EARLY EXPERIENCE OF THORACOSCOPIC HELLERS MYOTOMY

S. Rea, A. Nakreeb, C. Kelly, P. Broe.
Department of Surgery, Beaumont Hospital, Dublin.

Surgical myotomy is the mainstay of treatment for oesophageal achalasia. Minimally invasive surgical techniques, if feasible, reduce patient morbidity and hospital stay. In this study we review our initial experience of thoracoscopic Heller's myotomy. Thoracoscopic myotomy was undertaken in 5 patients (male=2, female=3, age 19-67 yr). One further patient who had a previous thoracotomy underwent a laparoscopic Heller's. Duration of symptoms ranged from 1 to 8 yr.

Diagnosis was based on barium swallow and oesophageal manometry studies. Two patients had previous dilatations and 1 had an open transabdominal myotomy. All patients had a 5 port thorascopic technique. Thoracoscopic Heller's myotomy was completed in 4 out of 5 patients. In 1 patient extensive oesophagitis and peri-oesophagitis precluded both a thorascoscopic and an open myotomy, an oesophagectomy was subsequently performed.

The mean duration of surgery was 142 min. Completion of myotomy and mucosal integrity was confirmed by intraoperative gastroscopy. All patients are now asymptomatic, with documented recovery. The mean hospital stay was 4 days. All patients are now asymptomatic, with documented weight gain. No patients have symptoms of reflux oesophagitis. Our preliminary experience would suggest that thoracoscopic Heller's myotomy is a safe alternative to open surgery, with satisfactory results and reduced hospital stay.

THE VALUE OF DIAGNOSTIC IMAGING FOR AXILLARY LYMPH NODES

M. Duff, A. D. K. Hill, T. O'Neill, S. G. Shering, B. Dunne*, P. Kelly, S. Kennedy*, E. W. McDermott, N. J. O'Higgins.
Departments of Surgery and Pathology*, University College Dublin, St. Vincent's Hospital, Elm Park, Dublin.

The single most important determinant of prognosis in early breast cancer is axillary node status. Clinical assessment of the axilla remains inaccurate. Surgical clearance of the axilla remains the only accurate method of determining prognosis in early breast cancer.

Imaging modalities such as MRI remain inaccurate. Formalin fixation caused a mean increase in nodal volume of 28.4 per cent. Thirty-eight per cent of positive nodes were less than 0.4 cm in diameter which would not have been detected by magnetic resonance imaging. We conclude that MRI is of little value in the quantitative assessment of axillary lymph node involvement in primary breast cancer. Assessment of axillary node status by surgical clearance of the axilla remains the only accurate method of determining prognosis in early breast cancer.

VARIATIONS IN ANATOMY OF THE SAPHENO-FEMORAL JUNCTION, 200 OPERATIVE DISSECTIONS

M. Cox, P. Madhaven, R. Garvey, M. Bresnihan, G. Brady, M. Feeley.
Department of Surgery, Meath Hospital, Heytesbury Street, Dublin 8.

The sapheno-femoral junction is described in anatomy textbooks as being constant with 5 named tributaries entering at or near the junction. Surgeons experienced in operative treatment of varicose veins know this to be misleading. Insufficient understanding of complex S-F junction variations may contribute to the high incidence of recurrent varicose veins.

We prospectively recorded the anatomy in 200 consecutive groin dissections for primary varicose veins. We recorded the anatomy of the junction, the number and configuration of tributaries, the presence of bifid long saphenous veins and the anatomy of the external pudendal artery.

Two S-F junctions were duplicate. The mean number of primary branches connected directly to the LSV within the operative field was 3.9, with 66 (33 per cent) having at least 5 primary branches. In addition 116 (58 per cent) had secondary tributaries joining the primary branches within the operative field. The number of tributaries ligated ranged from 1 to 11.55 (28 per cent) demonstrated junctional branches which joined the femoral directly or at the level of the junction proper. There was bifid LSV in 36 cases (18 per cent), ie both veins were stripped to below the knee, while 15 (8 per cent) had major branches that were stripped to above the knee.

