Conference Report

Conference Report 25th Annual Scientific Meeting of the American Pain Society (APS), San Antonio, USA, Wednesday to Saturday, May 3-6, 2006 – Part 2

> Dr Mike Butler,

Rheumatologist/Pain Medicine Specialist,

Conference Report

Conference Report 25th Annual Scientific Meeting of the American Pain Society (APS), San Antonio, USA, Wednesday to Saturday, May 3-6, 2006 – Part 2

> Dr Mike Butler,

Rheumatologist/Pain Medicine Specialist, Rheumatology Department, Greenlane Clinical Centre, Auckland,

Member of the Education and Training Committee, Faculty of Pain Medicine, ANZCA

Now to the Symposia.

In the first group I attended "What does it mean to have a right to pain relief?" mention being made of references Taylor S et al. Has the pendulum swung too far in post operative pain control? Am J Surg 2003;186:472-475, and Vila Jr H et al. The efficacy and safety of pain management before and after implementation of hospital wide pain management standards: is patient safety compromised by treatment based solely on numerical pain ratings? Anesth Analg 2006;101:474. Robert Kerns PhD, National Programme Director for Pain Management, VA Central Office Chief, Psychology Service, VA Connecticut Healthcare System and Professor of Psychiatry, Neurology and Psychology, Yale University, outlined the VHA National Pain Management Strategy, which has a focus on cancer pain management. JD Benrige, PhD, Associate Professor of Bioethics, University of California Davis School of Medicine reviewed "A right to pain: ethical, legal and public policy considerations," emphasising the uneasy relationship between ethics and law. Certain lessons from the jury box were reviewed. Mark Sullivan MD PhD, Professor of Psychiatry University of Washington, who was the FPMANZCA Visiting Professor in Auckland in 2005, covered complex territory "On the varieties of painful experience. Is there one right to pain relief?," with emphasis on pain at the end of life, then chronic non cancer pain management, in the latter case emphasising that pain relief cannot stand alone as the goal of clinical treatment. Reducing pain and function to zero may not necessarily be successful treatment except perhaps at the end of life. He commented that patient rights are a very blunt tool.

Alternative Symposia at that time were "The pain within: pain modulation by the amygdala,"(79 PP slides), "Understanding pain and social context: new findings from patient partner dyads" (66 PP slides), "Peripheral sensitisation and inflammation: sensory nerves are a two way street" (100 PP slides), and "Adverse events following cervical injections for pain" (72 PP slides, also an 8 page article on "Injection complications: cervical interlaminar epidural steroid injections and AA/AO joint injections" by Ray Baker MD, Clinical Professor, Department of Anaesthesiology University of Washington, and a 30 page article (not published in the literature) on "Cervical discography: diagnostic value and complications" by Richard Derby MD, ending with 58 references.

Some comments should be made on the Symposium "The pain within: pain modulation by the amygdala", as this region of the brain is becoming of particular interest to neuroscientists in relation to pain modulation. By "The pain within" is meant pain produced not (only) by exogenous tissue damage but triggered and/or amplified by endogenous CNS mechanisms (brain activation level), emotional effective state (stress, anxiety, depression), and cognitive processes (attention, vigilance). So why the importance of the amygdala (which is oval shaped and lies just anterior to the hippocampus)? It has been long known for its important role in attaching emotional significance to sensory stimuli, its involvement in emotional-affective states and disorders (learned fear, anxiety, depression), and there is now growing evidence that it is linked to the "pain matrix". It contains a subdivision dedicated to nociceptive processing (latero-capsular part of the central nucleus), and it receives relatively "unprocessed" nociceptive information directly without involving the thalamus and cortex. Inputs may then be transmitted to the central amygdala, and thereby to the thalamus and cortex. Amygdala outputs may be facilitatory/excitatory, as well as inhibitory, though it is not yet decided whether the facilitatory effects are due to inhibition of the descending inhibitory mechanisms thereby leading to disinhibition and increased pain, or increased activity in the descending facilitatory pathways. The bottom line is that the amygdala modulates pain through direct coupling to "downstream" and "upstream" targets, involving brain stem centres of the endogenous descending pain control system (PAG-RVM-dorsal horn), and the thalamo-cortical systems involved in cognitive processes (attention, vigilance).

