THE UNIVERSITY OF MELBOURNE

AUSTIN RESEARCH PRIZE

SURGERY AND ANAESTHESIA

Austin Health

SATURDAY, 26 NOVEMBER, 2005

LECTURE THEATRE
LEVEL 8, LANCE TOWNSEND BUILDING
AUSTIN CAMPUS

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8.30	**Breakfast**
9.00	**Introduction**
9.05	**Andrew J Barclay** – Obesity Surgery in a Rural Setting
9.15	**Bradley Newell** – Data Collection in Retrospective Cancer Research: Problems and Potential Solutions
9.25	**Timothy McIver** – Biochemical Criteria for Initiation of a Medical Emergency Team (MET) Response
9.35	**Nathan Lawrentschuk** – *In-vivo* Tumour Hypoxia, Angiogenesis and Characterisation of Carbonic Anhydrase IX Expression with Xenografted Human Renal Cell Carcinoma in Animal Models using ^{124}I-cG250 Positron Emission Tomography, Biodistribution, and Oxygen Studies
9.45	**Su-Wen Loh** – The Work on Gastrin Continues…
9.55	**Russell Hodgson** – The Role of Abdominal Surgery in Metastatic Melanoma
10.05	**Mehrdad Nikfarjam** – SMA-Pirarubicin Combined with Hyperbaric Oxygen Therapy for the Treatment of Colorectal Cancer Liver Metastases
10.15	**Christine Cuthbertson** – The Effects of Acute Pancreatitis on the Morphology and Pancreatic Microcirculation are Reversed by Hyperbaric Oxygen
10.25	**Benjamin J Dixon** – Preoxygenation Is More Effective in the 25° Head-up Position Than in the Supine Position in Severely Obese Patients
10.35	**Adjudication**
10.45	**Announcement of successful trainees**
10.55	**Presentation of Prize**

OBESITY SURGERY IN A RURAL SETTING

Authors: Andrew J Barclay, Steven R Clifforth, Olivia Warne

Background:
The authors set out to determine the ability to perform and the success of bariatric surgery within a rural setting.

Methods:
Patients were selected in a retrospective manner between January 1999 and March 2002. Over this period, 112 consecutive patients underwent an open vertical banded gastroplasty (VBG) by a single surgeon. 60 of these patients were contacted by phone and were asked to answer a standardized questionnaire. Their medical histories were also examined.
Results: 100% of patients were seen by the dietician (in both group and individual settings) and the anesthetist preoperatively. VBG was successful in more than 85% of patients, and weight loss was maintained over the study period. There was no mortality. Three patients required endoscopic stitch excision, one patient had the VBG reversed, and two required a repeat VBG.

Conclusions:
Obesity surgery can be achieved in a rural setting with minimal morbidity and successful weight loss.

DATA COLLECTION IN RETROSPECTIVE CANCER RESEARCH: PROBLEMS & POTENTIAL SOLUTIONS

Authors: B Newell, N Lawrentschuk, D Bolton

Background:

Surgical research is often performed retrospectively with advantages in study design including lower cost, decreased lead-time and reduced ethical considerations. Disadvantages include patient recall bias, differences in control and study groups, and interpretive bias of investigators obtaining the data. Furthermore, information available to the researcher may be of variable accuracy regarding completeness of data and if stored, may be difficult to extract or even be inappropriate for statistical analysis. There is a paucity of data regarding these difficulties in multi-centre research. The aim of this study is to highlight strategies and difficulties in creating a comprehensive database of retrospective data and to suggest potential solutions so that high quality data is collected and extracted in future studies.

Method:

As an example of creating a comprehensive retrospective database, we have been determining the role of CD151 as a prognostic tumour marker in prostate cancer with 220 patients examined thus far. Patients were initially recruited through anatomical pathology laboratories to ensure adequate tissue samples for CD151 immunohistochemistry. Once this cohort was established, the intention has been to correlate immunohistochemistry with disease progression and survival. Paper, microfilm medical records and electronic results were extracted from hospital files to extract demographic data, pathology results and outcome data from multiple institutions and departments. Data was extracted and entered in a newly constructed database after designing appropriate fields to capture all relevant and potentially relevant information for analysis.

