Correspondence

The Ralph Shackman Trust Travelling Fellowship

Report of a visit to the Division of Urology at the University of Pennsylvania School of Medicine and the Rocky Mountain Spinal Injury System, Denver, Colorado, USA.

Historically, the management of spinal cord injury (SCI) has been developed largely empirically. The success of this approach is attested by a nearly normal life expectancy in patients with SCI, particularly through improved urological care. Unfortunately, understanding of the pathophysiological processes in the bladder remains limited in SCI where collaboration between clinicians and scientists in the field of smooth muscle function is rare. The Oxford Continence Group, set up by Professor Alison Brading, has examined various aspects of detrusor dysfunction. As a member of the group I have concentrated on studying structural changes in the bladder in SCI. The Shackman Fellowship provided an opportunity to visit two pre-eminent centres. Professor Samuel Chacko’s group at the University of Pennsylvania has examined the contractile apparatus in detrusor pathology, establishing that B00 alters molecular isoforms, with potential clinical consequences. The Rocky Mountain Spinal Injury Center in Denver has achieved wide recognition for its integrated approach. For the last 9 years a team from the centre has visited Stoke Mandeville as part of a multicentre study of ageing.

My visit took place in August 1999: the schedule was necessarily ambitious from the outset, because I was inexperienced with molecular techniques. I received personal supervision from the Associate Professor, Michael diSanto, an enthusiastic and talented teacher. On successive days I learned how to extract RNA, generate complementary DNA, amplify specific areas of interest using the PCR and extract contractile proteins. The intensive, personalized course was an excellent introduction. Slightly surprisingly, there were no great differences in the myosin isoforms for samples from patients with SCI. However, the sample size was small, so we intend to pursue the studies further.

The Rocky Mountain Spinal Injury Centre is in Denver, at an altitude of 1600 m. It is part of a Level 2 trauma centre, which received several victims from Columbine High School after the shooting incident. The ethos of the unit is to tailor care for the individual, optimising the chance of an independent and rewarding life. In essence, the approach resembles that of enlightened centres in the UK, with little apparent difference in clinical management, and a similar chronic lack of nursing staff. The Rocky Mountain Centre sets an outstanding example with its research department. Twelve researchers, including doctors, computer staff and a statistician, obtain and analyse information in collaboration with other centres in the USA and UK, resulting in a substantial clinical database. Urologically, all aspects outside urodynamics are covered, providing detailed information on the effects of various management methods. As no member of the research department has a urological interest, this part of the database was little used before my visit. A large part of my time was consequently spent collating and checking the urological information for statistical analysis and interpretation.

The visit was a good mix of laboratory and clinical research, from which will ensue publishable work on the long-term sequelae of bladder management. After further work, we will also be able to report on changes in the detrusor contractile apparatus in SCI. The visits emphasized the need for cooperation across the clinical/scientific interface. Only by exposing individuals to both aspects can it be anticipated that new management approaches will be developed. I am indebted to the Ralph Shackman Fellowship Trust for this opportunity.

M. Drake
Former Research Fellow at the Oxford Continence Group and National Spinal Injury Centre, Stoke Mandeville

Low-grade left varicocele in patients over 30 years old: the effect of spermatic vein ligation on fertility

Sir,

The authors of this article [1] focused on the insignificant change of fertility 1 year after surgery, as the sperm quality in their patients was stable. As the BJU Int is a world-wide periodical for the training of residents in urology, several points should be clarified. It is well known that testicular lesions caused by varicocele are dynamic and responsible for infertility [2] as well as testicular damage, which is detectable in adolescent varicocele and deteriorates with time [3]. Although varicocele has been shown to compromise testicular development during the critical pubertal years, there is evidence attesting to progression and the duration-dependent nature of the effect. There is no consensus on treating varicocele in children. It has been proved that treating varicocele in pubertal boys prevents testicular growth arrest in two-thirds of them [4]. There is another view which suggests that correcting the varicocele leads to a small but significant increase in sperm number after varicocele occlusion, but there are no significant changes in either sperm motility or morphology [5]. In our experience venous reflux and testicular hypotrophy are two factors that lead to surgery to correct a low-grade varicocele. The third factor is represented by abnormalities in the sperm count (oligozoospermia). When one of these three factors is present surgery is proposed to the patient and his family, otherwise the persistence of these factors destroys the testicular parenchyma and creates irreversible damage, and probably exacerbates pre-existing infertility. In those patients described in the study from Milan, surgery was undertaken in patients aged 30–38 years. In our opinion the damage to the parenchyma was already permanent at that age because left varicocele usually appears during adolescence. Finally, the early investiga-
Impairment of corpus cavernosal smooth muscle relaxation by glycosylated human haemoglobin

Sir,

We read with interest this paper [1] on the reported impairment of rat cavernosal smooth muscle relaxation in the presence of glycosylated haemoglobin (HbA1c). The authors concluded, from this elegant study, that as well as acting as a marker for long-term diabetic control, HbA1c also has direct pathological effects. These are mediated by inhibiting the function of nitric oxide (NO) through the generation of superoxide anions. These findings further strengthen the view of our group that in diabetic erectile dysfunction (ED) oxidative stress may play an important role.

