Chapter 1

The paradoxical nature of nature

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Summary

Paradoxes abound in nature and in the realm of the human condition. Paradoxes have been evident in fields of science – from plant biology to human biology to physics – and in areas of human endeavour, ranging through political, literary and social activities. Paradoxes often represent instances where current knowledge may be deficient, and thus predictions based on such knowledge may be inconsistent with actual events or findings. At the level of scientific methodology, paradoxical phenomena offer powerful opportunities to test models and conceptual frameworks, and to enable true 'paradigm shifts' in certain areas of scientific inquiry. Insights from paradoxical phenomena in clinical sciences not only help us to understand mechanisms of function and dysfunction, they also provide clues as to therapeutic strategies, which may alleviate impairment and disability resulting from disease and injury. In addition, they may contribute towards a more positive, humanistic view of diverse states of the human condition.

Introduction

The word paradox is derived from the Greek: the prefix *para* means contrary or opposed, and *doxos* means opinion. The *Shorter Oxford English Dictionary* (2002) includes amongst its definitions of paradox 'a seemingly absurd or self-contradictory statement or proposition which, when investigated or explained, may prove to be well-founded or true'. In his philosophical treatise on paradoxes, Sainsbury (2009) has highlighted the paradoxical nature of paradoxes themselves: 'Paradoxes are fun. In most cases, they are easy to state and immediately provoke one into trying to "solve" them . . . Paradoxes are serious . . . To grapple with them is not merely to engage in an intellectual game, but to come to grips with key issues' (Sainsbury, 2009, p. 1). There are now a number of converging channels of scientific inquiry, across disciplines including the social, biological and physical sciences, that indicate the importance of harnessing paradoxical phenomena to advance our understanding of nature.

Pribram (quoted by Prigatano, 1999, p. 21) has remarked that when science resolves paradox, true knowledge emerges. The Nobel Laureate and former Director of the US National Institutes of Health, Harold Varmus (2009), has commented on the paradoxical nature of the scientific process itself: 'Science is inherently a paradoxical activity. Nearly all great ideas come from individual minds, and they are often first tested experimentally by a

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single person. But validation and acceptance of new information requires communication, convening and consensus building – activities that involve a community' (Varmus, 2009, p. 270).

Social and behavioural sciences

From the perspective of social and behavioural sciences – covering diverse fields such as management, cognition and politics – several authors have pointed to a number of paradoxes (e.g. Handy, 1995; Lewis, 2000; Farson and Keyes, 2002; Ofori-Danwa and Julan, 2004; Medawar and Pyke, 2001; Ariely, 2010). Thus, Lewis (2000) has commented 'Increasing technological change, global competition, and workplace diversity reveal and intensify paradox. Managers, for example, are asked to increase efficiency and foster creativity, build individualistic teams, and think globally while acting locally' (p. 760). Richards (2008) has discussed the paradoxes inherent in empires, such as that of the British Empire, where firm government and encouragement of self-government often went hand-in-hand. The political paradox of atomic science, with its inherent opportunities for good and for evil, has been highlighted by Alario and Freudenburg (2007).

Maurice Allais, who won the 1988 Nobel Prize in Economics, pointed to a paradox in economic behaviour that has become known as the Allais Paradox. Allais referred to the inconsistency of choices made when people make gambles, and how this contradicted the standard economic formulation at the time, 'Expected Utility Theory' (Munier, 1991). This would predict that individuals will make choices according to simple weighted probabilities of risk, whereas in fact they change their attitude towards risk in the direction of certainty when large costs are at stake (i.e. being influenced by 'loss aversion'). Thaler (1992) has also discussed paradoxes in economic life, for example why someone will not pay more than a 100 dollars for a ticket to an event, but will not sell for less than 200 dollars a ticket that they themselves own. More recent studies have highlighted how high rewards can lead to paradoxical decrements in performance (Ariely *et al.*, 2009; Mobbs *et al.*, 2009). Many of the observations of Kahneman (2003), for which he gained the 2002 Nobel Prize in Economics, were based around paradoxes in human reasoning. Droit-Volet and Gil (2009) have also observed the unfortunate paradox that, rather than speeding up when one is miserable, and enhancing pleasurable experiences by moving as slowly as possible, our subjective sense of time shows quite the reverse pattern.