The external pudendal artery is described as running in the "axilla" of S-F junction. In patients 35 (18 per cent) the artery crossed anterior to the LSV or its tributaries. Our study identifies the variability of branches that require ligation at the S-F junction and highlights some of the common pitfalls for the unwary.
RESTORATIVE PROCTOCOLECTOMY - A DECADE OF EXPERIENCE

F. J. Shannon, D. C. Grant, O. J. Clyne, T. J. Boyle, J. M. Hyland.
The Coloproctology Unit, Department of Surgery, St. Vincent’s Hospital, Dublin 4.

Restorative proctocolectomy (RPC) is now established as a surgical option in ulcerative colitis (UC) and other conditions requiring total proctocolectomy. The indications for surgery, surgical technique and early postoperative morbidity have been widely reported, but comprehensive reviews of long term follow-up are still awaited. Outcome in a consecutive series of patients undergoing restorative proctocolectomy over a 10 yr period is reported.

Sixty-eight patients (40F/28M; mean age=38/range=16-77) have undergone restorative proctocolectomy from 1986 to present. All were operated upon by 1 surgeon. Indications included UC (64 patients), idiopathic constipation (2), familial polyposis coli (2). Sixty-three patients had a J pouch and 5 had a W pouch. Five pouches were sutured and the remainder (63) were stapled. There was 1 one-stage, 20 two-stage and 47 three-stage procedures.

There was no operative mortality. Overall morbidity in 67 patients was 38.81 per cent (26) at a median follow-up of 3 yr. One patient died 3 months following a one-stage procedure from disseminated malignancy. Complications are listed:

- Pouch failure: 9 (13.43%)
- Small bowel obstruction: 7 (10.45%)
- Pouch-vaginal fistula: 2 (2.99%)
- Pouchitis: 6 (8.96%)
- Anastomotic stricture: 2 (2.99%)

Of the patients with intact pouches, 4 await closure of their defunctioning ileostomy and 2 (2.99 per cent) have had a defunctioning ileostomy refashioned for pouch related morbidity. The majority of patients with functioning pouches remain satisfied with their outcome.

Restorative proctocolectomy offers obvious advantages in terms of the restoration of gastrointestinal continuity. Despite significant morbidity, RPC is preferred to the alternative of panproctocolectomy with permanent ileostomy. RPC should only be undertaken in a specialist unit and after careful counselling of the patient.

GYNÆOLOGICAL EFFECTS OF LONG-TERM USE OF TAMOXIFEN IN BREAST CARCINOMA PATIENTS

D. A. McNamaara, P. G. Horgan, M. Varley, P. Crowley, W. A. Tanner, F. B. V. Keane.
Department of Surgery, Meath and Adelaide Hospitals, Dublin 8.

Tamoxifen is universally used as adjunctive endocrine therapy in the management of patients with breast carcinoma. The optimum duration of tamoxifen therapy is controversial with some evidence that long-term use is associated with an increased risk of endometrial dysplasia and neoplasia. Fifty patients with a past history of breast carcinoma and taking tamoxifen as adjuvant treatment for longer than 5 yr, were contacted by post. All were invited for out-patient gynaecological assessment. Twenty patients attended with a mean age of 59.7 yr (range 43-70 yr) with a mean duration of tamoxifen treatment of 82 months.

All patients had a detailed history, general examination and specifically a gynaecological examination. Thirty-five per cent of patients complained of vasomotor symptoms. A variety of gynaecological symptoms were present including vaginal dryness (n=8), abnormal vaginal discharge (n=5), pruritus vulvae (n=4) and intermittent vaginal bleeding (n=2). Eighty per cent of patients complained of at least one of these symptoms. On general examination none of the patients showed evidence of local regional recurrence of breast carcinoma. Pelvic examination revealed abnormalities in 2 patients (cystocele 1, cervical poly1). The histology of the cervical poly1 was benign. Atrophic changes were noted in 4 patients. Endometrial thickness was measured using pelvic ultrasound. Mean endometrial thickness was 2.35 mm (range 1-7 mm). Mean endometrial thickness of a control age matched population was 1 mm. Suction biopsies of endometrium were obtained and histology was entirely benign in all cases.

