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Book Reviews

Global Pharmaceutical Policy – Ensuring medicines for tomorrow's world, Frederick M. Abbott and M.N. Graham Dukes (Edward Elgar Publishing Ltd, Cheltenham, UK/Northampton, USA), 2009, 308 pp., ISBN 978 1 84844 090 6[1], £75.

> *"Today the [pharmaceutical] industry has got a very bad name. That is unfortunate for an industry that we should look up to and believe in, and that we should be supporting. I think there have to be some big changes."*[2]

The golden era of the pharmaceutical industry has brought the world many useful new medicines, a very powerful industry, and nice profits for shareholders. The global pharmaceutical market was worth USD 650bn in 2007, and has potential to grow, especially in middle-income countries. However, the free market mechanism that helped to shape the global pharmaceutical system now shows some distinct flaws. The consolidation of industry and risk-averse behaviour increasingly inhibit the development of new chemical entities and breakthrough products. The concentration of power in a few major markets has distorted government decision making. Medicines are getting more expensive due to ever-greening of patents and increased lobbying for market exclusivity. Advertising has sometimes more to do with seduction of consumers and influencing prescribing patterns of physicians than the transparent dissemination of evidence-based, objective and comparative information. Market failure has blocked the developing world from getting new medicines for its diseases of poverty. Two billion people still go without access to affordable, good quality, effective and safe essential medicines. The current global pharmaceutical crisis is complex and not easily resolved at national levels. New innovative ideas are needed how to change regional and global pharmaceutical policies.

This interesting book by Frederick Abbott and Graham Dukes, two eminent scholars in international law and pharmaceutical policy, aims to identify better ways to make use of the vast resources committed by governments and consumers for medicines, and to improve the level of prevention and treatment available to everyone.

The book's inspiration comes from an April 2007 round table seminar on "Global Pharmaceutical Regulation – tackling regional priorities" at Florida State University College of Law, Tallahassee, Florida, USA. It brought together 31 participants from across the globe and the pharmaceutical spectrum, who presented papers and discussed several problems affecting the global pharmaceutical sector. For example: high cost and roadblocks to genuine innovation in the USA; less research but more affordable access to medicines in Europe; huge generic exports but domestic regulatory problems in India and China; and finally the struggle in developing countries to provide access to essential medicines for not only the increasing HIV/AIDS, TB, and malaria epidemics, but also to address the current market failure for

[1] This book is also available as an e-book: ISBN 978 1 84980 184 3; from February 2011 also available as paperback: ISBN 978 1 84844 803 2, £25.

[2] Sir Richard Sykes, appearing before the UK House of Commons in April 2005, quoted on p. 292.

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developing treatments for neglected diseases, and to prepare for the coming chronic disease epidemics like hypertension, diabetes and cancer. Participants discussed policy solutions such as: possible alternatives for the current patent system, which fails to develop many needed medicines; how to regulate quality, safety and efficacy of medicines in international trade; and how to ensure that all people in developing countries get access to essential medicines.

The two authors have taken the 2007 round table discussions forward in this book, added more issues, and explain why some of the current policies are not working, and how to improve them. The authors identify several issues that need a wider international debate. They rely heavily on their personal professional experiences: this adds several interesting historical examples and rich informative nuances, but also means that some other policy proposals do not always get the attention they deserve.

One of the toughest global problems is how we research, innovate and develop the new medicines that the world needs. The pharmaceutical industry is fiercely defending the patent system as the basis for innovation, and has successfully expanded its global application through the 1995 WTO/TRIPS agreement. Pharmaceutical globalization may have lowered prices of essential medicines after patent expiry, but its market failure has not developed new medicines for diseases of poverty. The current patent system offers perverse incentives, and needs to change. The book argues that the current system is rather wasteful, as the world only gets only USD100bn worth of research for its USD 550bn purchase of branded products. A substantial share of basic pharmaceutical research is already being financed by governments, and public-private partnerships are now seeking new treatments that people in developing countries need for their neglected diseases. The book explores the history of innovation, analyzes the reasons for recently declining progress, discusses options for patent reform, and explores new ways of stimulating R&D, such as subsidies and prizes. It also analyzes the promise and problems of biotechnology.