Natural and physical sciences

Renfrew (2008) has referred to the 'sapient paradox' in evolutionary archaeology: why is it that the cultural and cognitive explosion in human development appears to have taken place only over the last 10,000 years, when the biological features necessary to support it seem to date back 60,000–100,000 years? Donald (2009) has discussed the nature of this paradox, and possible ways in which it may be explained – climactic factors such as the Ice Age may have impeded the development of human activities, peculiarities of the interaction between material culture and the brain which led to achievements such as symbolic communication, and a simple failure to detect key developments in the delay period (thus suggesting that there is in fact no delay and thus no paradox). McKay and Dennett (2009) have referred to another evolutionary paradox, where in some instances illusions and misbeliefs may have adaptive value.

In physical sciences such as meteorology, paradoxical phenomena have also been noted, such as types of rainfall normally associated with middle latitudes occurring in the tropics, or the observation that 'rain dries the air' as a result of using up water vapour (Humphreys, 1919; Houze, 1997). In the case of astrophysics, the Nobel Prize-winning Italian physicist, Enrico Fermi, calculated that our galaxy should be teeming with intelligent life, and that the absence of evidence for extra-terrestrial life was a major paradox – this observation came to be known as 'Fermi's paradox', and has generated much discussion (Landis, 1998; see also www.en.wikipedia.org/wiki/Fermi_paradox). Rees (1980) has also referred to a paradox in astrophysics as to how the different parts of the universe managed to start expanding in such a well-coordinated way, if there was at the time of the expansion no causal contact between them. Chandrasekhar's Physics Nobel Prize Lecture (1984) referred to a resolution of the 'Eddington Paradox', named after the famous English astrophysicist, whereby a star which had cooled to absolute zero somehow found the energy to undergo major expansion. Twenty years later, in 2004, the Nobel Prize for Physics was won by Frank Wilczek. His prize lecture was entitled *Asymptotic Freedom: from Paradox to Paradigm* (Wilczek, 2005). Wilczek referred to two paradoxical findings in physics that gave rise to the discovery of a new dynamical principle, 'asymptotic freedom'. The first paradox referred to the fact that one of the hidden building blocks of nature, quarks, are 'born free but everywhere they are in chains'. The second paradox related to the fact that two major theories in physics, Special Relativity Theory and Quantum Mechanics Theory, both seemed to be viable, even though they treated the concepts of space and time differently. Aharonov and Rohrlich (2005) show how errors and gaps in our understanding of phenomena in physics, together with contradictory findings, may result in paradoxes in quantum physics.

Clinical sciences

Entering the term 'paradox' into the online medical search engine PubMed yielded 7715 articles (August, 2010). Particularly in the realm of clinical science, paradoxes may be evident when what normally hinders may help, and what normally helps may hinder. While many medical advances are the result of slow, painstaking increments in knowledge (Sanghavi, 2010), the history of advances in medicine is one where paradoxical phenomena often have major prominence (cf. Ovsiew, 1997). One now-resolved paradox is vaccination, where the administration of a toxic agent results in long-term immunological benefits. Although forms of vaccination appear to have been part of folk medicine in countries such as India and China before 1700 (McNeill, 2000), vaccination gained prominence in the west as a result of a discovery in the late eighteenth century, when Benjamin Jesty and Edward Jenner noted that dairymaids who were infected by cowpox seldom developed smallpox, and reasoned that their exposure to cowpox may have been a factor in their non-infection (Horton, 1995; Pead, 2003, 2006). This led him to the development of vaccination against smallpox. Immunological paradoxes were at the heart of the observations made by Peter Medawar (1953) on the survival of the foetus within an alien female host – he posed the question, 'How does the pregnant mother contrive to nourish within itself, for many weeks or months, a foetus that is an antigenically foreign body?' Medawar gained the Nobel Prize in 1960 for his research into the immune system, and the immunological paradox about which he remarked has remained an active area of research (Billington, 2003; Moffett and Loke, 2004).

