

Forty Years in the Conceptual Wilderness

Merton Sandler

The Antidepressant Era. DAVID HEALY. Harvard University Press, Cambridge, MA, 1998. xii, 317 pp., illus. \$39.95. ISBN 0-674-03957-2.

On 6 September 1944, the first V2 rocket fell on West London, about a mile from Queen Charlotte's Hospital, where I spent most of my working life. In the following months, another thousand were fired at Southern England and three thousand more at targets in Europe. Early models were powered by ethanol and liquid oxygen; then supply problems led German engineers to use hydrazine. After the war, large stores of this noxious (caustic, poisonous, and explosive) fluid were discovered and became available to drug companies at knock-down prices.

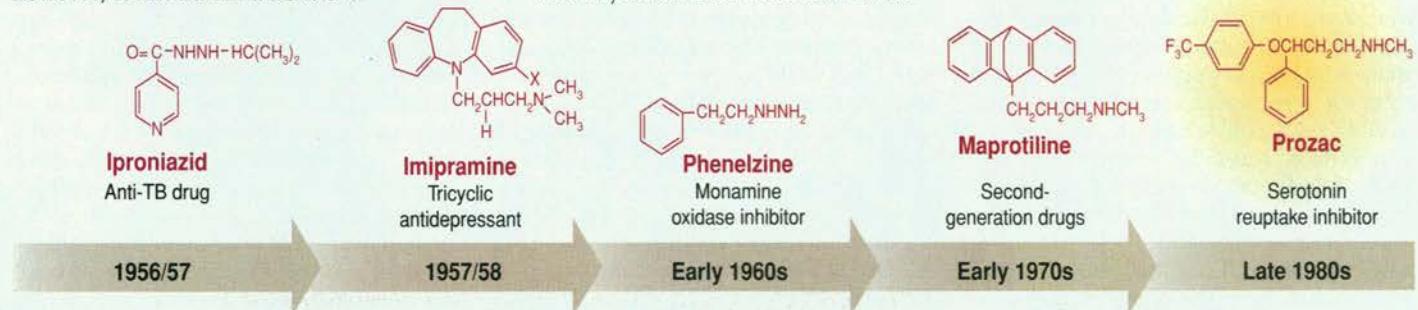
Tuberculosis was then a major scourge and a prime target for drug companies of the time. In 1951, Hoffmann-La Roche chemists synthesized a series of hydrazine derivatives, two of which, isoniazid and iproniazid, were found to be powerfully antitubercular. The latter also turned out to be an irreversible inhibitor of monoamine oxidase, an enzyme of little more than academic interest in those days. Iproniazid possessed euphoriant side effects, which almost resulted in its withdrawal from the market. Thanks, however, to the machinations of a

come out of a background of antihistamine studies in Europe. Barely a few months after Kline's discovery of iproniazid's effects, the first tricyclic antidepressant drug, imipramine, also appeared on the European scene. Rather more agonizingly, lithium was gradually accepted as a treatment for affective disorder. All in all, it seemed as if the psychiatric walls of Jericho were about to tumble. And yet, forty years have now elapsed without further major discoveries in this field. What is the reason?

The story of the antidepressants and their times is now familiar. In the normal run of things, it would not warrant a new book but David Healy has an important trick up his sleeve. He has emerged as a latter-day Boswell to a succession of scientific Dr. Johnsons. Assiduously and meticulously, he has taped an impressive series of interviews with leading psychopharmacologists. Having previously published two volumes of these unique data, Healy now presents a synthesis of the newly gained information with the results of his considerable historical scholarship. Healy is a natural raconteur and this book is a cornucopia, bursting with amusing anecdote. It would not do, however, to give the impression that he is just a stand-up comic. He can sift, rank, and evaluate like any statistician. He is both scath-

Healy, a trained psychiatrist, inclines to the biological, he is something of a fence sitter—in the nicest possible way. He points out that even the double-blind trial, that great pillar of pharmaceutical investigation, is not sacrosanct unless applied sensibly. Consider the 1965 [British] Medical Research Council (MRC) trial of the monoamine oxidase inhibitor, phenelzine. The results were negative, despite clear evidence from the literature that the drug works. In retrospect, the trial misled because the dose tested was too low, the duration of treatment too short, and the rating scale used to evaluate the effects was inappropriate.