An important reference is Ledoux. The emotional brain, fear and the amygdala. Cell Mol Neurobiol 2003;23:727-38 in which evidence is given that the amygdala has been shown to be an important substrate for fear conditioning, conditioned taste aversion, conditioned place preference, and probably chronic pain. RW Gereau, PhD, from the McDonnell Centre for Higher Brain Function at the Washington University Pain Centre presented evidence at this Symposium that in the rat paw inflammation leads to ERK activation in the CeLC (LC = locus coeruleus), this activation restricted to the right amygdala independent of the site of inflammation, apparently necessary for expression of inflammation induced increases in pain perception, and sufficient to induce pain sensitivity, the result suggesting a dominant role of the right amygdala in the processing of the affective component of pain.

Checking the Journal of Neuroscience since 2005 showed the following articles relating to the amygdala (authors names omitted in the interest of space):

- Unilateral storage of fear memories by the amygdala. 20/04/05 issue, Vol 25:4198-4205;
- Auditory fear conditioning and longterm potentiation in the lateral amygdala require ERK/MAP kinase signalling in the auditory thalamus: a role for pre-synaptic plasticity in the fear system. 15/06/05 issue, Vol 25:5730-5739;
- A subpopulation of neurons in the medial pre-frontal cortex encodes emotional learning with burst and frequency codes through a dopamine D4 receptor-dependent baso-lateral amygdala input. 29/06/05 issue, Vol 25:6066-6075;
- Prefrontal control of the amygdala. 10/08/05 issue, Vol 25:7429-7437; Bidirectional modulation of hypocampal longterm potentiation under stress and no stress conditions in basolateral amygdala lesioned and intact rats. 10/08/05 issue, Vol 25:7393-7340;
- Comparisons of the effects of bilateral orbital prefrontal cortex lesions and amygdala lesions on emotional responses in Rhesus monkeys. 14/09/05 issue, Vol 25:8534-8542;
- Previous stress facilitates fear memory, attenuates GABAergic inhibition, and increases synaptic plasticity in the rat basolateral amygdala. 21/09/05 issue, Vol 25:8725-8734;
- Lesions of the basal amygdala block expression of conditioned fear but not extinction. 19/10/05 issue, Vol 25: 9680-9685;
- Critical role of CGRP-1 receptors in the amygdala in synaptic plasticity in pain behaviour. 16/11/05 issue, Vol 25:10717-10728;
- Specificity in the projections of prefrontal and insular cortex for ventral striatopallidum and the extended amygdala. 14/12/05 issue, Vol 25:11757-11767;
- Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. 19/04/06 issue, Vol 26:4415-4425;
- Role of substantia nigra-amygdala connections in surprise-induced enhancement of attention. 31/05/06 issue, Vol 26:6077-6081;
- Cannabinoids potentiate emotional learning plasticity in neurons with the prefrontal cortex through basolateral amygdala inputs. 14/06/06 issue, Vol 26:6458-6468;
- Amygdala response to facial expression reflects emotional learning. 30/08/06 issue, Vol 26:8915-8922.

Also in the journal "The Neuroscientist" since 2005 there are references:

- Amygdala, longterm potentiation, and fear conditioning in the February 2005 issue, Vol 11:75;
- Vasopressin and oxytocin target different neurons in amygdala. August 2005 issue, Vol 11:267;
- Human amygdala and fear recognition. October 2005 issue, Vol 11:397.

I rest my case in regard to a considerable volume of neuro-science literature on the amygdala!