The Austrian psychiatrist, Julius Wagner-Jauregg, received the Nobel Prize in 1927 for his use of fever, by malaria inoculation, to cure mental disorders (Wagner-Jauregg, 1927). In recent years, there has been renewed interest in the possibility that, at least in some circumstances, fever may have clinical benefits (Matthews, 2010). An enlightened paradoxical observation that led to a major advance in clinical medicine was made by Philip Hench, who was awarded the Nobel Prize in 1950. On 1 April 1929, when Hench was in clinical practice, a 65-year-old lady with rheumatoid arthritis told him an unusual story, of how a recent occurrence of jaundice had resulted in a remission of her arthritis (cf. Crocker *et al.*, 2002). Hench (1950) built on this observation, and additional observations he made with regards to the remission of rheumatoid arthritis in pregnancy (cf. Straub *et al.*, 2005), to discover the beneficial effects of cortisone and adrenocorticotropic hormone in rheumatic and non-rheumatic conditions.

The concept that 'what normally hinders may help' is evident in a number of other clinical settings (see Stiehm, 2006), and while some issues remain a subject of debate, relevant phenomena include the following.

- Ischaemic preconditioning, whereby an initial transient reduction of blood flow/oxygen will somehow reduce the impact of a subsequent major ischaemic event (Dirnagl *et al.*, 2009; Kharbanda *et al.*, 2009).
- The reduction of certain forms of cancer in Down's syndrome (Baker and Kramer, 2007; Threadgill, 2008; Baek *et al.*, 2009).
- The obesity paradox in cardiac disease, which is controversial, but where it is claimed that some obese people with cardiac disease may have a better prognosis than non-obese individuals (LaVie *et al.*, 2007, 2009; Strandberg *et al.*, 2009; Bray, 2009; Frankenstein *et al.*, 2009).
- The beneficial effects early in life of genetic risk factors that may be harmful late in life, such as the APOE ϵ4 allele that has been implicated in Alzheimer's disease (Zetterberg *et al.*, 2009); similarly, insulin/IGF-1 signalling enhances growth process during development, but later in life can potentiate the ageing process. This has been called the insulin/IGF-1 paradox (Cohen and Dillin, 2008). The idea that some genes may be beneficial in some contexts but harmful in others, thus having multiple competing effects, has been termed 'antagonistic pleiotropy'; in this context, genes that enhance early survival and function may nevertheless be disadvantageous later in life.
- The protective effects of an inherited blood disorder (alpha+thalassemia) against malaria and other infections (Allen *et al.*, 1997; Enevold *et al.*, 2007).
- The role of infections and immune responses in the treatment of cancer (McCarthy, 2006; Gray *et al.*, 2006; Camus *et al.*, 2009).
- The reduced incidence of melanoma in those with vitiligo (Jin *et al.*, 2010), and of some cancers in those with Parkinson's disease (Fois *et al.*, 2010) and multiple sclerosis (Handel *et al.*, 2010).
- Instances where immune-cell infiltration in the central nervous system may be beneficial as well as detrimental (Wekerle and Hohlfeld, 2010).
- Better adjustment after irreversible compared to reversible colostomies (Smith *et al.*, 2009).
- The dramatic, beneficial effects of propranolol – normally used for hypertension – in resolving lesions associated with severe infantile hemangiomas (Léauté-Labrèze *et al.*, 2008; Sans *et al.*, 2009).
- Paradoxes in the realm of human emotion – for example, the occasional beneficial effects of low mood (Forgas, 2007); the negative hedonic consequences of instigating revenge (Carlsmith *et al.*, 2008); and the pleasure that may sometimes be associated with uncertainty following a positive event (Wilson *et al.*, 2005).

The reverse side of this form of paradox is situations where what normally helps may hinder. Apart from well-established observations such as the side-effects/unintended consequences of medical treatments or the occasional harmful consequences of modern transportation systems (either directly as in the case of accidents, or indirectly by the transmission of infectious diseases), a number of relevant phenomena have emerged, some of which are discussed in more detail in subsequent chapters. These include the following.

