

chemistry and microbiology, to which other biological sciences were mere appendages providing the necessary *in vitro* and *in vivo* screens. Studies of the products of mould and microorganism metabolism and their chemistry dominated drug research. This approach resulted in the discovery of many effective antibacterial and some useful anti-tumour agents. Others often resulted from chance findings, notably the anticancer drug cisplatin.

However, by the late 1980s drug discovery was in a rut, with the realization that random screening was an expensive and ultimately unscientific way to find agents with significantly superior activity and selectivity. The subsequent revolution in our understanding of the molecular basis of many diseases has prompted fundamental changes in approach. The current, more rational approach is based on an understanding of pathogen and malignant cell and molecular biology. The impact of the human genome project on the treatment of human disease promises to be even more profound.

Mann's parting message is that all this takes us full circle, back to the essence of Ehrlich's approach, based on the idea of specific chemoreceptors.

Inevitably, a small book with such an ambitious agenda has to emphasize some topics more than others. I would have expected to see a fuller (and illustrated) account of the impact of structure-based drug design, especially since there are several excellent recent examples now in the clinic, such as the anti-HIV protease inhibitors. There is no real mention of combinatorial chemistry, now having a profound impact in industry and even academia.

However, these are minor caveats for an engrossing book which serves its intended audience well. It has much of value for the interested layperson, as well as students and even professionals wishing to have a gentle yet erudite introduction to the past, present and future of chemotherapy. □

Stephen Neidle is in the CRC Biomolecular Structure Unit, The Institute of Cancer Research, Sutton, Surrey SM2 5NG, UK.

Drugs from other perspectives

On the one hand:

Bitter Pills: Inside the Hazardous World of Legal Drugs

by Stephen Fried

Bantam Books, \$24.95

And on the other ...

In Quest of Tomorrow's Medicine: An Eminent Scientist Talks About the Pharmaceutical Industry, Biotechnology, and the Future of Drug Research [Die verspielte Zukunft]

by Jürgen Drews, translated from the German by David Kramer

Springer, \$29.95, £22.50

Taming the black dog

Malignant Sadness: The Anatomy of Depression

by Lewis Wolpert

Faber & Faber: 1999. 186 pp. £9.99

Charles B. Nemeroff

In the past decade, a number of books have documented personal experiences with depression or manic-depressive illness. There are the rare public figures willing and able to share their voyages to hell and back. There are the professionals (including mental-health workers) who have, after an episode of depression, dramatically changed their view of the disorder. And there are the articulate patients wishing to educate both the lay public and health-care professionals on the diagnosis and treatment of this devastating disease. There are probably more than 20 such volumes available, many of them excellent. Do we need another? In contemplating the request to review this book, I had to take into consideration my current tardiness in several projects. So why did I agree?

For the biologists, the answer is obvious, but to the rest of you, it is simply because the author is Lewis Wolpert. Wolpert is an accomplished developmental biologist, who has not only made remarkable research contributions, but has helped frame many questions in biological research, cutting across a number of disciplines. In view of his scientific prowess and his role as a philosopher-

scientist, it was simply too tantalizing for me to resist the temptation to preview what he writes about a disorder that I have spent most of my professional life studying.

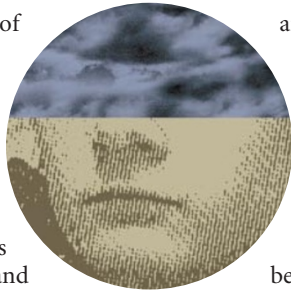
I was not disappointed; there is much good here. As he himself now recognizes, one of the major problems with depression is the stigma attached to it by both the public and many health-care providers. His willingness to share the pain, self-doubt, hopelessness and helplessness that is pathognomonic of this disorder will help many non-sufferers of depression to understand, and many depressed patients to fight this "black dog", as Churchill termed it. Wolpert's description of the severe sleep disturbance, obsession with suicide, anxiety, inability to concentrate, diurnal mood variation and bewildering physical symptoms is compelling. His grasp of the literature is, not surprisingly considering his biological background, very topical and generally accurate. He conveys the public-health implications of depression in a very readable manner, which is no small task. He highlights several facets of depression that are generally not emphasized enough, including its remarkably high prevalence worldwide, and the morbidity and mortality associated with it. In the United States, suicide is the ninth leading cause of death, in spite of the experts' acknowledgement that many, if not most, suicides go unreported.

Wolpert's repeated emphasis on depression as a systemic disease that affects several other organs, including the heart, is a well-established finding that has not received the recognition it deserves. He is one of the first authors to repeatedly remind us that the



DAVID NEWTON

spouses and family of depressed patients also suffer terribly, and must be partners in the treatment. His cogent discussion of the classification of mood disorders and the current diagnostic process and measurements of disease, by categorical and dimensional measures, respectively, is a godsend. I found his discussion of the nature and seriousness of postnatal depression particularly valuable. He also does a very good job of summarizing the neurobiology of depression, with an emphasis on the role of alterations in serotonergic and noradrenergic neuronal systems, and of the hypothalamic-pituitary-adrenal axis in the pathophysiology of mood disorders.