We conclude that the majority of patients on long-term tamoxifen therapy experience significant gynaecological symptoms. In addition thickening of the endometrium is universally present but in this small study no progression to dysplasia or carcinoma has been detected.

INDUCTION OF HEAT SHOCK PROTEIN 72 ATTENUATES ISCHAEMIC/REPERFUSION-INDUCED MICROVASCULAR INJURY

G. Chen, C. Kelly, K. Stokes, A. Leahy, D. J. Bouchier-Hayes.
Royal College of Surgeons in Ireland, Department of Surgery, Beaumont Hospital, Dublin.

Leucocyte adhesion to endothelium and migration into interstitial tissue is a pivotal step in the pathogenesis of ischaemia/reperfusion (I/R) injury. Exposure of cells to a sub-critical stress, such as hyperthermia (thermotolerance) may protect cells from subsequent injury, possibly by inducing 72 kD heat shock protein (HSP72) expression in vitro. However, the effect of thermotolerance on leucocyte-endothelial interaction in vivo is unclear. The objective of this study was to investigate the effect of thermotolerance on leucocyte adherence and migration caused by I/R injury in rat mesenteric post-capillary venules (28-32μm). Sprague-Dawley rats were randomised into sham I/R, I/R and thermotolerance (T)+I/R groups. Thermotolerance was induced 18h prior to I/R injury by elevating core body temperature to 41±0.5°C for 15 min. Ischaemic/reperfusion injury was established by occlusion of the superior mesenteric vascular pedicle for 10 min, followed by 60 min of reperfusion. The number of adherent (Na) and migrated (Nm) leucocytes, and their rolling velocity (Rv) were measured by intravital microscopy at baseline (-10 min), ischaemia (0 min) and 10, 30, 60 min after reperfusion. HSP72 expression in mesentery, intestine and lung was determined by Western Immunoblotting.

Results: Mean ± SEM, Stat: Student's t-test, at 60 min reperfusion

| Group  | Sham I/R | I/R | T+I/R |
|--------|----------|-----|-------|
| Na     | 4.3 ± 1.20 | 40.0 ± 3.85*+ | 7.3 ± 0.88 |
| Nm     | 4.7 ± 0.33 | 51.8 ± 9.46** | 12.7 ± 3.84 |
| Rv (μm/sec) | 46.2 ± 1.82 | 30.0 ± 3.06*+ | 46.6 ± 1.74 |

Results: Mean ± SEM, Stat: Student's t-test, at 60 min reperfusion

* P<0.05 vs sham I/R, † P<0.05 vs T+I/R

We conclude that the majority of patients on long-term tamoxifen therapy experience significant gynaecological symptoms. In addition thickening of the endometrium is universally present but in this small study no progression to dysplasia or carcinoma has been detected.
In this model, induction of ischaemia resulted in a 92-94 per cent reduction in blood flow. I/R significantly increased the Na and Nm at 30, 60 min, and decreased the RV of leucocytes at 10, 30, 60 min after reperfusion. Thermotolerance significantly reduced the increase in Na and Nm and the decrease in RV elicited by I/R. Expression of HSP72 was induced in all tissues by T. Thermotolerance attenuated I/R induced leucocyte-endothelial interaction, possibly by increasing tissue expression of HSP72.

Abbreviations - I/R: ischaemia/reperfusion; HSP 72: 72 kD heat shock protein; T: thermotolerance; Na: number of adherent leucocytes; Nm: number of migrated leucocytes; RV: rolling velocity of leucocytes.

**IN-VIVO SUICIDE GENE DELIVERY INHIBITS TUMOUR PROGRESSION IN A MURINE MODEL OF BREAST CANCER**

E. Coveney*, H. K. Lyerly.

Department of Surgery, Duke University Medical Center, Durham, N.C.