- The possible effects of exercise as a contributory factor to the origins of motor neurone disease (Chiò *et al*., 2005).
- Situations where there may be detrimental effects from power and privilege, or from expertise (Sternberg, 2002; Castel *et al*., 2007).
- Increase in size or number of lesions after initiation of chemotherapy in neurotuberculosis (Kumar *et al*., 2006).
- Lack of strict correspondence between wealth and happiness, sometimes known as the Easterlin Paradox, after the economist Richard Easterlin (Easterlin, 1974; Graham, 2008), and the occasional adverse effects of wealth on happiness and efficiency (Kahneman *et al*., 2006; Quoidbach *et al*., 2010).
- The possible evolutionary influence of language on the development of psychiatric conditions such as schizophrenia (Crow, 2000).

Paradoxes in public health medicine have also been pointed out (Worthman and Kohrt, 2005; Christakis, 2009; Partridge, 2009). These include increased longevity unmasking diseases associated with ageing, indirect side-effects of the treatment of infectious diseases, coupled with misuse of anti-infectious agents (antibiotics/antifungals/antivirals) where short-term use may alleviate symptoms, but may promote the survival of multi-resistant strains if the drugs are not taken for long enough to eradicate the entire population of the infectious organism. Perceived failures in health care delivery have been attributed to a basic paradox of training of staff to a high degree of excellence, but so stigmatizing errors that institutional learning from mistakes is impeded (Reason, 2008), with the result that excellence and incompetence may often go hand-in-hand (Kapur, 2009). Others have pointed to an 'information paradox', where the explosion of health-related information, and the concentration on evidence-based medicine, has detracted from the personal and social context of the individual patient, leading indirectly to limitations in patient care (Sweeney, 1998).

In recent years, the field of 'paradoxical pharmacology' has emerged (Bond, 2001), where counter-intuitive effects of drugs have encouraged new ways of thinking about pharmacological intervention. For example, drugs that traditionally would be considered to inflict stress on biological systems in the short term may in fact yield benefits in the long term ('short-term pain for long-term gain'). Bond points to a number of such paradoxes in the area of pharmacology, including the use of beta blockers in heart disease and also their possible use in treating asthma (Lipworth and Williamson, 2009). Venkatsubramanian (2010) has also noted instances where a drug may benefit one disease, while at the same time promoting another. Although the formalization and testing of the hypothesis that there may be a difference between the acute and chronic response of drugs may be a novel concept in pharmacology, there are numerous examples of it occurring not only in the treatment of disease, but even in nature itself. Indeed, as mentioned above, it could be argued that even bacteria, fungi and viruses become more resistant as a result of exposure to drugs used to kill them (an example of natural selection). In the case of plant biology, commentators have remarked on the paradoxical presence of plant biodiversity in situations where one would not logically expect it to occur (e.g. Shoresh *et al.*, 2008; Silvertown, 2008), while others have pointed to unusually long life-spans of normally short-living tree species in certain circumstances (Larson, 2001).

Lower doses of drugs may have contrasting effects on function, as in the case of stimulating effects of a sleeping tablet, Zolpiden (Brefel-Courbon *et al.*, 2007) and the calming effects of low doses of a stimulant in Attention Deficit Hyperactivity Disorder (Arnsten, 2006) – see Chapter 23 in this book. As Bond (2001) has argued, acute and chronic effects of interventions such as drug treatment, exercise, etc., may have opposite effects on a key outcome variable – e.g. exercise increases blood pressure in the short term but decreases it in the long term. One of the lessons from paradoxical pharmacology, argues Bond, is that incremental, chronic, intermittent exposure to a drug should be considered as a therapeutic option, especially in cases where the acute effects may be deleterious. Some of these observations have been subsumed in the emerging field of 'hormesis', where nonlinear dose–response curves for particular agents may sometimes result in paradoxical facilitation effects on human biological function (Ricci and MacDonald, 2007; Mattson, 2008; Calabrese, 2008; Jolly and Meyer, 2009). At the level of individual molecules, biological paradoxes have also been observed, as in the effects of acetylcholine on blood vessels, which sometimes produced relaxations and sometimes resulted in contractions of vessels. This paradox was both noted and resolved by Robert Furchgott, for which he subsequently gained the Nobel Prize, when he showed that the response of blood vessels depended critically on the innermost layer of cells lining the vessel, the endothelium – when the endothelium was present, acetylcholine relaxed blood vessels, but when it was removed, they contracted (Furchgott and Zawadski, 1980).

