Review article

Colonic manometry and sacral nerve stimulation in patients with severe constipation

PHILIP G. DINNING

Department of Medicine University of New South Wales, St George Hospital, Kogarah, NSW 2217, Australia

Abstract: The current treatment options that are available for patients with severe chronic constipation are unsatisfactory. Long-term high dose laxative therapy produces significant morbidity in some, with ongoing bloating and abdominal pain. In refractory cases subtotal colectomy has become increasingly popular. However this is a major abdominal procedure with all the normal associated risks. Less invasive procedures for the treatment of constipation are being sought. However, improved therapies can only stem from a better understanding of the phenomena underlying severe constipation. Colonic propagating pressure wave sequences (PSs) are responsible for discrete movements of content and are vital for normal defaecation. Deficiencies in PS frequency, amplitude and extent of propagation are all implicated in severe defaecatory dysfunction. Mechanisms that can normalise these aberrant motor patterns may help rectify the problem. Recently the novel therapy of sacral nerve stimulation (SNS) has been utilized for the treatment of severe constipation. The results from a limited number of studies are encouraging, with improved stool frequency commonly reported. However, little is known of the effects of SNS upon colonic motor patterns. Colonic manometry provides the ideal test-bed to examine this phenomenon. Additionally colonic manometry can be used as a measurement tool to evaluate a range of stimulus parameters and determine those that give the optimal colonic response.

Key words: Constipation; Colonic manometry; Sacral nerve stimulation.

CONSTIPATION, EPIDEMIOLOGY AND HEALTH CARE BURDEN

Constipation, a common cause of morbidity, is estimated to affect between 15 and 27% of the western world.[1] The prevalence increases to 30-40% of people aged over 65.[2] Direct and indirect costs and resource utilisation are substantial. Chronic constipation in the US accounts for 13.7 million days of restricted activity and 3.4 million days of bed disability.[3] The diagnosis and management of constipation leads to 5.7 million physician visits and 0.6 million hospitalisations per year, accounting for total costs of $US235M (2006 value).[4] Drug costs are high with $US368M per yr (1985 value) being spent on over the counter remedies [5] and an additional $US22M per year spent on prescription drugs.[6]

For many constipated patients laxative use will sufficiently alleviate their symptoms. However, for patients in whom laxatives do not restore normal bowel habit increased abdominal pain and bloating can result. Some patients, particularly those with obstructed defaecation can undergo a trial of biofeedback therapy, which can demonstrate significant improvement in quality of life and stool frequency.[7, 8] However, the long-term efficacy (>1yr) in patients with severe slow transit constipation is poor.[9, 10] Overall at least 36% of those presenting to the clinic subsequently fail non-surgical therapies (diet, bulking agents, laxatives, biofeedback).[11] These patients can be extremely debilitated with physiological functioning, mental health, general health and bodily pain all scoring poorly on quality of life questionnaires in comparison to health.[12] For such cases subtotal colectomy becomes an option. However as this is a major abdominal procedure it comes with all of the normal associated risks. In addition patients can develop post-operative small and large bowel complications such as intractable diarrhoea, small bowel obstruction, faecal incontinence and recurrent constipation.[13, 14]

COLONIC PROPULSIVE MOTOR PATTERNS IN HEALTH AND PATIENTS WITH CONSTIPATION

The cause of severe constipation remains undetermined; however abnormal colonic motor patterns are implicated. In health studies utilising combined colonic manometry and scintigraphy have shown that colonic propagating sequences (PS) and high amplitude propagating sequences (HAPS) are temporally associated with discrete movement of colonic content.[15-17] Studies in health also demonstrate that defaecation is preceded by a series of PSs and HAPSs in which the site of origin of each PS approaching stool expulsion moves in an orad direction (Fig. 1).[18] These data indicate that defaecation is a complex process incorporating the entire colon. Indeed in health motor activity in the proximal colon is an essential component of defaecation. Our own studies have also demonstrated that this pre-defaecatory colonic response is absent in patients with obstructed defaecation.[19]

It is recognised that both HAPSs and long-extent PSs are deficient or absent in severe slow transit constipation [20-22] although the neural apparatus necessary for the generation of these motor patterns appears to be intact because intraluminal irritant laxatives can trigger them.[16, 23] This observation suggests that extrinsic or intrinsic factors capable of modulating the propulsive characteristics of PSs are likely to contribute to the pathogenesis of constipation.