Results:

The database contains over 20,000 cells of entered information. Of the 220 patients, 42 (19%) have been excluded on the basis of lack of information. This cohort largely reflects poor record keeping by clinicians or medical record disposal policies of hospitals. Of the 178 patients remaining, only 64 (36%) to date have final outcome data. Extracting data from microfilm of destroyed medical records took up to 4 hours per record. Furthermore, data from microfilm was incomplete in a number of cases.

Conclusions:

Retrospective data collection can be difficult and laborious, and may involve multiple data sources (paper, microfilm, electronic), multiple departments (pathology, radiology, medical records) and multiple agencies (eg. public hospitals, Cancer Council). Numerous problems pertaining to extensive retrospective outcome studies were identified. In addition to incomplete data, these included alternate reference ranges, inconsistent reporting of investigations and institutional medical record variability. Study design needs to incorporate adequate sample size to counter bias introduced by such variances. Database design should not only be inclusive so that records need only be scrutinized once, but have preempted statistical analysis software integration. Where hospitals destroy records following inactivity or death, archived tissue at that institution becomes unusable to the clinical researcher. This has significant implications for the Austin Tissue Bank and should be corrected by mandatory storage of all associated medical files. Ideally, prospective databases solve many problems, but are costly and may not include data that is later found to be appropriate. With the recognition of these pitfalls hopefully many of the difficulties experienced in this large study can be avoided in future.

Biochemical criteria for initiation of a Medical Emergency Team (MET) response

Authors: A/Prof. David A. Story, Prof. Rinaldo Bellomo, Dr. Timothy McIver, Dr Daryl Jones

Departments of Anaesthesia and Intensive Care, Austin Health, Heidelberg, Victoria.

Background:
The Medical Emergency Team (MET), activated after the observation of abnormal physiological markers that could progress to cardiac arrest, has been demonstrated to significantly reduce in-hospital mortality by facilitating timely and effective clinical intervention. Given that potentially life-threatening biochemical derangements can occur without obvious clinical signs, and suggestions that significant biochemical derangements are often under-reported, the establishment of biochemical criteria for activation of the MET has been proposed. With current MET staff resources in mind, we suggest that the generation of a MET call based on biochemical criteria every 1-2 days (on average) would be appropriate. This study aims to investigate the frequency of critically abnormal biochemistry results at Austin Health, with a view to proposing a set of biochemical criteria for activation of a Medical Emergency Team response that would generate a MET call on average every 1-2 days.

Methods:
Pathology at Austin Health provided a database containing biochemistry results for every patient who had Urea and Electrolytes (U+E) performed over a one month period, as well as arterial blood gas (ABG) samples linked to a U+E. The database was progressively culled to produce data exclusively relating to Austin Health inpatients serviced by the Medical Emergency Team. This produced a database with 2,962 blood samples. Sodium, Potassium, Bicarbonate, $PaCO_2$, and arterial pH were selected as the most appropriate biochemical parameters to investigate, due to the potentially lethal effects of significantly abnormal levels. Data was sorted to determine the frequency of significantly abnormal test results. Several sets of criteria for generation of a MET call (estimated to produce a MET call every 1-2 days) were constructed.