Neurosciences

In the case of the human brain, we are traditionally taught to assume that the brain optimizes behaviour, and that superior brains result in better behavioural capacities. To many people, this traditional view implies that a lesion to the brain will invariably lead to a loss of function, that a second lesion will inevitably exacerbate the adverse effects of an initial lesion, that it is generally not possible to lose function by enhancing brain activity, and that mentally or developmentally delayed individuals or non-human species cannot outperform normally intelligent humans. However, all these assumptions appear to be incorrect. This has implications for how we understand brain–behaviour relations, and – critically – how we implement therapies in clinical settings.

'Neurology's favourite word is deficit, denoting an impairment or incapacity of neurological function', writes Oliver Sacks, in his widely read *The Man Who Mistook His Wife for a Hat* (1985, p. 1). In his sequel, published 10 years later, *An Anthropologist on Mars*, Sacks also wrote, 'Defects, disorders, diseases, in this sense, can play a paradoxical role, by bringing out latent powers, developments, evolutions, forms of life, that might never be seen, or even be imaginable, in their absence' (1995, p. xii). In 1929, Vygotsky made a similar point in his treatise 'The Fundamental Problems of Defectology', in which he commented on the importance of considering compensatory strategies and mechanisms in cases such as blindness (Vygotsky *et al.*, 1993). Vygotsky noted 'The doctrine of overcompensation has an important significance and serves as a psychological basis for the theory and practice of educating a child with a loss of hearing, sight and so forth. What horizons will open up to the pedagogue, when he recognizes that a defect is not only a minus, a deficit, or a weakness but also a plus, a source of strength and that it has some positive implications!' (1993, p. 29).

The study of brain–behaviour relationships from cases of cerebral pathology has traditionally been embedded in the lesion-deficit model. While this model has provided valuable insights into our understanding of the organization of function in the human brain, it suffers from a number of drawbacks. First, in focusing on negative changes, it potentially ignores gains in other domains, for example, that may result from plastic reorganization or from the release of another brain region from inhibition. Second, nature is not always so obliging as to provide clear-cut contrasts between what is impaired and what is spared after a brain insult. Third, the lesion-deficit model can lead us to misinterpret findings – we may attribute dysfunction to a single locus when the dysfunction is in fact the result of a general perturbation to the system, or disruption to several interconnected areas/networks. Fourth, it may discourage thinking about positive compensatory and adaptive strategies that could be employed in rehabilitation.

There is an exciting appeal to maverick theories than can lead to greater attention and indeed high-impact publication than theories lying squarely within accepted thought. Often, of course, there are solid statistical reasons why such outliers and the observations on which they are based are wrong, and why science is generally better advanced by convergence. However, entertaining different ideas about how we think about a topic, such as the effects of brain injury, by embracing paradoxes that do not fit within the prevailing deficit model could prove a fruitful method for illuminating underlying processes. To do so is not to decry other perspectives, or to suggest that, for example, most effects of an injury are not deleterious. However, thinking about exceptions may provide insights into how this highly complex organ functions, and how people who experience neurological, psychiatric or developmental difficulties may best be helped.

