LETTERS TO THE EDITOR

To the Editor

More Than 'Answers We Can Use', We Need to Ask the Right Questions

Re: Pelz D. CURES and the dilemma of unruptured intracranial aneurysms. Can J Neuro Sci. 2011 Mar;38(2):191-2.

We read with interest but some disappointment the editorial by Dr. David Pelz on "CURES and the Dilemma of Unruptured Intracranial Aneurysms" in the March (2011) edition of the Journal[1]. Questioning medical practice in the context of a randomized controlled is usually met with a certain amount of denial and resistance, but we are alarmed that our proposal is being misinterpreted in a negative light.

Trials are an admission that current knowledge is inadequate to accurately guide clinical decisions, and unruptured cerebral aneurysms are a good case in point. The editorial states that: "We actually do know quite a lot about them" followed by a list of statistics and figures which in fact come from biased observational studies and upon which widely used but equally uncertain clinical guidelines have been formulated[2]. It is not true that "The investigators have an a priori decision that unruptured intracranial aneurysms between 3 mm and 25 mm in diameter deserve to be treated." We have never suggested that all such aneurysms ought to be treated! Criteria used to place limits on a pragmatic trial are not indications for treatment. CURES was designed to address the question of what to do AFTER the decision to treat an unruptured aneurysm has been made—the decision and recommendation to treat being up to the physicians managing the patient.

We strongly disagree with a comment in the editorial that we already know the answers to the important questions asked in CURES regarding anatomical results of aneurysm treatment as well as treatment complications—if we did, why would we bother doing such a difficult and costly trial? Most importantly, we would like to emphasize that the first stage of CURES is a feasibility study requiring only 260 patients, and if it indeed proves feasible then all patients will be rolled into a much larger and hopefully international trial that can win proper agency funding and ask even bigger questions about long term patient outcome after aneurysm treatment by either clips or coils. CURES is a necessary first step, and by itself will provide very useful information. It is time to stop providing only lip-service support of randomized trials for unruptured intracranial aneurysms[3], and replace that with the hard work of trial participation, or at least unified support of trials being carried out by others.

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To the Editor

Unruptured Intracranial Aneurysms: Some Questions Answered, Many Questions Remain

Re: Pelz D. CURES and the dilemma of unruptured intracranial aneurysms. Can J Neuro Sci. 2011 Mar;38(2):191-2.

We read with interest the thoughtful editorial written by Dr. David Pelz[1]. Dr. Pelz has summarized some of the available data regarding the natural history of unruptured intracranial aneurysms (UIAs), and the morbidity and mortality of surgical clipping and endovascular coiling for these lesions. Dr. Pelz notes several significant concerns regarding the proposed feasibility trial of UIA treatment, the Canadian Unruptured Endovascular versus Surgery Trial (CURES)[2]. In that study, Dr. Jean Raymond and colleagues propose randomization of 260 patients with 3-25 mm UIAs to either surgery or endovascular therapy.

As Dr. Pelz describes, and as noted by many others, considerable controversy remains regarding the optimal management of unruptured intracranial aneurysms. This controversy is particularly noteworthy given that a UIA is a very common clinical entity—present in approximately 2% of the population--that is being detected with increasing frequency[3], making it an important public health problem[4].

The decisions regarding the most appropriate UIA management are complex and are optimally made based on an unbiased comparison of detailed natural history data relevant to the patient's specific aneurysm to the intervention morbidity and mortality, taking into account numerous patient- and aneurysm-specific factors. Several retrospective, meta-analyses, and few prospective observational studies have provided natural history data regarding selected samples of patients with UIAs, and their risk of hemorrhage over the short and intermediate term. The largest prospective study of UIAs, an international multi-center epidemiological cohort study called the International Study of Unruptured Intracranial Aneurysms (ISUIA)[5,6] enrolled over 5500 patients with UIAs. Despite the large size of this ISUIA cohort, the site- and size-specific rupture risk estimates are not reliable when one divides the cohort into location categories other than the most basic anterior circulation, posterior circulation and posterior communicating subgroups, and beyond very broad size categories. Particularly for smaller aneurysms,

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the ISUIA data can not be subdivided to provide aneurysm site- and size- specific rupture rates given the large confidence intervals around the point estimates.

Similarly, there are considerable data available regarding management risks, but limited data for the most contemporary interventions with carefully adjudicated, objective, and detailed outcome risks including death and functional and cognitive outcomes. Data from administrative databases and meta-analyses, while of interest, can not be easily extrapolated to an individual patient—and a specific aneurysm--seen in clinical practice.

Varying approaches to aneurysm management have been published[7]. Some of these available guidelines[8], cost-utility analyses[9], and expert opinion recommendations[10,11] were published prior to the availability of more detailed aneurysm site- and size-specific natural history data, and morbidity and mortality of surgery and endovascular therapies from large prospective cohort studies. Most experts are in agreement that larger UIAs and those that are symptomatic should be considered for interventional treatment[12-17] because of the unacceptably high risk of UIA rupture with conservative management. Mathematical modeling of aneurysm natural history and management risks have been conflicting, with some suggesting that small unruptured aneurysms may not benefit from a procedure[18]. Another decision and cost-effectiveness analyses suggested that treatment of very small aneurysms, <7 mm in diameter, is not cost-effective[19]. The early retrospective natural history data from ISUIA contributed to a 2000 American Heart Association guideline[8] which suggested that repair of small UIAs in patients with no history of SAH could "no longer be generally advocated". However, it is noteworthy that the guideline was developed prior to the availability of prospective ISUIA data, published in 2003[6].