Tumour cells that express the thymidine kinase (TK) gene are killed by exposure to the pro-drug ganciclovir. The widespread application of this effect to treat cancer is limited by the difficulty in transfecting tumour cells in vivo in sufficient numbers to induce a clinically significant 'bystander' effect. A novel gene delivery method was devised that produces efficient but transient transfection in primary tumours. Experiments were performed to examine the efficacy of direct in vivo introduction of a TK gene into murine breast cancer (4T1) using a liposome mediated approach. Balb/c mice (6/group) were inoculated s.c. with 1x10^6 4T1 tumour cells. On day 7, all tumours were injected with either 30 Âl of saline or 30ml of a plasmid DNA:liposome solution containing either an adeno-associated virus based TK gene (pMP6A/TK) or a control gene (pMP6A). At 48 hrs, groups of mice were either given intraperitoneal saline or ganciclovir (100 mg/kg) for 7 days. Animals were examined daily and tumour volume recorded using calipers.

| Treatment Group | Mean Tumour Vol: (cubic mm) |
|-----------------|----------------------------|
| In-vivo Gene Delivery | PBS | Ganciclovir |
| Saline | 810 | 740 |
| pMP6A | 680 | 760 |
| pMP6A-TK | 675 | 140* |

At 21 days, there was a significant reduction in growth of mouse tumours transfected with the TK gene (pMP61/TK) and treated with ganciclovir as compared with both untreated mice and all other control groups (P=0.001*, Kruskal-Wallis test). This result demonstrates that using liposome mediated suicide gene delivery, clinically effective in vivo treatment of human breast cancer can be achieved.

**IMPAIRED APOPTOTIC DEATH SIGNALLING IN INFLAMMATORY LUNG NEUTROPHILS IS ASSOCIATED WITH DECREASED INTERLEUKIN 1B CONVERTING ENZYME (ICE) EXPRESSION**

R. W. G. Watson, O. D. Rotstein, A. B. Nathens, J. Parodo, J. C. Marshall.

Department of Surgery, the Toronto Hospital and University of Toronto, CCRW 2-861, 200th Elizabeth Street, Toronto, M5G 2CA, Canada.

Termination of a PMN-mediated inflammatory response occurs in part through programmed cell death or apoptosis. Since persistent pulmonary leukocyte sequestration is characteristic of acute respiratory distress syndrome (ARDS), we hypothesised that PMN apoptosis may be impaired in acute lung injury.

Sprague-Dawley rats received 500 Âg intratracheally and were sacrificed 4 h later. Lung injury was quantified by the transpulmonary leak of 125I albumin, expressed as a permeability index (PI=lung/blood cpm). PMN were isolated from whole blood (WB) of control (Con) and LPS treated groups and from bronchoalveolar lavage fluid of LPS treated animals (BAL) (PMN) could not be isolated from Con lung). Rates of PMN apoptosis were quantified by flow cytometry using propidium iodide DNA staining and confirmed morphologically. PMN activation at 4 hr was measured as chemiluminescence (Chem) in response to PMA (5nM) and expressed as counts/5x10^6 PMN; CD11b expression was measured by flow cytometry as Lm mean channel fluorescence LmMCF).

LPS induced lung injury at 4 hr (P=0.22±0.03 Con, £p<0.05 vs Con). Lung exudate PMN (BAL) were activated and showed delayed apoptosis (Table).

| Group | % Apop 6h | 18h | 24h | Chem (x107) | CD11b (LmMCF) |
|-------|----------|-----|-----|------------|---------------|
| BAL | 34±9 | 48±7 | 62±3 | 21±1.3 | 32±10.2 |
| LPS WB | 13±3 | 30±9 | 44±6 | 1.9±0.2 | 39±13.3 |
| Con WB | 4±4* | 15±7* | 22±10* | 4.9±0.8* | 126±25.1* |