Several decades ago, the World Health Organization estimated that a hundred million people worldwide are probably depressed on any given day. Healy calls depression "almost the common cold of psychiatry." How can we come to terms with this problem? He draws attention to one important development, the emergence of a group of American psychiatrists he terms the neo-Kraepelinians, who believe in the importance of traditional medical diagnosis in psychiatry. Their approach holds "that psychiatry [is] a branch of medicine, that there [is] an identifiable boundary between the normal and the sick, that discrete and identifiable mental illnesses exist, and that psychiatry should treat these and not problems of living and unhappiness. Psychiatric research should, moreover, be geared to establishing the validity of diagnostic criteria. The creation



Pharmacological progress. The discovery of the antidepressant effects of antitubercular drugs led to the first-generation tricyclic antidepressants and monoamine oxidase inhibitors, which were followed by second-generation drugs and, finally, present-day selective serotonin reuptake inhibitors.

flamboyant New York psychiatrist, Nathan Kline, the drug emerged as the first true antidepressant. (Kline was fueled by enthusiasm and political savvy; characteristically he published the initial account of this drug trial in the *Congressional Record* of 1956.)

Only a year or two earlier, the first antipsychotic drug, chlorpromazine, had

ing and understanding about (indeed, he is slightly obsessed by) the role of the drug companies in what can only be termed "the making and marketing of depression."

On his crowded canvas, the polarization between the 19th-century belief system known as psychoanalysis and biological psychiatry can be seen in fine perspective. Healy is fair to both and would agree with the conclusion of the Italian writer Umberto Eco that "for every complex problem, there's a simple solution, and it's wrong!" Although

of DSM-III [*Diagnostic and Statistical Manual III*] was the Trojan horse by which the group effected entry into the citadel of psychoanalysis" (p. 233).

Even so, some theoretical framework, some testable hypothesis of depressive illness, is necessary to enable progress to be made. The monoamine hypothesis of depression, which crystallized in 1965, served as a useful model for drug development for many years. It is now outmoded and has outlived its usefulness. What do we put in its

The author is in the Department of Chemical Pathology, Queen Charlotte's & Chelsea Hospital, Goldhawk Road, London W6 0XG, UK.



place? A molecular and cellular theory of depression recently put forward by Ronald Duman and his colleagues from Yale (1) seems to fit the bill (2). Previous theories have been unable to explain the time lag between antidepressant drug administration and lightening of affect. Duman's group pinpoints intracellular mechanisms, acting in the right time frame, that decrease or increase the generation of neurotrophic factors necessary for the survival of specific neurons, particularly hippocampal ones. The new theory also suggests the answer to

our earlier question, "Why 40 years in the conceptual wilderness?" Simply because we were not yet ready technically. (I am specifically thinking of the molecular biological revolution, which has provided sophisticated new techniques for measurement.) Also of note is that the painstaking fundamental research underpinning the new theory stems not from the efforts of the big battalions—producing their me-too drugs to a set marketing recipe, the monoamine hypothesis of depression—but from the joint efforts of university-based research teams

and small, entrepreneurial companies based on molecular biology. A pity that Healy's book appeared just too early for him to pronounce on what may turn out to be the great leap forward of this psychiatric generation. Let us hope that he will do so in the next edition of this excellent and thoughtful work.

References

1. R. S. Duman, G. R. Heninger, E. J. Nestler. *Archives of General Psychiatry* **54**, 597 (1997).
2. R. M. Post. *Ibid.*, p. 607.

ENVIRONMENTAL POLICY

Locating Sustainability

Bryan G. Norton

Taking Complexity Seriously. Policy Analysis, Triangulation and Sustainable Development. EMERY ROE. Kluwer, Boston, 1997. xii, 138 pp., illus. \$98.50, NLG 215, or £65. ISBN 0-7923-8058-4.