Superoxide anions react with NO to produce peroxynitrite, which is far more ‘toxic’ to tissues [2]. To this effect, we recently showed that peroxynitrite significantly impairs rabbit cavernosal smooth muscle relaxation [3]. We have also shown, using a rabbit model of diabetes, that superoxide dismutase (SOD), the enzyme that breaks down superoxide anions to water (H2O2), significantly enhances impaired NO-mediated cavernosal smooth muscle relaxation [4]. These two findings, together with those of Cartledge et al. [1], support the concept that oxidative stress plays an important role in the pathogenesis of diabetic ED.

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**Reply**

The issue of the role of peroxynitrite, generated from superoxide anions, which is raised by Khan et al., is interesting. It certainly seems likely that both of these toxic species react with NO and subsequently impair smooth muscle relaxation. Data derived from studies on arterial tissue have also shown an increase in extracellular oxidants, but in the presence of glycated albumin [1]. However, the toxic species responsible for the dynamic impairment of smooth muscle in this model was hydrogen peroxide. In normal circumstances superoxide radicals would be cleared by SOD before the reaction with NO can proceed to generate peroxynitrite. In the presence of both advanced glycation end-products (AGEs) and a metal catalyst, superoxide anions react to form hydrogen peroxide before clearance by SOD is possible, perhaps because the action of SOD is impaired. SOD activity is reduced in the erythrocytes of diabetic patients; this effect is caused by non-enzymatic glycation of the enzyme [2]. The presence of AGEs has been reported in the penis [3]; they may yet prove to be the central unifying compounds in the dynamic process of diabetic ED.

**Bcl-2 expression identifies patients with advanced bladder cancer treated by radiotherapy who benefit from neoadjuvant chemotherapy**

Sir,

It was with great interest that we read this article [1]. The group have identified Bcl-2 protein expression as a marker of patients who do not benefit from neoadjuvant chemotherapy before radiotherapy. This is an important result and adds to the developing consensus that Bcl-2 expression in bladder tumours adversely affects chemosensitivity. Bcl-2 positivity is also known to adversely affect radiosensitivity [2] and to enhance the malignant potential of bladder tumours [3]. This study closely relates with our work of modulating the Bcl-2 protein using antisense oligonucleotides. In bladder tumour cell lines, we found that anti-sense oligonucleotides successfully down-regulated Bcl-2 expression and in some cases enhanced apoptosis in response to chemotherapy. We agree with the authors that the Bcl-2 protein is an important molecular target in bladder tumours and that further studies are warranted in other potential anti-apoptotic targets. The whole process of tumour cell response to chemotherapy and subsequent induction of apoptosis is complex and can be interrupted at several stages by groups of anti-apoptotic proteins. Studies such as that by Cooke et al. increase understanding of the role which patient/tumour genotype has in predicting the response to therapy. It also adds to mounting evidence that clinicians must think of the molecular pattern of a tumour before embarking on a course of chemotherapy. Further studies like this are needed, as in the future all cancer therapies will need to be tailored for each patient.

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**The indwelling ureteric stent: a ‘friendly’ procedure with unfriendly high morbidity**

Sir,

We read the article on the morbidity and complications of indwelling ureteric stents [1] with interest. Richter et al.
reported a very high incidence of stent-related morbidity or complications (103 of 110, 94%). This high incidence of complications is alarming. The migration of 8% of normally placed stents is unacceptable. This could be attributed to the routine use of multi-coil stents. We had a similar stent migration rate in our unit when we used multi-coil stents, but after switching to single-coil stents we have seen no stent migration. Multi-coil stents may have the advantage of not needing a large stent inventory; this is negated by their higher propensity to migrate. We attribute the higher rate of migration of multi-coil stents to its higher ‘shape memory’. The higher rate of silicone stent migration is probably caused by its low tensile strength [2] and not the smooth regular external surface, as mentioned in the article. Silicone is a flexible synthetic polymer and has a tensile strength of 2.4–6.8 MPa. Silicone stents have a limited internal diameter with smaller side-hole apertures, leading to low-flow drainage rates [3]. These low rates combined with the weaker coil strength from its low tensile strength leads to a higher chance of stent migration.

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