

of the key points of these studies is that nephrectomy should be offered only to patients with a good performance status. A major concern is that if nephrectomy is adopted as the standard for all patients with metastatic disease, many elderly or infirm and dying patients will be subject to inappropriate surgery.

These two trials, which show the value of a combined surgical and biological approach to metastatic renal cancer, will deservedly be recognised as classic studies. They will also serve as the basis for further studies of new biological and mechanistic agents that are active against this difficult and challenging disease. For future studies of metastatic renal cancer, adjunctive radical nephrectomy should be viewed as the standard of care.

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- 1 Flanigan RC, Blumenstein BA, Salmon S, et al. Cytoreductive tumor nephrectomy in metastatic renal cancer: the results of Southwest Oncology Group Trial 8949. *J Urol* 2000; **163** (suppl): 154 (abstr. 685).
- 2 Montie JE, Stewart BH, Straffon RA, et al. The role of adjunctive nephrectomy in patients with renal cell carcinoma. *J Urol* 1977; **117**: 272–75.
- 3 Myers GH, Fehrenbaker LG, Kellais PP. Prognostic significance of renal vein invasion by hypernephroma. *J Urol* 1968; **100**: 420–23.
- 4 Oliver RTD. Surveillance as a possible option for management of metastatic renal cell carcinoma. *Semin Urol* 1989; **7**: 149–52.
- 5 Elhilali MM, Gleave M, Fradet Y, et al. Placebo-associated remissions in a multicentre, randomized, double-blind trial of interferon gamma-1b for the treatment of metastatic renal cell carcinoma. The Canadian Urologic Oncology Group. *BJU Int* 2000; **86**: 613–18.
- 6 Gleave ME, Elhilali M, Fradet Y, et al. Interferon gamma-1b compared with placebo in metastatic renal-cell carcinoma. Canadian Urologic Oncology Group. *N Engl J Med* 1998; **338**: 1265–71.
- 7 Umeda T, Niiijima T. Phase II study of alpha interferon on renal cell carcinoma. Summary of three collaborative trials. *Cancer* 1986; **58**: 1231–35.
- 8 Belldegrun A, Koo AS, Bochner B. Immunotherapy for advanced renal cell cancer: the role of radical nephrectomy. *Eur Urol* 1990; **18** (suppl 2): 42.
- 9 Minasian LM, Motzer RJ, Gluck L, et al. Interferon alfa-2a in advanced renal cell carcinoma: treatment results and survival in 159 patients with long term follow up. *J Clin Oncol* 1993; **7**: 1368–75.

### New developments in impulsivity

Impulsivity, a dimension of personality, is the failure to resist an impulse, drive, or temptation that is harmful to oneself or others.<sup>1</sup> It is a measurable feature of behaviour, manifesting as impatience (including the inability to wait for rewards), carelessness, risk-taking, sensation-seeking and pleasure-seeking, an underestimated sense of harm, and extroversion. Impulsivity is a core symptom of a broad spectrum of psychiatric disorders, including disorders of impulse control (pathological gambling, intermittent explosive disorder, pyromania, kleptomania, and trichotillomania), impulsive aggressive personality disorders (borderline, antisocial, histrionic, and narcissistic), neurological disorders associated with disinhibition of behaviour, and substance abuse.<sup>1</sup> Furthermore, other psychiatric disorders, notably attention deficit hyperactivity disorder (ADHD) and mania, also contribute to the expression of impulsivity.<sup>1</sup> The impulse-control disorders may belong to a group lying at one end of a spectrum of compulsive-impulsive disorders related to risk taking or avoidance, with impulsive disorders being driven by pleasure or arousal, and compulsive disorders being driven by reduction of anxiety.<sup>2</sup>