What didn't I like? The author's understanding of the data from controlled clinical trials related to the treatment of depression was a bit disappointing. Perhaps I expected too much, but we get a relatively non-critical and superficial view of a very complex field. For example, Wolpert says that the literature reveals all antidepressants to be equally efficacious. Although this is technically true, in that no regulatory agency in any country has ever recognized one antidepressant as more effective than another, there is a raging controversy in the field over this issue. There are data that suggest that certain of the older tricyclic antidepressants, such as chlorimipramine, are more effective than some of the newer agents. This is obviously not a trivial point, and may relate to the older drugs' effects on more than one neurotransmitter system, compared with the newer, more selective agents.

Perhaps more important is the lack of communication of the following observation, which is well known among psychiatrists: most depressed patients treated with an antidepressant respond only partially or not at all. Unfortunately, many general practitioners and even psychiatrists do not use measures of depression severity to follow their patients' progress, and therefore never realize that their patients have, in fact, not completely recovered. It is also important to determine whether the depressed patient has delusional (psychotic) thinking; such patients do not respond to antidepressant monotherapy, and require combination treatment with an antidepressant and an antipsychotic medication.

Another minor disappointment is Wolpert's discussion of the role of psychotherapy in treating depression, and the (perhaps) related issue of placebo response of depressed patients. It is difficult for the uninitiated to understand how depression can, on the one hand, be as severe as it is described (severe functional impairment, increased risk of heart disease and stroke,

and increased risk of suicide) and, on the other, respond relatively well to placebo treatment. The answer lies, at least in part, in that the depressed patient assigned to the placebo group receives all of the treatment except the drug (the contact with a myriad of research personnel will be a form of therapy). In terms of the psychotherapies themselves, suffice it to say that the more severe the depression, the less likely that it will respond to psychotherapy alone. Moreover, as Wolpert points out, the decreases in concentration and cognitive dysfunction characteristic of severe depression hardly make the patient a candidate for psychotherapy. He aptly points out the important theoretical underpinnings of psychoanalysis and psychoanalytically oriented psychotherapy in the aetiology and treatment of depression, but surprisingly fails to highlight the lack of evidence for the efficacy of this approach.

I was not surprised by his attraction to genetics, as this field will probably shed considerable light on depression research over the next decade, perhaps more than any other

field. The completion of the Human Genome Project will provide the field with tools that will surely advance depression research. I believe that functional brain imaging will also contribute much, as will the burgeoning pipeline of promising therapies.

In summary, *Malignant Sadness* will stand up well with other personal descriptions of depression, including some he refers to in his volume: Kay Redfield-Jameson's *An Unquiet Mind* and Kathy Cronkite's *On The Edge of Darkness*. It is a fitting companion to others who have written eloquently on this subject, including Tracey Thompson's *The Beast: A Reckoning with Depression* and Martha Manning's *Undercurrents*. In view of the growing evidence for the role of adverse early experience in the pathogenesis of depression, the only solution may be to offer Wolpert a sabbatical to share his developmental biology expertise, together with his personal knowledge of this disorder, to help design experiments to uncover biological causes of this observation. □

Charles B. Nemeroff is in the Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia 30322, USA.

Starr book wins Los Angeles Times prize

Douglas Starr's book *Blood: An Epic History of Medicine and Commerce* was announced as the winner of the science and technology category of the 1998 Los Angeles Times Book Prize last Friday (23 April). Starr was one of five finalists in the science and technology category:

The Baltimore Case: A Trial of Politics, Science and Character

by Daniel J. Kevles
W. W. Norton, \$29.95, £21

"Daniel Kevles performs a signal service by applying his historian's acumen to the mountain of documents accumulated by all those investigations, and to his own detailed interviews with the participants, to give us an orderly narrative of the whole affair. He did so, he says, because it seemed to him likely to 'throw some light on science in late-twentieth-century American society.'" Jon Turney, *Nature* 395, 30-31 (1998).

Phantoms in the Brain: Probing the Mysteries of the Human Mind

by V. S. Ramachandran and Sandra Blakeslee
William Morrow, \$27, £17.99

"*Phantoms in the Brain* is structured around the life histories of patients with unusual, often bizarre, neurological disorders. The narrative structure of biography has undoubted pedagogic value, but the worst examples of the genre come uncomfortably close to modern-day equivalents of a travelling freak-show. To their credit, this pitfall is skilfully avoided by Ramachandran and Blakeslee, who keep the ideas they are seeking to

communicate centre stage." Raymond J. Dolan, *Nature* 396, 639-640 (1998).

Taking Wing: Archaeopteryx and the Evolution of Bird Flight

by Pat Shipman
Simon & Schuster, \$25.

"Shipman makes an outstanding analysis of the contribution of *Archaeopteryx* to discussions about the origin of flight." Jose Luis Sanz, Bernardino P. Perez-Moreno & Francisco J. Poyato-Ariza, *Nature* 393, 32-33 (1998).

Blood: An Epic History of Medicine and Commerce

by Douglas Starr
Knopf, \$27.50, £20

"While the value of a barrel of crude oil has fallen to \$12, an equivalent amount of blood is now worth around \$60,000. How this came about is lucidly recounted by Douglas Starr in this history of blood transfusion. The book is accessible to a wide-ranging audience." Fred S. Rosen, *Nature* 398, 303-304 (1999).

Mendel's Dwarf

by Simon Mawer
Harmony, \$23 (hbk); Anchor, £6.99 (pbk)