Recent years have seen a number of studies, which have begun to challenge the lesion-deficit model. There are instances where there may be limited correspondence between lesion load and dysfunction or disability (Rovaris and Filippi, 2005; Strasser-Fuchs *et al.*, 2008; Savva *et al.*, 2009), or where lesions may be 'silent' for a number of years without any clinical manifestation (Krampla *et al.*, 2008; Kuratsu *et al.*, 2000; Hakiki *et al.*, 2008). The paper by Kapur (1996) provided an earlier review of some paradoxical phenomena in brain research and offered a framework, such as competitive interaction between excitatory and inhibitory systems, that might explain some paradoxical findings. In human lesion studies (reviewed in Chapter 3), the major sets of paradoxical cognitive phenomena generally take one of two forms – enhanced cognitive performance of neurological patients vis-à-vis neurologically intact individuals, and alleviation or restoration to normal of a particular cognitive deficit following the occurrence of a brain lesion. A third set of paradoxical cognitive phenomena represents what may be termed 'inverse effects', where a variable that produces facilitation or detriment of performance in normal subjects results in opposite effects in neurological patients. A fourth set of similar paradoxical effects, sometimes seen in animal lesion studies and very occasionally evident in human studies, arises when there is an inverse relationship between lesion size and functional deficit, with larger lesions leading to less marked functional impairment. Other developments in recent years have included emphasis on the positive features of conditions such as autism (Hermelin, 2001; Frith and Happé, 2009), and the large number of studies that have reported facilitation of function following transient disturbance induced by transcranial magnetic stimulation (Fecteau *et al.*, 2006). The modulation or improvement of cognitive and psychological functions by ablative or blocking influences has hitherto been largely ignored in classical texts in neuropsychology and behavioural neurology.

Almost 40 years ago, Pribram (1971) alluded to more general indications of paradoxical phenomena in the study of brain–behaviour relationships that were evident at that time, including the co-existence of seemingly contradictory facts or observations about the brain, and the unexpected absence of predicted outcomes after brain lesions. For example, Pribram pointed to the ostensive contradiction between greater interconnectivity of the human brain compared to other species and the apparently greater regional specialization of function, to the surprising absence of effects resulting from frontal lobe lesions, to the dissociation between physiological and behavioural indices of a response, and to the unexpectedly close harmony between sensory and motor cortex. Although some of these findings might not now be seen as particularly paradoxical, Pribram's observations and intuitions at that time provide an important historical context to current brain–behaviour paradoxes.

Conclusions

'A prevailing paradigm is likely to be more strongly affected by a new concept than by a new discovery', noted the evolutionary biologist Ernst Mayr (2004, p. 168). To the extent that embracing paradoxical phenomena entails a major change of paradigm in scientific methodology, it may fall under the rubric of Kuhn's criteria for a paradigmatic shift in scientific thinking (Kuhn, 1996).

Weatherall (1999) has alluded to the importance of applying fundamental approaches in biology to the clinical sciences. In particular, he notes the key questions – What, How and Why? This book is very much tentatively in the What mode – it is intended to give as fair and as comprehensive a picture as possible of paradoxes as they relate directly or indirectly to the human brain. Some authors have rightly and courageously offered to answer the How question, and to offer hints as to responses to the Why question, but these two questions will need to await replication of many of the observations that have been reported, and also documentation of the parameters/boundary conditions of particular findings.

The chapters in this book examine paradoxical phenomena from the perspective of clinical and cognitive neuroscience. From a general therapeutic perspective, a number of the chapters highlight the strengths that may accompany functional deficits, either directly or indirectly, and lend weight to the concept of 'neurodiversity' (Armstrong, 2010). This emphasis on strengths rather than weaknesses in neurological conditions has parallels in the field of positive psychology, which is now well established with books, journals, organizations and government reports devoted to the topic (Baumgardner and Crothers, 2009). There is also concordance with some approaches in clinical psychology, where there has been an increasing focus on phenomena such as 'post-traumatic growth', whereby a major physical or mental illness may sometimes result in enhanced adjustment and well-being (Joseph and Linley, 2008). The field of positive neurology appears to be less well defined. To our knowledge, the term 'positive neurology' has only been briefly used on a couple of occasions (Eide and Eide, 2006; Chatterjee, 2004), and the term 'positive neuropsychology' has only briefly been used once in a conference presentation (Eslinger, 2005). This book is intended to set the foundation for the field of positive neurology, and to demonstrate how it may have far-reaching theoretical and therapeutic implications. Such an approach in turn encourages a positive, more humanistic, view of differing or 'impaired' states of the human condition, a form of 'humanistic neuroscience'.

