VII GENOTYPE DETERMINES FACTOR VII COAGULANT ACTIVITY IN THE ECTIM STUDY

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Raised plasma level of factor VII coagulant activity (fVIIc) has been implicated as a risk factor for myocardial infarction (MI) and so genetic factors determining an individual's fVIIc level may influence risk of MI. We have, therefore, genotyped individuals taking part in the ECTIM study for the Arg/Gln$_{353}$ polymorphism of the factor VII gene. This polymorphism has previously been shown to be strongly associated with plasma fVIIc. This was confirmed in the ECTIM study, where the Gln allele was associated with significantly lower fVIIc levels in both MI cases and controls in all centres, with the exception of Lille controls where a similar but non-significant trend was observed. Among the MI cases, the mean fVIIc level in the Arg/Arg homozygotes was 115% of standard, in the heterozygotes was 102% and in the Gln/Gln homozygotes was 78%, with $p<0.0001$ (by ANOVA). The corresponding values for the controls (excluding those on oral anticoagulants (OACs) and those with coronary heart disease (CHD)) were, respectively, 118%, 104% and 91%, with $p<0.0001$. The frequency of the Gln allele did not differ significantly between centres or between cases and controls, with the frequency in the controls (excluding CHDs and those on OACs) being 0.12 (95% CI 0.10-0.14) and in the MI cases being 0.11 (0.08-0.12). This suggests that the factor VII Arg/Gln$_{353}$ polymorphism may not be a strong determinant of risk of MI despite its effect on fVIIc levels. A previous study had suggested that the correlation of plasma fVIIc and triglyceride levels may be stronger in Arg/Arg homozygotes than in Gln allele carriers, however, this was not confirmed in the ECTIM study, with the possible exception of the Belfast sample which showed a similar trend.

ASSOCIATION BETWEEN VARIATION IN THE PROMOTER REGION OF THE PLASMINOGEN ACTIVATOR INHIBITOR-1 (PAI-1) GENE AND PLASMA PA1-1 ACTIVITY: THE ECTIM STUDY

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We have studied the association of a common insertion/deletion polymorphism in the plasminogen activator inhibitor-1 (PAI-1) gene promoter with plasma levels of PAI-1 activity in 474 patients with myocardial infarction and 638 matched controls from the four centres participating in the ECTIM study. In the Belfast samples PAI-1 levels were higher in patients than controls (8.0% $p<0.05$), while in the three French centres levels were higher in the controls than in the patients. The frequency of the deletion allele (4G) was similar in patients and controls (0.57 and 0.55 respectively) and it was associated with elevated levels of plasma PAI-1 in both groups. The effect of genotype on PAI-1 levels was consistent in all regions and was greater in patients than controls, but was statistically significant only in the patients from Belfast and Strasbourg and in the patient sample as a whole ($p<0.05$). After adjusting for differences between centres, body mass index and plasma triglycerides, which affect levels of PAI-1, patients and controls homozygous for the 4G allele had mean PAI-1 activities, respectively, 17.6% and 6.5% higher than 5G homozygotes, with heterozygotes having intermediate values. In both patients and controls from Belfast there was a positive correlation between plasma fibrinogen levels and PAI-1 activities in 4G homozygotes ($r=0.23$ $p=0.06$, $r=0.24$ $p=0.08$ respectively), while in those with other genotypes this correlation was negative. This relationship was observed only weakly in the patients and controls from the French centres. These data are consistent with a previous study showing a differential effect of cytokines on transcription from the two alleles in HepG2 cells, and confirm that variation at the PAI-1 locus contributes to inter-individual differences in plasma PAI-1 levels, especially during the acute phase. This suggests that this polymorphism may be one of the genetic factors that determines an individual's risk of thrombotic disease.

ACE INSERTION/DELETION POLYMORPHISM: A NEW RISK FACTOR FOR MYOCARDIAL INFARCTION?