Lesion studies in animals and man have begun to elucidate the neurocircuitry of impulsivity. Rudolf Cardinal and colleagues<sup>3</sup> have reported that lesions of the nucleus accumbens core (AcbC), a key brain region of reward and reinforcement, induce persistent impulsive choices in rats. These rats consistently chose small or poor rewards that were immediately available in preference to larger delayed rewards. The animals also exhibited locomotor hyperactivity, another sign of the hyperactive-impulsive subtype of ADHD, and so lesions in the AcbC in rats may represent an animal model of the disorder. Earlier imaging studies have implicated two AcbC cortical afferents, the anterior cingulate cortex and medial prefrontal cortex in impulsivity, and in processes regulating choice between alternative reinforcers.<sup>4,5</sup> Moreover abnormal function of these areas have been found in some individuals with ADHD and in other impulse disorders.<sup>4,5</sup> However, Cardinal and colleagues found that lesions in these two areas did not induce impulsive choice, which suggests that ventromedial or orbitofrontal afferents might play a role in control of impulsive choice. This finding complements recent work in man with bilateral ventromedial prefrontal cortical lesions who, on a gambling test, opted for choices that yield high immediate gains despite high future losses.<sup>6</sup> Decision-making deficits associated with lesions in these areas are similar to those found in other impulsive disorders, such as stimulant, opioid, and alcohol abuse.<sup>7</sup> Such patients also show a disregard for future consequences that is related to, but not entirely explained by, the construct of impulsivity.<sup>8</sup> Lesions in the amygdala have also been associated with impaired decision-making<sup>9</sup> and a complex modulation of aggressive and impulsive behaviours. Frontal-lobe abnormalities are associated with an inability to delay or inhibit acting on impulse, and an inability to calculate odds of negative risk or outcome. Aspects of impulsivity are core symptoms of several of frontal-lobe syndromes, and frontal-lobe hypofunction has been observed in impulsive individuals. And metabolic abnormalities have been observed in the orbital frontal, adjacent ventral medial, and cingulate cortex in patients with impulsive-aggressive disorders.<sup>4</sup> Thus, the orbitofrontal, nucleus accumbens, and amygdala regions seem to play an important role in mediating aspects of impulsivity.

The impulsive disorders are modulated by various neurotransmitter systems. Serotonergic dysregulation and a presynaptic deficit of available serotonin have been observed in human beings with various impulsive disorders, as well as animal models of impulsivity and aggression. Knockout mice lacking the serotonin receptor 5HT1B display increased impulsive aggression and a liking for cocaine and alcohol,<sup>10</sup> and polymorphisms of tryptophan hydroxylase (the rate-limiting enzyme for serotonin synthesis) have been associated with impulsive-aggressive behaviours.<sup>11</sup> Specific impulse-control disorders, such as pathological gambling, probably involve abnormalities of dopamine receptors and reward pathways, as well as noradrenergic and serotonergic dysfunction.<sup>12</sup> Dopamine function, particularly within the mesocorticolimbic pathways, is critical in the mediation of reward and reinforcement behaviours. Association studies of genes related to dopamine receptors have supported a genetic influence in impulsive behaviours, and  $\mu$ -opioid receptors are involved in the regulation of these pathways. Peptides such as vasopressin have also been implicated in aggressive behaviours. Nevertheless, a better understanding of the role of neurotransmitters

modulating relevant neurocircuitry (ie, ventromedial cortex and AcbC) is needed to develop specific treatments for pathological impulsivity across various disorders.

Therapeutic approaches involving pharmacological manipulation of neurotransmitters have been undertaken in an attempt to ameliorate pathological impulsivity in several psychiatric disorders. Much research to date has focused on modulation of serotonin transmission. Selective serotonin-reuptake inhibitors and other enhancers of serotonergic transmission have reduced impulsive behaviours in a wide range of different disorders, including pathological gambling, borderline personality disorder, sexual addictions, and disorders in the obsessive-compulsive spectrum.<sup>1,2,12,13</sup> Another pharmacological group of drugs that affect various neurotransmitter systems, including  $\gamma$ -aminobutyric acid, that has been reported to improve impulsive and aggressive behaviour in disorders as diverse as borderline personality disorder and autism are the anticonvulsant mood stabilisers, such as valproic acid.<sup>14</sup> Although serotonin dysregulation and hypofunction seem to play a central role in these disorders, impulsivity is probably influenced to differing degrees by the highly interconnected serotonergic, noradrenergic, dopaminergic, opioid, and  $\gamma$ -aminobutyric-acid systems. It is impossible to manipulate the effect of one neurotransmitter system on a set of neurons to the exclusion of surrounding neurons.