The actual mechanisms involved in the induction of these propulsive pressure waves are only partially understood.

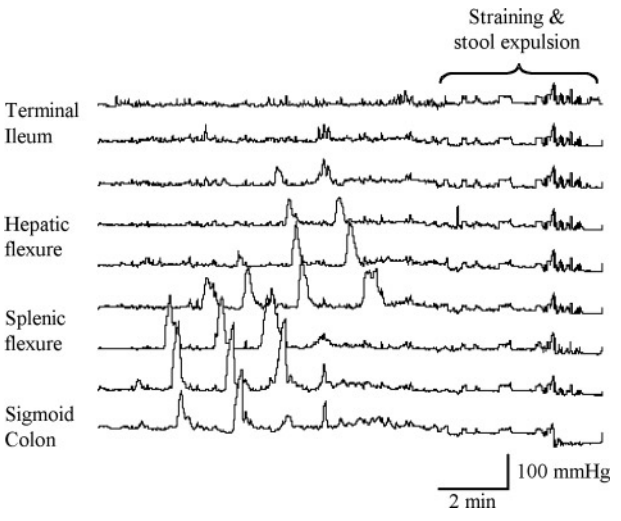

Fig. 1. – The pre-defaecatory array of propagating sequences (PS). Note that with each PS approaching stool expulsion the site of origin of the PS shifts in an orad direction.

TABLE 1. – *Sacral nerve stimulation in patients with constipation.*

Reference No.	*No. of patients*	*Constipation Type #*	*Intervention Technique*	*Study Design*	*Outcome Measure*	*Response*
Ganio et al.[38]	12	OD	PNE	Uncontrolled	Successfull Evacuation StoolFrequency	66%* 25%
Malouf et al.[39]	8	STC	PNE	Uncontrolled	Stool Frequency	25%
Kenefick et al.[40]	4	STC	PNE & Permanent	Uncontrolled	Stool Frequency Stool Frequency	100% 75%
Kenefick et al.[41]	2	STC	Permanent	RCT	Stool Frequency	100%
Dinning et al.[46]	8	STC	PNE	Uncontrolled	Coloc motor response Stool Frequency	100%* 75%*

OD = Obstructed defaecation; STC = Slow Transit Constipation * $P < 0.05$

The enteric nervous system provides the direct neuronal control of colonic motility, modulated through the sympathetic, parasympathetic and extrinsic afferent pathways. The vagal nerves provide parasympathetic innervation to the caecum, ascending colon and most of the transverse colon, whilst parasympathetic fibres from the second to the fourth sacral sections of the spinal cord innervate the distal part of the transverse colon, the descending colon and the rectosigmoid colon. Therefore intuitively, stimulation of pelvic nerves would be expected to have a motor response confined to the distal colon and ano-rectum. Yet evidence exists to suggest that stimulation of pelvic nerves is capable of inducing pan-colonic motor patterns. For example rectal chemical stimulation in the healthy human colon induces proximal colonic PSs presumably through long recto-colonic afferent pathways.[24] This pathway appears to be blocked in at least one form of constipation.[25]

It is possible that this attenuated pathway can be re-established through electrical stimulation of pelvic nerves. Indirect evidence supporting this hypothesis can be extrapolated from a case study in which a young female with severe constipation, received direct electrical stimulation to the anal canal and demonstrated significantly increased stool frequency.[26] As defaecation in health is preceded by proximal colonic pressure waves and that patient demonstrated improved stool frequency, we could make the reasonable assumption that the electrical stimulation of the anal canal helped to re-establish pre-defaecatory, pan-colonic pressure waves. Similar results were also obtained in patients with severe constipation and spinal cord injury. Here direct high voltage stimulation to the sacrum induced spontaneous stool evacuation.[27-30] While high voltage stimulation can not be applied to patients with an intact spinal cord, applying direct low-voltage stimulation to the sacral nerves can achieve comparable results. For example a high proportion of patients undergoing sacral nerve stimulation treatment for urinary or faecal incontinence reported an incidental increase in stool frequency.[31, 32] Finally data recorded in vivo from a canine colon suggested that electrical stimulation of sacral nerves can generated a similar colonic pre-defaecatory PS response to that observed during spontaneous defaecation.[33] Taken collectively we can form the hypothesis that electrical stimulation of the pelvic floor nerves may be capable of inducing proximal colonic propulsive pressure waves in severe constipation, which in turn may improve constipation symptoms. This hypothesis prompted our lab to examine both the symptomatic and colonic response of the novel therapy sacral nerve stimulation (SNS) in a severely constipated cohort of patients.