Now to the clinical arena

There is a growing research literature relating to the possible role of amygdala dysregulation in chronic visceral pain, in this Symposium a contribution being given by Emeran Mayer MD from his group at the Centre for Neurovisceral Sciences and Women's Health, David Geffen School of Medicine at UCLA. Mayer's group have developed a valid and reliable psychometric instrument which measures gastrointestinal symptom-specific anxiety. The final unidimensional 15-item scale, the Visceral Sensitivity Index, demonstrated good content, convergent, divergent and predictive validity. Labus JS et al. The Visceral Sensitivity Index: development

THE AMYGDALA MODULATES PAIN THROUGH DIRECT COUPLING TO "DOWN-STREAM" AND "UPSTREAM" TARGETS, INVOLVING BRAIN STEM CENTRES OF THE ENDOGENOUS DESCENDING PAIN CONTROL SYSTEM, AND THE THALAMO-CORTICAL SYSTEMS INVOLVED IN COGNITIVE PROCESSES.

Broad societal interest in pain provides strong impetus for improving pain curriculum for medical (and other) undergraduates.

and validation of a gastrointestinal symptom-specific anxiety scale. Aliment Pharmacol Ther 2004;20:89-97. As patients with mild chronic inflammation of the rectum or ileum have reduced perceptual responses to rectosigmoid distension compared with patients with irritable bowel syndrome (IBS) they then undertook a study seeking to identify differences in regional cerebral blood flow during rectal distension which might correspond to these perceptual differences. IBS patients showed greater activation of the amygdala, rostroventral ACC, and dorsomedial frontal cortical regions, whereas in contrast no significant differences were observed between ulcerative colitis (UC) and controls. When the two non-IBS groups were combined, functional connectivity analyses showed that right lateral frontal cortex (RLFC) activation positively correlated with activation of the dorsal pons/periaqueductal gray, a key region involved in endogenous pain inhibition. In the sample studied (7 male IBS patients, 8 male UC patients in clinical remission, and 7 healthy male controls) the primary difference between functional and quiescent inflammatory disease of the colon was in terms of greater activation of limbic/paralimbic circuits in IBS, and inhibition of these circuits in UC and controls by the RLFC. Mayer EA et al. Pain 2005;115:398-409. In a further study, reviewed in this Symposium, it was sought to evaluate hyper-vigilance in IBS visceral hypersensitivity and associated brain activity. PET was used in a subset of 12 (20) female IBS patients and 14 healthy controls, studied 6 times over 12 months, obtaining images during baseline, rectal distensions, and anticipation of an aversive distension during the first and last session. Perceptual ratings of the rectal distensions normalised over 12 months, whereas IBS symptom severity did not. Stable activation of the central pain matrix was observed over 12 months, activity in limbic, paralimbic, and pontine regions decreasing, but during the anticipation condition there were significant decreases in amygdala, dorsal anterior cingulate cortex, and dorsal brainstem activation at 12 months. Covariance analysis supported the hypothesis of changes in an arousal network including limbic, pontine, and cortical areas underlying the decreased perception seen over the multiple stimulations. Summarising, in IBS patients, repeated exposure to experimental aversive visceral stimuli results in the habituation of visceral perception and central arousal, in spite of stable activation of networks processing visceral pain and its anticipation. Naliboff BD et al. Longitudinal change in perceptual and brain activation response to visceral stimuli in irritable bowel syndrome patients. Gastroenterology 2006;131:352-365.

Also in relation to irritable bowel syndrome there are important articles Cremonini F, Talley NJ. Treatments targeting putative mechanisms in irritable bowel syndrome. Gastroenterology and Hepatology (Nature Publishing Group) 2005; 2:82-88; Enck P. Factors affecting therapeutic placebo rates in patients with irritable bowel syndrome. Gastroenterology and Hepatology (Nature Publishing Group) 2005;2:354-437; and (just published) Talley NJ. Irritable bowel syndrome (clinical perspectives). Internal Medicine Journal 2006;36:724-728 (= the official journal of the RACP).

Second group of Symposia

I attended "Beyond psychogenic pain: "explaining" unexplained pain", other options in that session being "Recent insights into analgesic mechanisms of acupuncture and TENS" (82 PP slides and a one page reference list), "Palliative care and acute care in outpatient settings" (88 PP slides and 8 pages of assessment scales palliative care screening tool, and palliative performance status scale), also "Cardiovascular and pain regulatory system interactions: implications for hypertension risk and chronic pain" (74 PP slides and one page of references), and "Pathways to pain: injury and the regulation of neuronal calcium (115 PP slides).