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About 25% of the variability of plasma ACE level is associated with an Insertion (I)/Deletion (D) polymorphism of the ACE gene which is a marker for an unknown functional variant situated within or close to the ACE gene. As a chronic exposure to high ACE levels may modulate the activity of peptides involved in vasoconstriction and smooth muscle cell proliferation and predispose to myocardial infarction (MI), we considered that the ACE gene could be a candidate for MI. To test this possibility, the frequency of the ACE I/D genotypes was compared in patients with MI (n=610) and controls (n=733) participating in the ECTIM study in Belfast, Lille, Strasbourg and Toulouse. The DD genotype was more frequent in patients than in controls, especially in those considered to be at low risk (plasma Apo B<1.25 g/l and BMI<26 kg/m^2). In this subgroup which represented 13% of the patients, the relative risk of MI associated with the DD genotype was approximately 3 and the attributable risk was 30%. In control subjects, parental history of fatal MI was associated with a significantly higher frequency of the D allele in Belfast as well as in France. These results which will have to be confirmed in other studies and other populations suggest that the ACE/ID polymorphism is a new potent risk factor for MI.

ECTIM AND FUTURE STUDIES IN BELFAST

Kee F[1], Tiret L[2], Weston J E[1], Bard J-M[3], Evans A E[1], McCrum E E[1], Cambien F[4], Fruchart J-C[5], Luc G[5], McMaster D[6].

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Some caution is appropriate before the results from ECTIM to date are more widely generalised. Ongoing MONICA registration and the ECTIM Family study in Belfast may allow some of this reservation to be addressed in extensions of the protocol.

i In particular, ECTIM cases were recruited within nine months of *surviving* a myocardial infarction. The fact that some alleles (such as the ACE insertion/deletion polymorphism) seem to confer greater risk to surviving patients with an otherwise low risk profile suggests that these alleles may be implicated in *fatal* MI in patients with other established risk factors. It is thus intended that post-mortem tissue from subjects dying early in the course of MI is retrieved (n=200), DNA recovered from the archived material and the frequency of "susceptibility" genotypes determined.

ii Although the incidence of ischaemic heart disease in men is substantially greater than in women, coronary heart disease is one of the most common causes of death in both sexes. Though there is epidemiological evidence indicating a gradient of risk to women from "traditional" risk factors such as smoking, hypertension or raised serum cholesterol, the attributable risks are often found to be somewhat smaller than in men. The Belfast ECTIM extension will recruit 200 female cases and 200 female controls. This will allow a comparison with the findings in Belfast men on the importance of the lipoparticle profiles and specific genetic determinants of risk. This may point to the need for further studies in other centres.

iii A natural extension of the study of population associations between genotypes and disease is to discover whether the "susceptibility" alleles segregate with the disease (or trait) in specific families. The validated family history data on Belfast ECTIM subjects will allow ready identification and recruitment of at-risk families for linkage and, eventually, intervention studies.

BELFAST HYPERLIPIDAEMIA STUDY

Evans AE[1], Nicholls PD[2], McMaster D[3], O'Kane M[2], Cambien F[4], Kee F[1], McCrum E E[1].

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It is well established that when LDL receptors are deficient, LDL cholesterol accumulates and coronary risk is greatly increased. Similarly, it is known that certain variants of apolipoprotein B 100 (eg when there is a mutation in the codon for the amino acid 3500) result in poor binding between the apolipoprotein and the LDL receptor with cholesteryl ester-enriched LDL particles consequently accumulating in the plasma. The 3500 polymorphism was rare in the ECTIM Study. The Belfast Hyperlipidaemia Study will investigate those types of Frederickson hyperlipoproteinaemias which are associated with increased levels of apolipoprotein B 100, mainly (Type IIA, IIB and IV) in relation to several polymorphisms of the apolipoprotein B gene. Two hundred previously untreated patients will be recruited from the lipid clinic of the Royal Victoria Hospital, Belfast. Male patients aged 40-64 years and female patients aged 50-64 years will be eligible. All should have types IIA, IIB or IV hyperlipoproteinaemia and both of their parents should have been born in the historical entity of Ulster. Twenty mls of blood will be drawn at EDTA after a full overnight fast. Polymorphisms of the apolipoprotein B gene of special interest are (1) variants already published: Apo B/XbaI, EcoRI, signal peptide, 3500, 4311 biallelic polymorphism; Apo B 3'HVR (2) new variants of the apolipoprotein B gene identified in the ECTIM Study and (3) other polymorphisms. Biochemical estimations will be carried out in the Department of Medicine, The Queen's University of Belfast and the apolipoprotein B and other polymorphisms are to be investigated at INSERM SC7, Paris. It is estimated that the study will take 18 months – 2 years to complete.