Results:
The frequency of hyponatraemia was surprising, with 184 (from total of 2962 = 6.2%) of blood samples returning a [Na]<130mmol/L. 6 samples (0.2%) had a [Na]<120mmol/L. Hypernatraemia was less common; 14 samples (0.5%) had a [Na] > 150mmol/L, and 1 sample had a [Na] > 160mmol/L. Regarding other electrolytes, 2 samples had a [K] > 7.0mmol/L, 3 samples a [K] < 2.5mmol/L, and 1 sample a $[HCO_3]$ < 10mmol/L. Only 8 ABG samples were recorded, but 2/8 had a $PaCO_2$ > 60mmHg, and 1/8 had a pH < 7.25. An example of 3 sets of biochemical criteria that would tend to generate a MET call every 1-2 days are:

Criteria 1: Na>155, Na<120, K>7.0, K<2.5, Bicarb<12, pH<7.25, pCO2>60 = 21 MET calls

Criteria 2: Na>160, Na<120, K>7.0, K<2.5, Bicarb<12, pH<7.25, pCO2>65 = 18 MET calls

Criteria 3: Na>160, Na<120, K>7.0, K<2.0, Bicarb<10, pH<7.25, pCO2>65 = 13 MET calls

Conclusions:
Potentially life threatening derangements of blood biochemistry occur quite frequently in the Austin Health inpatient population. A set of reasonable biochemical thresholds for activating the MET system is proposed.

In-vivo tumour hypoxia, angiogenesis and characterisation of carbonic anhydrase IX expression with xenografted human Renal Cell Carcinoma in animal models using ^{124}I-cG250 Positron Emission Tomography, Biodistribution, and Oxygen studies.

Authors: Nathan Lawrentschuk, C Murone, A Rigopolous, A Mountain, D Wang, G O'Keefe, G Jones, FT Lee, Ian Davis, Andrew M Scott, Damien M Bolton

University of Melbourne, Departments of Surgery and Urology; Ludwig Institute for Cancer Research and the PET Centre, Austin Health.

Introduction:

Hypoxia stimulates angiogenesis and has been demonstrated in tumours where it correlates with resistance to treatment and poor prognosis. We have demonstrated hypoxia in human Renal Cell Carcinoma (RCC). The purpose of animal models was to further evaluate oxygen levels within RCC whilst also focusing on expression of the protein carbonic anhydrase IX (CA IX). This protein is stimulated by hypoxia and involved in angiogenesis and may be a potential tumour target for imaging and future therapies. The human antibody cG250 binds to CAIX in vivo allowing biodistribution and PET studies when radiolabeled with iodine-124 (I^{124}).

Method:

Balb/c nude mice had human RCC (SK-RC-52) xenografted subcutaneously. Tumours were grown to different volumes with oxygen levels measured. Further groups then had the radiolabelled monoclonal antibody ^{124}I-cG250 (that binds to CA IX) injected intravenously and had Positron Emission Tomography (PET), gamma counting and oxygen studies performed on days 0, 1, 2, 3, 5, 7, 10 and 14 post injection. Immunohistochemistry and autoradiography was also performed.

Results:

An inverse relationship between tumour volume and hypoxia within the model was established ($P<0.001$). Furthermore, CA IX was expressed by tumours with maximal uptake of ^{124}I-cG250 on days 2/3 by distribution with gamma counting that could be correlated with uptake on PET imaging. Also, ^{124}I-cG250 as read by gamma counter correlated with noninvasive PET scanning standardised uptake values of the radioisotope within tumours. .

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Conclusions:

The xenograft model confirms our previous findings that human RCC are relatively hypoxic compared to normal tissue. Also, that the level of hypoxia is inversely proportional to tumour size. CAIX was confirmed as an imaging and potential therapeutic target in RCC. Finally, a correlation was made between PET scanning with ^{124}I-cG250 and biodistribution within tumours by gamma counting confirming the potential to serially PET scan animals rather than sacrifice in future biodistribution studies. This has major implications for animal ethics and the design of future biodistribution studies that are routinely used to characterised new radioisotopes and radiolabeled antibodies used to treat a variety of cancers.

THE WORK ON GASTRIN CONTINUES …

Author: Su-Wen Loh

The University of Melbourne, Department of Surgery, Austin Health.