SACRAL NERVE STIMULATION IN CONSTIPATION

The techniques of sacral nerve stimulation (SNS) and its use in patient's with urinary and fecal incontinence has been documented in several recent reviews.[34-37] Briefly, SNS is a minimally invasive surgical technique that allows for direct electrical stimulation of the sacral nerves S2-S4 via an electrode placed through the sacral foramen. Of the three sacral roots used S3, which contains afferent sensory, efferent autonomic motor nerves and voluntary somatic nerves, provides the most satisfactory clinical response.[37] The SNS technique involves two stages. The first, commonly termed

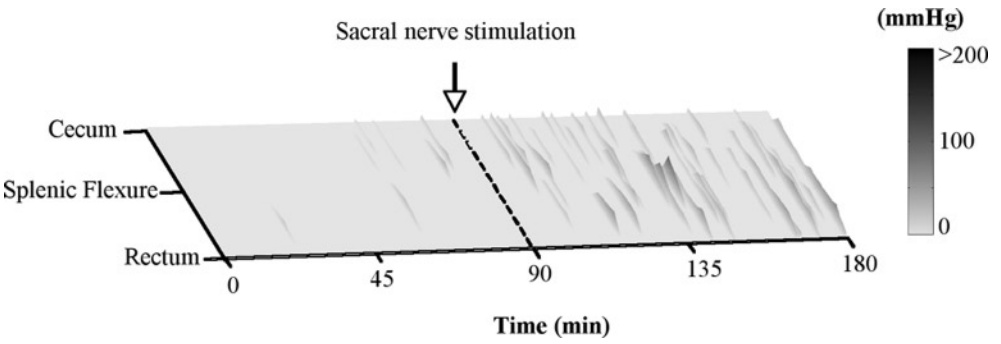

Fig. 2. – Iso-contour map of antegrade colonic motility in a patient with severe slow transit constipation, pre- and post sacral nerve stimulation. Each individual ridge represents an individual propagating sequence (PS) at the time the PS was initiated. The start of each ridge indicates the site of origin of the PS and the length of the ridge the extent of propagation of the propagating sequence. The shades of grey within each ridge represent the amplitude of each individual propagating pressure wave. The map highlights the dramatic increase in the frequency, amplitude and extent of propagation of PSs during sacral nerve stimulation.

the peripheral nerve evaluation (PNE), is conducted over two to three weeks and involves a temporary wire, with a single electrode, being introduced to the sacral root and connected to an external stimulator. Patients that respond favorably to the PNE move on to the second stage where a pulse generator (Interstim®) connected to a tined lead with 4 electrodes, is implanted permanently.[37]

In comparison to SNS use in urinary and faecal incontinence, investigation of the effects of SNS in patients with constipation is still in its infancy. Only 4 previous studies had been published each with a small sample size ($\leq$ 12).[38-41] (Table 1). The patients chosen to participate in these studies were carefully selected with all having long standing symptoms of constipation (unrelated to pelvic surgery) that had failed to respond to non-surgical therapy.[38-41] In such patients the data suggests that SNS can improve stool frequency and reduce the percentage of time patients suffer from bloating and pain. Importantly these studies also report very few adverse events. However, it should be stressed that the majority of these data are derived from the short-term PNE phase (Table 1).

While SNS appears to influence stool frequency in constipated subjects the in vivo effects of SNS upon colonic motor function remained unknown. The only available data in humans had come from previous studies of patients with faecal incontinence, from which SNS had been shown to alter ano-rectal motor function.[32, 42-45] In our own study of SNS in severe constipation we used our validated technique of pan-colonic manometry to simultaneously record colonic motor patterns during periods of SNS.[46] The data obtained from this study indicates that SNS appears to induce both proximal and distal colonic motor patterns. Furthermore we observed an increase in the frequency of long extent PSs and the frequency of HAPSs (Fig. 2). As mentioned above these particular motor patterns are linked to both colonic transit and defaecation in health. During the 3-week PNE phase 75% of the patients reported improvement in stool frequency (Table 1).