Third group of Symposia

I attended "Advances in medical education about pain". The comment was made that "curricular sclerosis" is an endemic disease in most medical schools, and efforts at improving the standard, and increasing time, of pain education meet with frustration most of the time owing to other sub-specialities feeling threatened. This Symposium was very much a Johns Hopkins School of Medicine presentation, a pain curriculum development team having been formed and the suggested Johns Hopkins Curriculum (working document) was:

1 **core:** epidemiology in public health, anatomy, pain basic terminology, mechanisms of pain treatments, approach to patient with pain ie. assessment/diagnosis/treatment, pain alphabet, pain psychophysics;

2 PHARMACOLOGY: COX inhibitors, neuromodulating agents, opiates, applied basic science/drug development;

3 CLINICAL SKILLS: interview skills, examination skills, treatment decisions, team communication, counselling pain patients, practice prescribing;

4 TREATMENTS: medical/pharmacological, interventional management, rehabilitation, acupuncture, clinical psychological approaches;

5 SPECIFIC: pain diseases: acute and surgical pain, paediatric pain, low back pain, headache, neuropathic pain, oncologic pain, visceral pain, bone pain, cognitively impaired populations; and

6 PAIN CHALLENGES: the difficult patient, personality disorders, employment issues, drug addiction, comorbid illness, medicolegal ie. licensing and documentation, and pain emergencies.

A specific curriculum agenda with times was shown, but the PowerPoint slide reproduction gives printing too small to see, though one could email the presenter for a copy. Teaching methods that will foster active learning were summarised as: patient testimonials with interactive Q and A, pain lab encounters – psychophysics of pain, video clips poor/better/best techniques, role playing/scripting with emphasis on interview skills, directed journal article reading with critical analysis, computer simulations with case based practical pharmacology, practice writing prescriptions with emphasis on reduction of errors, painful procedures for patients with student survey of patients, small group discussions of specific diseases, brief written assessment of a pain problem, and standardised patients to teach exam skills. The summary of medical student education was that broad societal interest in pain provides strong impetus for improving pain curriculum for medical undergraduates that medical students should learn about pain, but that the factors apparently leading to lack of interest in medical students (and medics) in pain science/diagnosis/management are unclear. The hypothesis was offered that a clinically oriented curriculum will hold more appeal, and important considerations include the extent to which immersion improves the understanding of pain medicine by generalists, and the utility of various educational methods.

Other options in that session of Symposia were "Links between pain and emotional regulation: neurobiological and cognitive mechanisms" (76 PP slides and one page of references), "Small interfering RNA as experimental therapeutics for pain" (19 PP slides), "Cross cultural validity in pain assessment measures (40 PP slides), and "Discogenic low back pain: making sense of the range of new therapeutic options" (98 PP slides and one page of references).

Fourth group of Symposia

I attended "Current understanding of pelvic pain disorders: implications for multidisciplinary approaches" (124 PP slides, and reproduction of the article Wesselmann U. Chronic pelvic pain. (eds) Turk DC, Melzack R. Handbook of pain assessment 2nd edition 2001, The Guilford Press, Chapter 29 pp 567-578).

Other options in that session were "Systemic lignocaine: does it have a place in modern pain management?" (60 PP slides, 3 page summary, and 7 pages of references), "Hypnotic analgesia: new findings and applications" (60 PP slides), "Individual differences in pain and analgesia: a blessing not a curse" (no PP slides), and "Pain gain in the brain (and spinal cord): ion channel modulation in central sensitisation" (68 PP slides, the final slide giving references).

Fifth group of Symposia

I attended "Spinal second messenger pathways under different pain conditions" (40 PP slides), other options "Assessment and educational intervention in paediatric palliative care: bridging the health care provide – patient gap" (64 PP slides), "The epidemiology of prescription opioid abuse" (no PP slides), "Sexual dysfunction in chronic pain" (43 PP slides with article Danielle H W. Hypogonadism in men consuming sustained action oral opioids. The Journal of Pain 2002;3:377-384, and "Predicting acute and chronic pain: genetic, psychological and neural factors," (79 PP slides).