First revealed by region specific radioimmunoassays and the sequencing of Gastrin cDNA decades ago, the multiple processing steps of Progastrin to Gastrin have been extensively studied over the years. This has enabled us to both understand better the mechanisms of post-translational processing and to determine the regulation of Gastrin production.

3 main types of amidated Gastrin (Gamide) are produced - G_{34}, G_{17} and G_{14} - containing 34, 17, and 14 amino acid residues respectively.
G_{17} is the principal form, and its main physiologic actions are two-fold:

1) to stimulate gastric acid and pepsin secretion in the stomach (*secretory action*) and,
2) to promote growth of the stomach and bowel mucosa (*trophic action*).

In recent times, we have shown that the non-amidated, glycine-extended form of Gastrin (Ggly) has actions independent of Gamide and is likely to work via a novel receptor. Ggly is more concerned with promoting the growth of bowel mucosa as opposed to the production of gastric acid and pepsin, i.e. its actions are mainly, or even solely, trophic. However, Ggly has a very short (2-3 minute) half-life.

Our current work focuses on the establishment of a more stable Ggly analog, in the hope of developing a "super agonist". Since substitution with D-amino acids often leads to increased stability against proteolysis, we will test, *in vitro*, the stereochemically inverted peptide (Acle$_5$ayamide), with and without reversal of the sequence (Acyae$_5$lamide). Biological activity *in vivo* will be assessed by restoration of colonic mucosal proliferation in gastrin-deficient mice.

The immediate benefit of such an agent would be the ability to further explore the *in vivo* effects of Ggly with a compound that is not metabolised within several minutes. Administration of the agent would be kinder, more practical and convenient.

In the long-term, these studies may well lead to new treatments for gastrointestinal disorders characterised by reduced mucosal function, such as in patients with gastrointestinal mucosal atrophy or those on prolonged total parenteral nutrition. In addition, defining effective antagonists to these peptides could open new doors in the inhibition of tumour growth for patients suffering from susceptible carcinomas.

THE ROLE OF ABDOMINAL SURGERY IN METASTATIC MELANOMA

Authors: Russell Hodgson, Michael Fink and Robert Jones

Liver Transplant Unit, Austin Health.

***Background*:**
Melanoma is the most common malignancy to metastasise to the gastrointestinal tract. With recent advances in radiological imaging increasing numbers of asymptomatic patients present with abdominal melanoma metastases. It has been common practice to offer surgery to all patients with isolated lesions, however the evidence that this practice alters disease progression is lacking. Surgery is also offered to those patients presenting with obstruction, gastrointestinal bleeding or constitutional symptoms. Our aim was to evaluate factors that predict improved survival following resection of intra-abdominal melanoma metastases. Factors studied included resection with curative (controlled extra-abdominal disease and complete macroscopic clearance of abdominal disease) or palliative intent, symptomatic versus asymptomatic status, age, number, size and location of metastases, time since diagnosis of primary, depth of primary, serum albumin and LDH.

***Methods*:**
This was a 7.5 years observational study conducted in the Department of Surgery at the Austin Hospital from 1997 to 2005. All patients who underwent surgery for abdominal metastatic melanoma were included. Twenty-five patients were recruitedData were analysed by Kaplan-Meier and logrank test.

***Results*:**
The median survival for the whole cohort following abdominal surgery was 8.3 (range 0.4 – 41.1) months. Eight of the 25 patients remain alive with three of these patients currently disease free. Fourteen patients who underwent resection with curative intent had improved survival compared with 11 patients who underwent palliative resection (12 month survival 89% vs 10%, respectively, $p<0.0001$). Other significant positive prognostic indicators were age less than 60, number of metastases up to two, serum albumin greater than 35 g/l and solid organ location of lesions. Factors that were not predictive of survival included symptomatic versus asymptomatic status, size of metastases, time since diagnosis of primary, depth of primary and serum LDH. Of patients with pre-operative symptoms, 87% had resolution of these symptoms. Overall operative morbidity was 12% and 30-day mortality was 4%.