THE PRIME STUDY

Evans A E[1], Richard J L[2], McMaster D[3], Cambien F[4], McCrum E E[1], Sykes D[5], Bingham A[2], Bard J-M[6], Kee F[1], Fruchart J-C[6], Arveiler D[7], Shaffer P[7], Amouyel P[8], Luc G[8], Scarabin P Y[2], Ducimetière P[2], Cambou J-P[9], Douste-Blazy Ph[9], Ruidavets J-B[9], Gey F[10], Juhan I[11], Aillaud M F, Perret B[9], McConville M[1], Yarnell J W G[1].

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The PRIME Study is a prospective study of the determinants of coronary heart disease incidence and mortality in 50-59 year old males in the MONICA Centres in France and Northern Ireland. The Study is building on the findings of the ECTIM Study. The four centres provide a stark contrast in ischaemic heart disease incidence with rates in Belfast four times those in Toulouse and more than three times those in Lille and Strasbourg. Subjects are drawn from General Practice, Health Check-up Centres and Industry in the four centres and are screened after a full overnight fast. Total intake to the study will be close to 11,000 and already approximately 8,500 subjects have been recruited. Screening began in mid 1991 and will be completed later this year and thereafter 5-7 year follow-up will take place. The high-risk lipid profile, i.e. low LPA1 and high LPE:B and LP(a) observed in Belfast will receive special attention and these factors will be measured in fresh plasma from each subject. The environmental factors of special interest are diet (in particular fatty acids and the major antioxidant vitamins A, E and C). Alcohol consumption with special reference to type of beverage and amount and pattern of drinking, physical activity, cigarette consumption, drug intake, psychosocial factors including shift work and family histories are also being investigated. Gene environment interactions are of key interest, especially in relation to polymorphisms of the apolipoprotein B gene and the DD polymorphism of the ACE gene. The study will also look at other lipid parameters, thrombotic factors and hormones.

POSTSCRIPT

After the meeting Dr Pierre Ducimetière unveiled a plaque at 7 Marcus Square, Newry to commemorate Dr Samuel Black, the pioneer Cardiologist who lived there from 1819 - 1832. Dr Black was first to notice the large disparity in heart disease between the north of Ireland and France. The plaque was erected by the Ulster History Circle with the generous assistance of Newry and Mourne District Council.

ACKNOWLEDGEMENTS

The ECTIM study and its extensions in Belfast are supported by the DHSS (NI), the British Heart Foundation, the Northern Ireland Chest, Heart and Stroke Association and INSERM (Institut Nationale de la Santé et Recherche Médicale). The PRIME Study is supported by INSERM and Merck, Sharpe and Dohme and the ECTIM Study in France is supported by INSERM, Bristol-Myers Squibb, MGEN (Mutuelle Générale de l'Education Nationale), Parke-Davis, Sandoz (Pharm Lab) and SANOFI-Clin Midy (Pharm Lab).

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Book reviews

J J R Macleod: The Co-discoverer of Insulin. By Michael J Williams (pp 125. £5.00). Proceedings of the Royal College of Physicians of Edinburgh, July 1993 Vol 23 No 3. The Royal College of Physicians of Edinburgh, Edinburgh.

Much has been written about the events and personalities involved in the discovery of insulin. A television programme on these events used the title "Glory Enough for All". But, either because of the four personalities involved — Banting, Best, Collip and Macleod — or because the Nobel Prize Committee only recognized two, Banting and Macleod, there ensued more acrimony than this glorious discovery should rightly have created.

Despite being a committed supporter of Banting, I have to acknowledge the considerable flaws in his character and this book makes it easier to appreciate the patience and endurance of J J R Macleod. This is a very sympathetic and proud account of Professor Macleod's life, beginning with early schooling in Aberdeen, undergraduate and postgraduate career in Aberdeen and London, leading to his appointment to the Chair of Physiology at Western Reserve University, USA at the startlingly early age of 27 years. Later, when Macleod was in Toronto there was the fateful meeting with Banting on Monday, 8th November 1921. The story continues to the award of the Nobel Prize in Medicine on 25th October 1923.