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References

Aharonov, Y., & Rohrlich, D. (2005). *Quantum Paradoxes: Quantum Theory for the Perplexed*. Weinheim: Wiley-VCH.

Alario, M., & Freudenburg, W. (2007). Atoms for peace, atoms for war: probing the paradoxes of modernity. *Sociological Inquiry*, **77**: 219–40.

Allen, S. J., O'Donnell, A., Alexander, N. D., *et al.* (1997). Alpha+Thalassemia protects children against disease caused by other infections as well as malaria. *Proceedings of the National Academy of Sciences*, **94**: 14,736–41.

Ariely, D. (2010). *The Upside of Irrationality*. New York, NY: Harper Collins.

Ariely, D., Gneezy, U., Loewenstein, G., & Mazar, N. (2009). Large stakes and big mistakes. *Review of Economic Studies*, **75**: 1–19.

Armstrong, T. (2010). *Neurodiversity*. Cambridge, MA: Da Capo Press.

Arnsten, A. F. (2006). Stimulants: therapeutic actions in ADHD. *Neuropsychopharmacology*, **31**: 2376–83.

Baek, K. H., Zaslavsky, A., Lynch, R. C., *et al.* (2009). Down's syndrome suppression of tumour growth and the role of the calcineurin inhibitor DSCR1. *Nature*, **459**: 1126–30.

Baker, S. G., & Kramer, B. S. (2007). Paradoxes in carcinogenesis: new opportunities for research directions. *BMC Cancer*, **7**: 151.

Baumgardner, S., & Crothers, M. (2009). *Positive Psychology*. New York, NY: Prentice Hall.

Billington, W. (2003). The immunological problem of pregnancy: 50 years with the hope of progress. A tribute to Peter Medawar. Invited Editorial. *Journal of Reproductive Immunology*, **60**: 1–11.

Bond, R. A. (2001). Is paradoxical pharmacology a strategy worth pursuing? *Trends in Pharmacological Sciences*, **22**: 273–6.

Bray, G. (2009). Risk factors: the obesity paradox – an artifact of small sample size? *Nature Reviews Cardiology*, **6**: 561–2.

Brefel-Courbon, C., Payoux, P., Ory, F., *et al.* (2007). Clinical and imaging evidence of zolpidem effect in hypoxic encephalopathy. *Annals of Neurology*, **62**: 102–5.

Calabrese, E. J. (2008). Hormesis and medicine. *British Journal of Clinical Pharmacology*, **66**: 594–617.

Camus, M. Tosolini, M., Mlecnik, B., *et al.* (2009). Coordination of intratumoral immune reaction and human colorectal cancer recurrence. *Cancer Research*, **69**: 2685–93.

Carlsmith, K., Wilson, T., & Gilbert, D. (2008). The paradoxical consequences of revenge. *Journal of Personality and Social Psychology*, **95**: 1316–24.

Castel, A., McCabe, D., Roediger, H. L., & Heitman, J. (2007). The dark side of expertise. *Psychological Science*, **18**: 3–5.

Chandrasekhar, S. (1984). On stars, their evolution and their stability (Nobel Lecture). *Angewandte Chemie International Edition in English*, **23**: 679–89.

Chatterjee, A. (2004). The controversy over enhancing movement, mentation, and mood. *Neurology*, **63**: 968–74.

Chiò, A., Benzi, G., Dossena, M., Mutani, R., & Mora, G. (2005). Severely increased risk of amyotrophic lateral sclerosis among Italian professional football players *Brain*, **128**: 472–6.

Christakis, N. (2009). Indirectly doing harm. *British Medical Journal*, **339**: 782.

Cohen, E., & Dillin, A. (2008). The insulin paradox: aging, proteotoxicity and neurodegeneration. *Nature Review Neuroscience*, **9**: 759–69.

Crocker, I., Lawson, N., & Fletcher, J. (2002). Effect of pregnancy and obstructive jaundice on inflammatory diseases: the work of P S Hench revisited. *Annals of the Rheumatic Diseases*, **61**: 307–10.