***Conclusion*:**
In a highly selected group of patients with intra-abdominal melanoma metastases (those with controlled extrahepatic disease who underwent resection with macroscopic clearance of intra-abdominal disease), resection of intra-abdominal metastases resulted in prolonged survival compared with patients who underwent palliative resection. However, those who underwent palliative resection had good relief of symptoms. In addition to surgery with curative intent, age less than 60, number of metastases up to two, serum albumin greater than 35 g/l and solid organ location of metastases were associated with improved survival.

SMA-PIRARUBICIN COMBINED WITH HYPERBARIC OXYGEN THERAPY FOR THE TREATEMENT OF COLORECTAL CANCER LIVER METASTASES

Authors: M Nikfarjam, H Maeda, I Millar, C Christophi.

Department of Surgery, University of Melbourne, Austin Health.

Background:
Styrene Maleic Acid Tetrahydropyrandol doxorubicin (SMA-Pirarubicin) is a reactive oxygen species (ROS) generating drug with highly selective tumour retention properties. The combination of SMA-Pirarubicin with Hyperbaric oxygen (HBO) may have synergistic effects and was tested in a murine model of colorectal liver metastases.

Methods:.
Colorectal liver metastases were induced in CBA strain mice using a murine cell line. After ten days animals were randomly divided into four groups (n=8): 1.Control, 2.HBO therapy only, 3.SMA-Pirarubicin (75mg/kg) and 4.SMA-Pirarubicin (75mg/Kg) plus HBO therapy. Four courses of HBO were administered at 2.4 atmospheres for 90 minutes during the course of divided drug administration. Animals were killed 21 days following tumour induction and the cross-sectional area of tumours (n=100-200) were determined by stereological analysis. Tumour vasculature was assessed by scanning electron microscopy of microvascular resin casts.

Results:
No clinical evidence of toxicity was detected in any animals. Mean cross-sectional tumour diameter in mm^2(S.E) Group 1.Control: 5.9 mm^2 (0.17), Group 2. HBO therapy: 6.8 mm^2 (0.22) (not statistically different P=0.155), Group 3. SMA-Pirarubicin: 1.42 mm^2 (0.04) ($P<0.001$ vs control), Group 4. SMA-Pirarubicin + HBO: 1.22mm^2 (0.03) (P=0.015 vs SMA-Pirarubicin alone). Complete tumour remission was seen in only the combined therapy group. SMA-Pirarubicin, with or without HBO, produced marked disruption of tumour microvasculature compared to controls.

Conclusions:
SMA-Pirarubicin is effective in the treatment of colorectal liver metastases. Its effect on tumour growth is further improved by the administration of HBO.

THE EFFECTS OF ACUTE PANCREATITIS ON THE MORPHOLOGY OF PANCREATIC MICROCIRCULATION ARE REVERSED BY HYPERBARIC OXYGEN.

Authors: C. Cuthbertson, K. Su, C. Malcontenti-Wilson, V. Muralidharan, C. Christophi

University of Melbourne, Department of Surgery, Austin Health.

Introduction:
Severe acute pancreatitis is characterised by alterations to the microcirculation, particularly affecting the capillary tree, which leads to pancreatic necrosis. The morphology of the pancreatic microvasculature is known to be affected in severe pancreatitis, but the effect of hyperbaric oxygen (HBO) is unknown. This study assesses the effect of severe pancreatitis on pancreatic capillary morphology and the impact of HBO on these changes.

Methods:
Sixty six male albino Wistar rats weighing 250-350g were induced with severe pancreatitis by biliopancreatic infusion of 4% sodium taurocholate. Animals were randomised to either HBO treatment or control. HBO treatment (100% oxygen for 90 minutes at 2.5 Atmospheres) was commenced 6 hours following induction of pancreatitis, and continued 12-hourly. Surviving animals underwent microvascular polymer casting of the pancreas at 24 and 48 hours following commencement of treatment, and equivalent time points for control animals. Microvascular casts were created by the injection of freshly prepared Mercox resin through a cannula in the thoracic aorta. Scanning electron micrographs of the casts were compared using stereological analysis of capillary diameter, heterogeneity of capillary diameter and capillary density. Results (Mean ± SE) were compared by ANOVA analysis (post-hoc Tukey).