The mechanism of action of SNS in relation to initiating pan-colonic motor patterns remains unknown. It is likely that efferent neural pathways are activated but it is almost certain that afferent pathways are also activated. The rapidity of the colonic response to SNS [46] is certainly compatible with a neural pathway.

THE FUTURE OF SACRAL NERVE STIMULATION IN PATIENTS WITH SEVERE CONSTIPATION.

The reported positive outcome in carefully selected patients, coupled with minimal adverse side effects suggests that SNS is a reasonable option for patients who are faced with surgical procedures such as a colectomy in order to relieve their constipation symptoms. In addition SNS, at least in treating faecal incontinence, has been shown to be highly cost effective in comparison to other surgical intervention.[47] However, further work is still required. As yet only one randomized control trial has assessed the effects of SNS in costipated patients and that study had a sample size of two.[40] Cleary data derived from adequately powered radomised control trials and long-term follow-up in patients with permanent implantation are still required. As is data determining which patients may benefit form SNS treatment.

In addition while a colonic response to SNS in constipation has been shown, the stimulation parameters necessary to optimise this colonic response remain unclear. Assessing the merits of various combinations of parameters (i.e. alteration to pulse width, frequency and amplitude) can be time consuming if the yardstick is a clinical response which can take weeks or even months to develop.[41] Measurement of the immediate colonic contractile responses in the laboratory setting may prove to be a direct and powerful means of evaluating a wide range of stimulus parameters in order to help define the optimal ones.

REFERENCES

1. Thompson WG, Irvine EJ, Pare P, Ferrazzi S, Rance L. Functional gastrointestinal disorders in Canada: first population-based survey using Rome II criteria with suggestions for improving the questionnaire. Dig Dis Sci 2002; 47: 225-35.
2. Talley NJ, Fleming KC, Evans JM, O'Keefe EA, Weaver AL, Zinsmeister AR, Melton LJ. Constipation in an elderly community : a study of prevalence and potential risk factors. Am J Gastroenterol 1996; 91: 19-25.
3. Sonnenberg A, Koch TR. Epidemiology of constipation in the United States. Dis Colon Rectum 1989; 32: 1-8.
4. Martin BC, Barghout V, Cerulli A. Direct medical costs of constipation in the United States. Manag Care Interface 2006; 19: 43-9.
5. Glaser M, Chi J. Thirty-fifth annual report on consumer spending. Drug Topics 1983; 126: 18-20.
6. Sonnenberg A, Everhart JE, Brown DM. The economic cost of constipation. In: Kamm MA, Lennard-Jones JE, eds. Constipation. Bristol (PA): Wrightson Biomedical Pub Ltd, 1994.
7. Heymen S, Scarlett Y, Jones K, Ringel Y, Drossman D, Whitehead WE. Randomized, controlled trial shows biofeedback to be superior to alternative treatments for patients with pelvic floor dyssynergia-type constipation. Dis Colon Rectum 2007; 50: 428-41.
8. Rao SSC, Seaton K, Miller M, Brown K, Nygaard I, Stumbo P, Zimmerman B, Schulze K. Randomized controlled trial of biofeedback, sham feedback, and standard therapy for dyssynergic defecation. Clin Gastroenterol Hepatol 2007; 5: 331-8.
9. Battaglia E, Serra AM, Buonafede G, Dughera L, Chistolini F, Morelli A, Emanuelli G, Bassotti G. Long-term study on the effects of visual biofeedback and muscle training as a therapeutic modality in pelvic floor dyssynergia and slow-transit constipation. Dis Colon Rectum 2004; 47: 90-5.
10. Chiarioni G, Salandini L, Whitehead WE. Biofeedback benefits only patients with outlet dysfunction, not patients with isolated slow transit constipation. Gastroenterology 2005; 129: 86-97.
11. Rantis PC, Jr., Vernava AM, 3rd, Daniel GL, Longo WE. Chronic constipation – is the work-up worth the cost? Dis Colon Rectum 1997; 40: 280-6.
12. Dennison C, Prasad M, Lloyd A, Bhattacharyya SK, Dhawan R, Coyne K. The health-related quality of life and economic burden of constipation. Pharmacoeconomics 2005; 25: 461-76.
13. Lubowski DZ, Chen FC, Kennedy ML, King DW. Results of colectomy for severe slow transit constipation. Dis Colon Rectum 1996; 39: 23-9.
14. Knowles CH, Scott M, Lunniss PJ. Outcome of colectomy for slow transit constipation. Ann Surg 1999; 230: 627-38.
15. Cook IJ, Furukawa Y, Panagopoulos V, Collins PJ, Dent J. Relationships between spatial patterns of colonic pressure and individual movements of content. Am J Physiol Gastrointest Liver Physiol 2000; 278: G329-G341.
16. Kamm MA, van der Sijp JRM, Lennard-Jones JE. Observations on the characteristics of stimulated defaecation in severe idiopathic constipation. Int J Colorect Dis 1992; 7: 197-201.
17. Bazzocchi G, Ellis J, Villanueva-Meyer J, Narasimha Reddy S, Mena I, Snape W, Jr. Effect of eating on colonic motility and transit in patients with functional diarrhea: Simultaneous scintigraphic and manometric evaluation. Gastroenterology 1991; 101: 1298-1306.
18. Bampton PA, Dinning PG, Kennedy ML, Lubowski DZ, de Carle DJ, Cook IJ. Spatial and temporal organization of pressure patterns throughout the unprepared colon during spontaneous defecation. Am J Gastroenterol 2000; 95: 1027-1035.