The subsequent distinguished career of Professor Macleod in Toronto, and after 1928 in Aberdeen, is given in sympathetic and proud detail up to his death in 1935. This book is highly commended because of much new detail, carefully annotated, and the overall achievement is a true and lasting tribute to J J R Macleod, Fellow of the Royal Society and Nobel Laureate, and considerable benefactor of humanity.

J A WEAVER

Churchill's Doctor. A Biography of Lord Moran. By Richard Lovell. (pp xiv and 457. £25). Royal Society of Medicine Services Ltd. London. 1992. ISBN 1-85315-183-1.

This valuable biography sends us to our Archives, and we see in the Students Register of the Belfast General Hospital, now the Royal Victoria Hospital, that John Forsythe Wilson, of Gortmore, Magilligan, County Derry, enrolled for the clinical classes of the hospital beginning in the Summer Session of 1870. He had come from a farm at Gortmore, off the Bishop's Road, some seven miles north of Limavady, behind Benevenagh. In the Winter Session of 1870-71 he paid the hospital a fee of five guineas to become a perpetual student, and the registration fee for the year of half a guinea. In the summer of 1872 he was a resident clinical assistant and paid no fee. His last entry in the register is for the Winter Session of 1872-73. He had attended the classes of the Faculty of Medicine in The Queen's College, Belfast. Wilson graduated in The Queen's University in Ireland in 1873, receiving the degrees of MD and MCh. He might have been forgotten if he had not been the father of the subject of this biography, Charles Wilson, Lord Moran, President of the Royal College of Physicians of London 1941-1950. John Forsythe Wilson's wife, the mother of Charles, was Mary Jane Hanna, daughter of the Reverend John Hanna, Presbyterian Minister of Clogher, County Tyrone.[1] Charles was born in Skipton in 1882, in the upper reaches of the Aire valley, in West Yorkshire, where his father had settled in practice. It is of interest to this reviewer that his grandfather was practising at the same time, some ten miles lower down the Aire Valley at Bingley. West Yorkshire was easily accessible by sea and rail from Belfast. Ulster doctors in the area were known to send to Belfast for their horses, and on one occasion live geese were sent from Ballyclare to Bingley in a box with airholes in full confidence that they would arrive safely.

Lord Moran had substantial achievements to his credit, his own distinguished early career (we read that he received a Gold Medal with his MD), the development of St Mary's Medical School, his Presidency of his College, his part in the founding and development of the National Health Service, his attendance on Churchill. He had made a happy marriage, his wife was a Yorkshire Unitarian, Miss Dorothy Dufton. He had two good sons. His truly important book, the Anatomy of Courage, will always, or should always, be read by doctors in the Armed Services. He had served as a regimental medical officer in France in the Great War and received the Military Cross for gallantry in the field. But this does not seem to be the life-story of a happy or contented man. He does not seem to have much wanted to be a doctor, and the amount of clinical experience he had would be thought inadequate nowadays for the self-training and development of a physician. His practice was never

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large and it disappeared during the war. His famous book on Churchill brought him much strident reproach from the Churchill family and friends. He admired Churchill's leadership and diplomacy in the war, and there is nothing offensive or unworthy in the book. But it was not in Moran to be a sentimental or emotional hero-worshipper. And after all Churchill was notoriously hostile to Ulster, and Moran was an Ulsterman. One feels that he was never really assimilated into English life.

Those who presented themselves for the examination for the membership of the Royal College of Physicians of London just after the war, in the late 1940's, if they succeeded in passing the successive trials of the written examination, the clinical, and the clinical and pathology oral, were called to the final oral. They found themselves in the Censors' room in the old college building in Pall Mall, surrounded by its ancient wooden panelling. The candidate was seated at the foot of the table, facing the President, he being flanked by the four Censors. The Censors wore black gowns. The President, Lord Moran, was splendid in black and gold. He looked exactly like the famous Annigoni portrait. After a silence, a Censor, perhaps the senior Censor, asked this reviewer to describe the peripheral neuritis of diphtheria. One knows now that he only wanted to hear one speak, and cared little about one's views on diphtheria. He may have done Ulster candidates a good turn, because the President would then know that we were from Ulster. At any rate we passed, and Miss Cooke immediately took forty guineas off us.