Results:
The normal pancreas had a dense capillary network with mean diameter of 6.3μm (±0.20), with minimal heterogeneity (SD 2.54 ±0.164). The capillary density was 1185 ± 39.5 μm^{-1}. At 24 hours post pancreatitis, the mean capillary diameter was significantly larger than normal in both control and HBO groups (10.3 ±0.33μm and 9.5 ± 0.21μm; $p<0.001$ and $p=0.043$, respectively). The remaining morphological comparisons were not significantly different from normal, and the treatment and control groups were similar. At 48 hours post induction of pancreatitis, the control animals had increased pancreatic capillary diameter (11.9 ±0.54μm vs. 6.3 ±0.20μm, $p<0.001$), increased heterogeneity of capillary diameter (5.00 ±0.52 vs. 2.54 ±0.16, $p=0.007$) and decreased capillary density (735 ±23.7μm^{-1} vs. 1185 ±39.5μm^{-1}, $p<0.001$). Treatment with HBO caused a significant reduction in capillary diameter (8.29 ±0.15μm vs. 11.9 ±0.54μm, $p<0.001$), reduction in heterogeneity (2.83 ±0.12 vs. 5.00 ±0.52, $p=0.015$) and increased capillary density (895.72 ±13.5 μm^{-1} vs. 735 ±23.7 μm^{-1}, $p=0.001$).

Conclusion:
Pancreatic capillary morphology is significantly changed by acute pancreatitis and 24 and 48hours. Hyperbaric oxygen therapy influences these changes and reverts the pancreatic microvasculature toward the normal state. It is likely that HBO treatment in pancreatitis mediates its effects at least partially via effects on the microvasculature.

PREOXYGENATION IS MORE EFFECTIVE IN THE 25° HEAD-UP POSITION THAN IN THE SUPINE POSITION IN SEVERELY OBESE PATIENTS

Authors: B J Dixon, J B Dixon, J R Carden, A J Burn, L M Schachter, J M Playfair, C P Laurie, P E O'Brien

Background:
Class III obsess patients have altered respiratory mechanics, which are further impaired in the supine position. The authors explored the hypothesis that preoxygenation in the 25° head-up position allows a greater safety margin for induction of anaesthesia than the supine position.

Methods:
A randomized controlled trial measured oxygen saturation and the desaturation safety period after 3 min of preoxygenation in 42 consecutive (male:female 13:29) severely obese (body mass index > 40 kg/m^2) patients who were undergoing laparoscopic adjustable gastric band surgery and were randomly assigned to the supine position or the 25° head-up position. Serial arterial blood gases were taken before and after preoxygenation and 90 s after induction. After induction, ventilation was delayed until blood oxygen saturation reached 92%, and this desaturation safety period was recorded.

Results:
The mean body mass indexes for the supine and 25° head-up groups were 47.3 and 44.9 kg/m^2, respectively (P = 0.18). The group randomly assigned to the 25° head-up position achieved higher preinduction oxygen tensions (442 ± 104 *vs.* 360 ± 99 mmHg; P = 0.012) and took longer to reach an oxygen saturation of 92% (201 ± 55 *vs.* 155 ± 69 s; P = 0.023). There was a strong positive correlation between the induction oxygen tension achieved and the time to reach an oxygen saturation of 92% (r = 0.51, P = 0.001). There were no adverse events associated with the study.

Conclusion:
Preoxygenation in the 25° head-up position achieves 23% higher oxygen tensions, allowing a clinically significant increase in the desaturation safety period – greater time for intubation and airway control. Induction in the 25° head-up position may provide a greater safety margin for airway control.

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