Sixth and final group of Symposia

I attended "Migraine: understanding the influences of sex hormones on the pathogenesis, clinical presentation, and management of migraine in women" (88 PP slides), an excellent session, other options being "New techniques in the treatment of acute and procedural pain in children" (article on "Topical anaesthetics: an update" by Constance Houck MD, Department of Anaesthesiology, Perioperative and Pain Medicine, Children's Hospital, Boston which is excellent and concludes with good references, article on "Virtual reality analgesia" by multiple authors from the University of Washington and Seattle with excellent references, noting also additional PP slides 28), "Role of spinal glutamate transporters in pain and opioid tolerance" (42 PP slides), "Predicting treatment efficacy to analgesic drugs in neuropathic pain: lessons from the worlds of epilepsy and depression" (no PP slides), and "Sex, pain, and the primary afferent" (51 PP slides).

Final comments

The discipline of Neurology is now being encouraged to look

at Pain Medicine more seriously as a sub-specialty. Particularly important is the publication of the book (ed) Pappagallo M. The neurological basis of pain. McGraw-Hill Medical Publishing Division. 2005 (ISBN 0-07-144087-9). This is a pain medicine textbook (673 pages) published as a companion to the popular Adams and Victor's "Principles of Neurology." The interesting comment is made in the Preface by Marco Pappagallo MD ..."While our book is addressed to neurologists, a variety of professionals....will benefit from it...Thus, even pain specialists should find this textbook a source of the most recent information and references"..... For those of us interested in pain medicine over many years I find myself speechless at the phrase.. "even pain specialists"....!!

It is also interesting to note a recent article in the journal Neurology by Lalani I. Emerging subspecialties in neurology: pain medicine. Neurology 2006;67:1522-1523, in which the comment is made ..... "pain medicine was recognised in 1998 by the American Board of Medical Specialties (ABMS) as a neurologic subspecialty. The first pain medicine certification examination was given by the American Board of Psychiatry and Neurology (ABPN) in 2000. There are currently four approved pain medicine fellowship programmes listed on the Accreditation Council on Graduate Medical Education (ACGME) website (www.acgme.org), while 18 neurologists were certified in pain medicine in 2005 (www.abpn.org). Other specialties with accredited pain medicine fellowships include anaesthesiology (90 programmes), physical medicine and rehabilitation (11 programmes), and psychiatry (1 programme). The ACGME has uniform accreditation criteria for all pain fellowships. These include training in interventional procedures, behavioural and psychological approaches, pharmacotherapy, and rehabilitation. Several non neurology based pain fellowships also accept neurology applicants but there remains a need for expanding access for neurologists to multidisciplinary pain fellowships".....the final sentence of the article is..... "further work remains to be done to encourage neurologists to specialise in pain medicine". Perhaps of some relevance to this is a significant article on the issue of educating the public, school students in particular, on the value of science in general, and neuroscience in particular (some excellent websites are given). Schwartz-Bloom R. Science education: a neuroscientist's view of translational medicine. J Neurosci 5005;25:5667-5669 (15/06/05 issue).

To come full circle back to the American Pain Society, the most recent issue of its official journal "The Journal of Pain" has an Editorial by GF Gebhart updating members of the American Pain Society (who receive the monthly journal as part of their subscription) on the progress of the journal. The monthly page count will now increase from approximately 75 to 90 pages per issue as the number of submitted manuscripts increases. The Impact Factor (ISI-Thomson Scientific) increased by more than one-half point in the past year to 2.885. The Impact Factor, a measure of the number of times articles in the journal are cited in the literature, and thus a reflection of their "impact," has steadily increased over the past four years. The journal now ranks a clear second among all pain-related journals within the specialty categories of "clinical neurology" and "neurosciences."

The next ASM of the APS will be in Washington, DC May 2-5, 2007. I do hope more New Zealander and Australian pain-interested health professionals will be there, than at the last few Meetings! ■

This Conference Report has deliberately summarised the PP slide numbers for presentations for which they were available, so should the reader particularly like to have these in relation to a particular topic/topics, please email me: mbutler@adhb.govt.nz making sure that you send your postal address.