Crow, T. J. (2000). Schizophrenia as the price that *Homo sapiens* pays for language: a resolution of the central paradox in the origin of the species. *Brain Research Reviews*, **31**: 118–29.

Dirnagl, U., Becker, K., & Meisel, A. (2009). Preconditioning and tolerance against cerebral ischaemia: from experimental strategies to clinical use. *Lancet Neurology*, **8**: 398–412.

Donald, M. (2009). The sapient paradox: can cognitive neuroscience solve it? *Brain*, **132**: 820–4.

Droit-Volet, S., & Gil, S. (2009). The time–emotion paradox. *Philosophical Transactions of the Royal Society B*, **364**: 1943–53.

Easterlin, R. (1974). Does economic growth improve the human lot? In: David, P. & Reder, M. (Eds). *Nations and Households in Economic Growth: Essays in Honor of Moses Abramovitz*. New York, NY: Academic Press, pp. 89–125.

Eide, B., & Eide, F. (2006). The mislabelled child. *The New Atlantis*, Spring, pp. 46–57.

Enevold, A., Alifrangis, M., Sanchez, J. J., *et al.* (2007). Associations between alpha+ thalassemia and *Plasmodium falciparum* malarial infection in northeastern Tanzania. *Journal of Infectious Diseases*, **196**: 451–9.

Eslinger, P. (2005). Practising positive Neuropsychology. *Meeting of International Neuropsychological Society, July 2005*. Dublin.

Farson, R., & Keyes, R. (2002). *The Innovation Paradox*. New York, NY: The Free Press.

Fecteau, S. Pascual-Leone, A., & Théoret, H. (2006). Paradoxical facilitation of attention in healthy humans. *Behavioral Neurology*, **17**: 159–62.

Fois, A., Wotton, C., Yeates, D., Turner, M., & Goldacre, M. (2010). Cancer in patients with motor neuron disease, multiple sclerosis and Parkinson's Disease: record linkage studies. *Journal of Neurology, Neurosurgery and Psychiatry*, **81**: 215–21.

Forgas, J. P. (2007). When sad is better than happy: negative affect can improve the quality and effectiveness of persuasive messages and social influence strategies. *Journal of Experimental Social Psychology*, **43**: 513–28.

Frankenstein, L., Zugck, C., Nelles, M., Schellberg, D., Katus, H. A., & Remppis, B. A. (2009). The obesity paradox in stable chronic heart failure does not persist after matching for indicators of disease severity and confounders. *European Journal of Heart Failure*, **11**: 1189–94.

Frith, U., & Happé, F. (Eds). (2009). Autism and talent. *Philosophical Transactions of the Royal Society, B*, **364**: Issue Number 1522.

Furchgott, R., & Zawadski, J. (1980). The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by ACh. *Nature*, **288**: 373–6.

Graham, C. (2008). Happiness and health: lessons and questions for public policy. *Health Affairs*, **27**: 72–87.

Gray, J., Johnson, P. W., & Glennie, M. (2006). Therapeutic potential of immunostimulatory monocolonal antibodies. *Clinical Science (London)*, **111**: 93–106.

Hakiki, B., Goretti, B., Portaccio, E., Zipoli, V., & Amato, M. P. (2008). 'Subclinical MS': follow-up of four cases. *European Journal of Neurology*, **15**: 858–61.

Handel, A., Joseph, A., & Ramagopalan, S. (2010). Multiple sclerosis and lung cancer: an unexpected inverse association. *Quarterly Journal of Medicine*, **103**: 625–6.

Handy, C. (1995). *The Age of Paradox*. Cambridge, MA: Harvard Business School Press.

Hench, P. (1950). The reversibility of certain rheumatic and non-rheumatic conditions by the use of cortisone or of the pituitary adrenocorticotropic hormone. In: Nobel Foundation. *Nobel Lectures, Physiology or Medicine, 1942–62*. Amsterdam: Elsevier.

Hermelin, B. (2001). *Bright Splinters of the Mind*. London: Jessica Kingsley.