In *Taking Complexity Seriously*, Emery Roe steps boldly into an important and under-discussed area—the current state of confusion in environmental policy analysis. The book must be taken seriously both because of the importance of the issues raised and because the author's pluralist viewpoint is sure to be provocative. Taking the debate surrounding sustainable development as a case study, Roe addresses three related issues: (i) problems of policy analysis in complex situations; (ii) the development of "triangulation," a comprehensive method of analysis for complex policy problems, which proposes a particular sort of "meta-narrative" to guide policy; and (iii) the exploration of four, particular narrative analyses. Each of these narratives, based on a different method, develops a very different understanding of sustainability debates. Hopefully, the book will continue and clarify the lively debate over the problems and prospects of sustainable development. This debate was fanned in 1993 by Ludwig, Hilborn, and Walters' *Science Policy Forum* "Uncertainty, Resource Exploitation, and Conservation: Lessons from History," and continued in a collection of responses by ecologists and environmental managers in a special feature in *Ecological Applications* that same year (1). Roe argues that differing notions of "management in the face of uncertainty and complexity" ensure that these ar-

guments will fail to achieve consensus, and that the only way to address such a complex situation is through his pluralistic method of triangulation.

One of the strengths of Roe's book is the author's success at bringing insights from the literature of mainstream policy analysis to bear on the sustainable development debate. Using some common typologies and jargon from organization theory, Roe leaps over one much-discussed aspect of the sustainability disputes—the clash between mainstream economic approaches and the "ecological" economists such as Herman Daly and Robert Costanza. If I understand the argumentative terrain, Roe goes beyond that debate to insist that an economic analysis of policies, even if ecologically informed, would provide at best only one tool among many in the arsenal of policy analysts. So, while accepting economic and other optimization methodologies as perhaps useful in other situations, Roe holds them to be of little value in the sustainability debate, because of their "palpable shortcomings in underwriting and stabilizing the assumptions for decision making in the face of high uncertainty and complexity" (p. 8). Under these conditions, Roe recommends a method of triangulation—using several, alternative methodologies based on quite different assumptions.

The least convincing aspect of the book is the meta-narrative developed to relate the four analyses explored in the process of triangulation (Girardian economics, cultural theory, critical theory, and the local justice framework) to one another. In particular, it is unclear exactly why these four approaches qualify as a part of the triangulation while other approaches fail to do so. Roe chose the approaches because "each provides a powerful, albeit radically different, tack on the complex management is-

ues core to sustainable development" (p. 23). But I did not find his argument for considering these particular approaches "orthogonal" in important respects either clear or compelling. Roe contrasts his own method with the recommendation of traditional policy analysts, who have suggested that, in the face of disagreement over both ends and means, the best we can do is to hope for "inspiration." It is not clear how triangulation, based on several incommensurable narratives delivered to the policy-maker from multiple perspectives, does much more than prepare the ground for a still-necessary inspiration. What seems missing is an account of the logic of the method of triangulation, some theory that explains why triangulating—and which triangulation(s)—leads to convergence on new problems and new solutions.

Fortunately, the four narratives themselves succeed despite problems with the meta-narrative that relates them to one another. By actually showing how exploring sustainable development within several analytic frameworks broadens and transforms the problems, Roe makes at least an important aspect of his case for a more pluralistic approach to policy analysis. So this is a useful book, both for what it accomplishes (linking the discourse of traditional policy analysis with that of sustainable development, developing and applying four alternative, less traditional analytic approaches) and also for what it does not. It does not, I think, provide a clear and general understanding of the logic of pluralistic and multi-criteria analyses of environmental problems. Perhaps, however, Roe's success in using such criteria, and his provocative comments on the nature of policy process, may stimulate further discussion and improved understanding of pluralistic environmental policy analysis and its uses.

References

1. D. Ludwig, R. Hilborn, C. Walters, *Science* **260**, 17 (1993); S. A. Levin, Ed. *Ecol. Appl.* **3**, 545–589 (1993).

The author is in the School of Public Policy, Georgia Institute of Technology, Atlanta, GA 30332, USA. E-mail: bryan.norton@pubpolicy.gatech.edu