The concept of clinical equipoise suggests that there "exists genuine uncertainty within the expert medical community regarding the preferred treatment for a specific entity"[20]. It is apparent from the diverse recommendations for UIAs, especially the smaller UIAs, that the available data are not sufficient to make the most optimal management decision and that there is genuine uncertainty in the medical community regarding the optimal management of these lesions[21-24].

Despite the data nicely summarized by Dr. Pelz, numerous important questions remain regarding the management of UIAs: 1) do we have valid and reliable aneurysm-location and size-specific natural history data for the spectrum of UIAs so commonly seen in clinical practice, 2) do we have contemporary data regarding the objective outcomes—included death and major functional and cognitive morbidities—for surgical and endovascular management of UIAs, 3) if we manage conservatively, what is the risk of UIA growth (which should likely mandate surgical or endovascular intervention), 4) are there aneurysm characteristics, beyond those published in the available observation studies and in the realm of morphological characteristics and computational fluid dynamics, which might assist us in defining the long term rupture risks at the time of UIA detection, 5) in the absence of a clinical trial, can we directly compare the available natural history and interventional data via some other analytic approach, such as a propensity analysis, 6) are there genotypic predictors of aneurysm occurrence, rupture, growth and morphology change, or biomarkers and genotypic predictors of outcome of aneurysm management, 7) is there clinical equipoise in the management of some subgroup of patients with UIAs such that a randomized clinical trial should be performed and what would be the best design of such a trial, 8) given that cigarette smoking and hypertension are risk factors for subarachnoid hemorrhage in general and for UIA formation, would aggressive treatment of these risk factors lower the likelihood of rupture, and 9) are there medical treatments such as aspirin[25] that could conceivably lower the risk of aneurysm rupture?

We agree with Dr. Pelz that considerable data exist, but it is clear that many questions remain, and many of us in the neuroscience community are dedicated to answering these questions. It is apparent from the available data that many larger aneurysms likely should be treated, and apart from those found in elderly patients, it would be difficult to suggest that clinical equipoise exists for those patients. So how should we advise our patients with smaller UIAs—aneurysms we so frequently have the opportunity to see in clinical practice? For this group of patients clinical equipoise does exist and there is clearly a gap in the available data which are necessary to guide their management. The ISUIA Study Group has previously proposed randomized clinical trials to assess the optimal management of UIAs. Issues have been raised including the importance of including a conservative management arm, and more recently, the feasibility of such a trial. A clinical trial of UIAs that includes patients with small and large aneurysms, which covers a very diverse spectrum of natural history and management outcomes, is unlikely to be feasible, and will not lead to the aneurysm location- and size-specific data necessary to best guide our patients. Instead, we are now at a point that concentrating on those UIAs for which clinical equipoise appears to exist—patients with smaller UIAs—may be most appropriate.

The available data simply do not answer the questions regarding the optimal management of such UIAs, and additional long-term large scale observational data or a clinical trial which includes a conservative management arm concentrating on these smaller UIAs should be funded, for without additional objective data, the optimal management for these patients will remain unclear.

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To the Editor

Ethanol Abuse After a Right Temporal Lobe Resection for Intractable Epilepsy

In temporal lobe epilepsy, surgery is shown to be superior to medical therapy[1]. Although a large number of patients may become seizure free post surgically (>50%), the relationship between seizure freedom and the psychosocial adjustment is complex and not always has a positive linear relationship.

One of the main challenges that patients face post epilepsy surgery is to give up the sick role. The occurrence of post-operative cognitive changes, mood disturbance and psychosis have been reported[2]. Moreover, behavioural changes such as hypergraphia, anxiety, panic attacks and lack of behavioural flexibility are reported after unilateral mesial temporal resection; however, ethanol abuse after temporal lobectomy has not been not reported before[3]. We report a patient that became seizure free after right temporal resection, however, his quality of life was negatively affected by a prominent ethanol abuse that started post-surgery.

We describe a 47-year-old right hand dominant male with a 17 year history of complex partial seizures with secondary generalization. His seizures were well controlled with carbamazepine (CBZ) 600mg bid for 14 years and after that, they became intractable despite his compliance. Lamotrigine (LTG) 150 mg bid was added to the treatment and seizures were controlled for a few months but he continued to have simple partial and complex partial seizures at least twice per week and progressive difficulty with memory (possible medication related). The auras were referred by the patient as an epigastric rising sensation.

The patient had some episodes of mood swings and obsessive behaviour in the past but never had to be treated. His brother also had anxiety disorder and his mother had suffered from depression and committed suicide. The patient had no history of substance abuse but his father and brother abused ethanol. His neurological exam was unremarkable. Magnetic resonance imaging (MRI) of his brain and multiple outpatient electro-encephalograms (EEGs) were normal.

A video-EEG telemetry recorded eight seizures all originating from right temporal region and two psychogenic non-epileptic events. He underwent neuropsychological testing which showed no contraindication for right temporal lobectomy. He underwent standard right temporal lobectomy guided with electro-corticography (ECoG), showing mesial and neocortical temporal spikes. There were no complications postoperatively and the

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