*Results=Mean±SD, ANOVA, *p<0.05 vs Con WB and LPS WB

Since LPS induces TNF-â, a trigger of apoptosis in vitro, we investigated the effects of intratracheal TNF-â (100 ng), similar reductions in apoptotic rates occurred in lung PMN following TNF-â at 6 h (6±7 per cent Apop, 18 h (11±10 per cent Apop) and 24 h (15±19 per cent Apop)) (n=5, £p<0.05 vs Con WB). Fas, a member of the TNF superfamily is a key trigger of PMN apoptosis. Both TNF-â (64±10 per cent) and Fas antibody (Clone CH-11, 100ng/ml) (68±7 per cent) increased the rates of Con WB PMN (45±5 per cent) apoptosis in vitro (n=3, p<0.05), but TNF-â (14±11 per cent) and Fas antibody (18±9 per cent) failed to induce apoptosis in transmigrated BAL PMN (17±8 per cent) (n=3). Fas receptor expression in con WB (4±0±0 LmMCF) and BAL (4.3±0.0 LmMCF) PMN was similar. Fas and TNFR1 are membrane proteins that signal for apoptotic cell death by downstream activation of the ICE family. ICE protein was measured by Western blot analysis in Con WB and VAL PMN and showed a decrease in Pro and Active ICE protein in the BAL PMN.

Conclusion: PMN transmigrating into an inflammatory focus are activated and have delayed apoptosis (Table). Transmigrating renders PMN refractory to subsequent signals for apoptosis from Fas/TNF and is associated with reduced levels of Pro and Active ICE protein. Altered responsiveness to physiologic apoptotic stimuli prolongs PMN functional survival during acute inflammation and may contribute to the tissue injury.
CELLULAR ORIGIN AND EFFECTS OF PROINFLAMMATORY CYTOKINES IN PATIENTS WITH OESOPHAGEAL CANCER

L. O'Mahony¹, J. Rothwell¹, J. Jackson², C. Feighery³, T. P. J. Hennessy¹, K. Mealy¹.
Department of Surgery¹ and Immunology², St. James’s Hospital, Dublin 8.

The proinflammatory cytokines may mediate the paraneoplastic phenomena associated with cancer. The aim of this study was to examine the regulation of proinflammatory cytokine production in patients with oesophageal carcinoma.

A novel flow cytometric technique allowed the detection of intracellular cytokine in peripheral blood mononuclear cells (PBMCs), from normal controls (n=18), pre-treatment oesophageal cancer patients (n=30 and in tumour and normal epithelium (n=11).

Intracellular tumour necrosis factor (TNF-α) and interleukin 6 (IL-6) levels from PBMC T cells and monocytes, were increased significantly (p<0.05) in the cancer patients when compared to normal controls at 0, 24, 48 and 72 h in culture, with or without PMA stimulation. Slight increases were observed for interleukin 1 (IL-18) in monocytes. The results for PMA stimulated TNF-α levels are expressed as median fluorescent intensity ± SEM and are given in the table.

|          | TNF-α          |
|----------|----------------|
|          | 0h             | 24h         | 48h         | 72h         |
| T cells  |                |             |             |             |
| Cancer   | 30±3           | 73±9        | 100±11      | 116±15      |
| Control  | 20±2*          | 43±7*       | 61±8*       | 67±12*      |
| Monocytes|                |             |             |             |
| Cancer   | 72±8           | 177±27      | 147±13      | 150±18      |
| Control  | 40±3*          | 113±16*     | 109±10*     | 108±18      |

*P<0.05 as determined by ANOVA analysis.

Changes in cytokine levels were also elevated in the cancer patients. TNF-α and IL-6 were increased in tumour infiltrating monocytes and T cells compared to cells from normal mucosa. There was also increased TNF-α and IL-6 in tumour epithelial cells when compared to normal epithelium. Maximal TNF-α and IL-6 levels were seen in those cancer patients who had lost weight, compared to those whose weight remained stable. This is the first report which conclusively demonstrates a global dysregulation of proinflammatory cytokine production in patients with solid gastrointestinal tumours. Cytokine responses appear to be associated with increased weight loss and acute phase response. These cytokines may provide novel therapeutic targets to alleviate both patient morbidity and mortality.