Lesion studies to better identify the neurocircuitry of specific impulsive behaviours may be helpful, and Cardinal and colleagues' tentative localisation of the neuroanatomical basis for delayed reinforcement may eventually lead to new diagnostic imaging or therapeutic procedures. Pharmacological manipulation of neurotransmitter or peptide systems specifically targeted at the AcbC and its relevant afferent pathways may moderate impulsive behaviours more specifically than do current therapies, and in view of the discrepancy between Cardinal and colleagues' findings<sup>3</sup> and previous work,<sup>4,5</sup> an obvious next step is to elucidate the afferent paths by which information on the value of delayed reinforcers is supplied to the AcbC. The basolateral amygdala may have a role, as may the orbitofrontal cortex. Orbital lesions of the prefrontal cortex have been associated with increases in reflexive emotional responses to environmental stimuli.<sup>15</sup>

The ability to moderate pathological impulsivity is of great clinical and public-health relevance because impulsive disorders incur large costs to society, and are associated with substantial morbidity, mortality, social, family, and job dysfunction, accidents, suicide, violence, aggression, criminality, and excessive use of health-care, government, and financial resources.<sup>1</sup> The localisation of impulsive choice in an animal model<sup>3</sup> may represent a new direction towards the understanding of a core behavioural symptom domain that cuts across various psychiatric disorders and contributes to substantial societal costs.

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- Hollander E, Posner N, Cherkasky S. The neuropsychiatry of aggression and impulse control disorders. In: Yudofsky SC, Hales RE, eds. American Psychiatric Press textbook of neuropsychiatry. Washington DC: American Psychiatric Press, Inc (in press).

- Hollander E. Treatment of obsessive-compulsive spectrum disorders with SSRIs. *Br J Psychiatry Suppl* 1998; **35**: 7–12.
- Cardinal R, Pennicott D, Sugathapala C, Robbins T, Everitt B. Impulsive choice induced in rats by lesions of the nucleus accumbens core. *Science* 2001; **292**: 2499–01.
- Siever LJ, Buchsbaum MS, New AS, et al. d,l-fenfluramine response in impulsive personality disorder assessed with (18F)fluorodeoxyglucose positron emission tomography. *Neuropsychopharmacology* 1999; **20**: 413–23.
- Ernst M, Zametkin A, Matochik J, Jons P, Cohen R. DOPA decarboxylase activity in attention deficit hyperactivity disorder adults. A([fluorine-18]fluorodopa positron emission tomographic study. *J Neurosci* 1998; **18**: 5901–07.
- Bechara A, Tranel D, Damasio H. Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. *Brain* 2000; **123**: 2189–02.
- Rogers RD, Everitt BJ, Baldacchino A, et al. Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: evidence for monoaminergic mechanisms. *Neuropsychopharmacology* 1999; **20**: 322–39.
- Bechara A, Damasio H, Damasio AR. Emotion, decision making and the orbitofrontal cortex. *Cereb Cortex* 2000; **10**: 295–307.
- Bechara A, Damasio H, Damasio AR, Lee GP. Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. *J Neurosci* 1999; **19**: 5473–81.
- Brunner D, Hen R. Insights into the neurobiology of impulsive behavior from serotonin receptor knockout mice. *Ann N Y Acad Sci* 1997; **836**: 81–105.
- New AS, Gelernter J, Yovell Y, et al. Tryptophan hydroxylase genotype is associated with impulsive-aggression measures: a preliminary study. *Am J Med Genet* 1998; **81**: 13–17.
- Hollander E, Buchalter A, DeCaria C. Pathological gambling. *Psychiatric Clinics North Am* 2000; **23**: 629–642.
- Hollander E, DeCaria CM, Mari E, et al. Short-term single-blind fluvoxamine treatment of pathological gambling. *Am J Psychiatry* 1998; **155**: 1781–83.
- Hollander E, Allen A, Lopez RP, et al. A preliminary double-blind, placebo-controlled trial of divalproex sodium in borderline personality disorder. *J Clin Psychiatry* 2001; **62**: 199–203.
- Luria AR. Higher cortical functions in man. New York: Basic Books, 1980.

## Health economics without tears

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It was once thought that expenditure on Britain's National Health Service might even diminish with time as a backlog of ill-health was cleared. Nobody believes that today, not for the NHS or for any other method of delivering health care, and clinicians have been forced to come to terms with economics. So has *The Lancet*; time and again research papers would arrive at the office carrying the throwaway line that adoption of such-and-such a seemingly expensive drug, operation, or test would actually save money in the long run. To sift the valid claims from the wishful thinking, the journal now uses specialist health-economics reviewers and has been fortunate to have the services of a panel set up by Martin Meltzer at the US Centers for Disease Control and Prevention. This week, beginning with Dr Meltzer's introduction to this important but not, I hope, arcane subject, *The Lancet* embarks on a five-part series on health economics. Those general principles, such as expenditure on one service means not funding something else and the fact that "value for money" will depend on the perspective from which the service is viewed, will be illustrated in the subsequent articles on surgery, drug treatment, diagnostic tests, and prevention.

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