19. Dinning PG, Bampton PA, Andre J, Kennedy ML, Lubowski DZ, King DW, Cook IJ. Abnormal predefecatory colonic motor patterns define constipation in obstructed defaecation. Gastroenterology 2004; 127: 49-56.
20. Bassotti G, Gaburri M, Imbimbo BP, Rossi L, Farroni F, Pelli MA, Morelli A. Colonic mass movements in idiopathic chronic constipation. Gut 1988; 29: 1173-1179.
21. Bassotti G, Imbimbo BP, Betti C, Dozzini G, Morelli A. Impaired colonic motor response to eating in patients with slow transit constipation. Am J Gastroenterol 1992; 87: 504-508.
22. Rao SS, Sadeghi P, Beaty J, Kavlock R. Ambulatory 24-hour colonic manometry in slow-transit constipation. Am J Gastroenterol 2004; 99: 2405-16.
23. De Schryver AMP, Samson M, Smout AJPM. Effects of a meal and bisacodyl on colonic motility in healthy volunteers and patients with slow transit constipation. Dig Dis Sci 2003; 48: 1206-1212.
24. Bampton PA, Dinning PG, Kennedy ML, Lubowski DZ, Cook IJ. The proximal colonic motor response to rectal mechanical and chemical stimulation. Am J Physiol 2002; 282: B443-G449.
25. Dinning PG, Bampton PA, Kennedy ML, Lubowski DZ, King DW, Cook IJ. Impaired proximal colonic motor response to rectal mechanical and chemical stimulation in Obstructed Defecation. Dis Colon Rectum 2005; 48: 1777-1784.
26. Chang HS, Myung SJ, Yang SK, Yoon IJ, Kwon OR, Jung HY, Hong WS, Kim JH, Min YI, Yu CS. Functional constipation with impaired rectal sensation improved by electrical stimulation therapy: report of a case. Dis Colon Rectum 2004; 47: 933-936.
27. Varma JS, Binnie N, Smith AN, Creasey GH, Edmond P. Differential efects of sacral anterior root stimulation on anal sphincter and colorectal motility in spinally injured men. Br J Surg 1986; 73: 478-82.
28. MacDonagh RP, Sun WM, Smallwood R, Forster D, Read NW. Control of defaecation in patients with spinal injuries by stimulation of sacral anterior nerve roots. Br Med J 1990; 300: 1494-7.
29. Chia YW, Lee TK, Kour NW, Tung KH, Tan ES. Microchip implants on the anterior sacral roots in patients with spinal trauma: does it improve bowel function? Dis Colon Rectum 1996; 39: 690-4.
30. Binnie NR, Smith AN, Creasey GH, Edmond P. Constipation associated with chronic spinal cord injury: the effect of pelvic parasympathetic stimulation by the Brindley stimulator. Paraplegia 1991; 29: 463-9.
31. Pettit PD, Thompson JR, Chen AH. Sacral neuromodulation: new applications in the treatment of female pelvic floor dysfunction. Curr Opin Obstet Gynecol 2002; 14: 521-5.
32. Kenefick NJ, Vaizey CJ, Cohen RC, Nicholls RJ, Kamm MA. Medium-term results of permanent sacral nerve stimulation for faecal incontinence. Br J Surg 2002; 89: 896-901.
33. Hirabayashi T, Matsufuji H, Yokoyama J, Hagane K, Hoshino K, Morikawa Y, Kitajima M. Colorectal motility induction by sacral nerve electrostimulation in a canine model: implications for colonic pacing. Dis Colon Rectum 2003; 46: 809-17.