This is a valuable biography and it was good of Doctor Lovell to undertake the labour. The work of John Forsythe Wilson and his son Charles has not been in vain. There is a lesson however in the story. That is, unless compelled by duty, not to undertake to be domestic physician to the great. It is not a happy task.

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REFERENCE

1. Fasti of the Irish Presbyterian Church. Part xi. Seventh Period 1820-1840. Number 1134.

Postscript

The Archives Office of the Royal Victoria Hospital is fortunate to possess the Student Register for the years 1866 to 1916, and the years 1949 to 1970. Missing are all the years before 1866, and also the years 1917 to 1948. If anyone knows the whereabouts of the missing sections of the register, the Archives Office would be very glad of the information.

1991 Public Health Matters. The Fourth Annual Report of the Director of Public Health, Dr G J Scally. Prepared by the Department of Public Health Medicine, Eastern Health and Social Services Board, Belfast, October 1992 (pp 100).

We have now come to expect the Annual Report of the Director of Public Health of the Eastern Board. This report has to be prepared and published every year, and I suppose that all clinicians have an idea of what it contains, and do not spend too much time reading it. However, closer study is rewarding!

The report falls into three main sections. The first is a description of the health and social environment of the Eastern Board Area. Highlighted in this section is the fact that the population of Belfast is moving out to the suburbs and to adjacent areas like Lisburn and North Down. But this does not mean that patients leave their city doctors and register with a suburban doctor, or do not come to city hospitals. There is some evidence that this might happen about ten years after the movement. Therefore, there is a need for a plan to create better hospital services in these areas. There is no evidence that the EH&SSB has any long-term plans in this area.

The second section of this report is about the assessment of need in the Eastern Board Area. One of the most challenging and exciting things about the recent Health Service Reforms is that Health Boards have a responsibility for assessing the health needs of their population. Boards have been very slow to take up this challenge, probably because of lack of resources. But this report tells us that the Eastern Board have set up a "needs assessment" group, which is to assess the needs of the Board's population for hip replacements, prostatectomy and cataract surgery, and to assess the needs of diabetic patients and the elderly. In this report the results of the needs assessment of cataract surgery are published. In the Eastern Board, cataract surgery operations are below Department of Health targets and the waiting list for cataracts is large and long. It is also anticipated that the need will increase. Having said this, the report takes it very little further. There is no real suggestion as to how

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this need may be met, or how much money would be needed to meet this need. It is suggested that more cataracts could be done as day cases, but this may only keep up with the increasing need.

The discussions on day surgery and the elderly are superficial, and a survey of woman's experience of maternity care is reported (page 36). This is a very good survey, and points to the overlapping of antenatal care, which the Board are in a good position to correct, within the contracting process. The responses of women to questions about breast feeding are interesting. They suggest that only 12% of mothers breast feed their babies for longer than a week, and that this might be part of the reason as to why we have such a high incidence of breast cancer in Northern Ireland.[1] Breast cancer is the commonest cause of death in women aged between 25 and 75, but the needs assessment group does not appear to be going to consider it.

The next two chapters are about health and the environment and about infectious disease, and they say very little that is controversial to a medical audience. The last section is statistics and there are 21 "core" tables, which have been updated from previous reports and which appear in the reports of the Director of Public Health of the Northern, Western and Southern Boards In themselves they are unexceptional, but they contain well known "inaccuracies" which make their use difficult. For example, it is well known that cancer registration is poor, and death certificates are often inaccurate, so what reliance can we put on these figures? The attempt to calculate the health losses of these deaths (PYLL) is a laudable one, and to my mind much better than using QALY's.

I was glad to have an opportunity to read this report, and to get an insight into what the Board are doing in the area of needs assessment. The report is well presented and easy to read. Clearly the Department of Public Health are doing a good job, but the report makes it clear that they could do a much better and more effective job, if they were properly financed.

WILLIAM ODLING-SMEE

REFERENCE

1. Kee F, Gorman D, Odling-Smee W. Confidence intervals and interval cancers . . . needles and haystacks? *Public Health* 1992; **106**: 29-35.

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