34. Tjandra JJ, Lim JF, Matzel K. Sacral nerve stimulation: an emerging treatment for faecal incontinence. ANZ J Surg 2004; 74: 1098-106.
35. Matzel KE, Stadelmaier U, Besendorfer M. Sacral nerve stimulation. Acta Chirurgica Iugoslavica 2004; 51: 49-51.
36. Kenefick NJ, Christiansen J. A review of sacral nerve stimulation for the treatment of faecal incontinence. Colorec Dis 2004; 6: 75-80.
37. Jarrett MED, Mowatt G, Glazener CMA, Fraser C, Nicholls RJ, Grant AM, Kamm MA. Systematic review of sacral nerve stimulation for faecal incontinence and constipation. Br J Surg 2004; 91: 1559-1569.
38. Ganio E, Masin A, Ratto C, Altomare DF, Ripetti V, Clerico G, Lise M, Doglietto GB, Memeo V, Landolfi V, Del Genio A, Arullani A, Giardiello G, de Seta F. Short-term sacral nerve stimulation for functional anorectal and urinary disturbances: results in 40 patients: evaluation of a new option for anorectal functional disorders. Dis Colon Rectum 2001; 44: 1261-7.
39. Malouf AJ, Wiesel PH, Nicholls T, Nicholls RJ, Kamm Ma. Short term effects of sacral nerve stimulation for idiopathic slow transit constipation. World J Surg 2002; 26: 166-70.
40. Kenefick NJ, Nicholls RJ, Cohen RG, Kamm Ma. Permanent sacral nerve stimulation for treatment of idiopathic constipation. Br J Surg 2002; 89: 882-888.
41. Kenefick NJ, Vaizey CJ, Cohen CR, Nicholls RJ, Kamm MA. Double-blind placebo-controlled crossover study of sacral nerve stimulation for idiopathic constipation. Br J Surg 2002; 89: 1570-1.
42. Matzel KE, Stadelmaier U, Hohenfellner M, Hohenberger W. Chronic sacral spinal nerve stimulation for fecal incontinence: Long-term results with foramen and cuff electrodes. Dis Colon Rectum 2001; 44: 59-66.
43. Leroi AM, Michot F, Grise P, Denis P. Effects of sacral nerve stimulation in patients with fecal and urinary incontinence. Dis Colon Rectum 2001; 44: 779-789.
44. Kenefick NJ, Vaizey CJ, Nicholls RJ, Cohen R, Kamm MA. Sacral nerve stimulation for faecal incontinence due to systemic sclerosis. Gut. 2002; 51: 881-3.
45. Ganio MD, Luc AR, Clerico G, Trompetto M. Sacral nerve stimulation for treatment of fecal incontinence: A Novel Approach for Intractable Fecal Incontinence. Dis Colon Rectum 2001; 44: 619-631.
46. Dinning PG, Fuentealba SE, Kennedy ML, Lubowski DZ, Cook IJ. Sacral nerve stimulation induces pan-colonic propagating pressure waves and increases defaecation in patients with slow transit constipation. Colorectal Disease. 2007; 9: 123-32.
47. Hetzer FH, Bieler A, Hahnloser D, Lohlein F, Clavien PA, Demartines N. Outcome and cost analysis of sacral nerve stimulation for faecal incontinence. Br J Surg 2006; 93: 1411-7.

Supported by: NHMRC & Medtronic Australia.

Correspondence to:
Dr. PHIL DINNING PhD
Department of Gastroenterology
St George Hospital, Kogarah, NSW, 2217 - Australia
Tel +61 2 91132208 - Fax +61 2 91133993
Email: P.Dinning@unsw.edu.au