The chapter on drug regulation provides interesting insights into the historic lessons why regulation of the pharmaceutical sector is needed. The authors argue that the current country-specific regulatory system is not efficient, and that we need much more regional and global collaboration, especially in an era of Internet and counterfeits. They also plead for less secrecy and more transparency in the medicines registration process; remind us of the importance of the "need clause" and warn against market and data exclusivity, which can delay the introduction of more affordable generic medicines. What is missing a bit is a description of the much needed fundamental paradigm shift in global drug regulation, and how we can strengthen regional drug regulation in the developing world.

The "Medicines for the developing world" chapter correctly outlines the importance and validity of the WHO essential medicines concept. In the discussion more analysis could however be presented why it is so difficult to implement such policies. The "transfer of technology" section is rather long with 13 pages, but is an important contribution. This is one of the few aspects in the TRIPS agreement that is advantageous for developing countries, as it will support local production of essential medicines. Unfortunately, the developed countries and pharmaceutical industry up to now have largely failed to honour this promise.

Rational use of medicines is probably an area where the world can make its biggest achievements, as a high percentage of the value of medicines is lost in the last two metres by incorrect diagnosis and/or prescribing by health workers, and irrational demands and use by patients. The authors correctly argue that better education of health professionals, increased awareness of consumers, and more evidence-based and comparative information can promote rational use of medicines. However, the huge marketing and promotion effort of the pharmaceutical industry and direct-to-consumer-advertising may distort these rational messages, and needs to be strictly regulated.

The role of the courts and the importance of civil liability proceedings may feel a bit uneasy for public health professionals, and pharmaceutical litigation may be seen as a typical American habit. However,

the authors (being lawyers) speak from first-hand experiences, and plead to maintain these possibilities, especially where states are not adequately regulating the sector through their public institutions.

Specialised sections in the book discuss issues around vaccination, control of blood products, alternative and traditional medicines, and the dangers of counterfeits and too much self-medication. Overconsumption in rich countries and poor access to essential medicines in developing countries are exposed. Neglected diseases are not only a problem in the developing world: rich countries also have problems how to deal with treatments for rare and/or costly diseases.

The book concludes that regional and global policy approaches are needed, as the current national policies are too much influenced by lobby groups and national interests. Working towards a global solution is not easy, as the problems are complex, and the known solutions face several obstacles.

The current inequity of access to essential medicines between rich and poor countries is a thorny issue that will require more donor aid, more appropriate research and development funding, and a more honest transfer of technology towards developing countries. If the pharmaceutical industry wants to keep the trust of society, and be seen as a "health care" industry, it will need to pay due attention to these issues and to the still too few innovative leaders that are calling for a change of the global pharmaceutical system. Business as usual is not an option!

The book ends with six important recommendations: (1) the system for promoting innovation should be refocused on the development of new therapeutic classes, with less emphasis on extending existing product lines through minor modifications. This needs a retooling of the current patent system and the development of subsidy, prizes and other incentives. (2) The system to assess, approve and control medicines should become more transparent. (3) Direct to consumer advertising needs to be curtailed as it causes both direct costs of promotion and indirect costs of increased demand. (4) Private civil litigation should remain a viable option to improve transparency, identify pharmaceutical risks, and redress injury. (5) Medicines regulation needs much more regional and global collaboration. (6) Developing countries need to maintain focus on essential medicines policies, and the developed world should continue its support to enable access to essential medicines for the 2 billion people who at present cannot enjoy their human right to essential medicines and health.

The book is well written but not easily digestible: the 308 page book is densely written, and could have benefitted from more graphs or tables. Text boxes add useful country experiences, but their layout could be improved. The facts in the book are accurate and well referenced. The index and table of contents provide quick access to important issues.

This book brings important new ideas to resolve the current crisis in the global pharmaceutical system. It does not claim to address all issues, but it has achieved its goal of inviting the global players to take note of these issues. The book is an important contribution for a complex topic that too often is reduced to oversimplified yes/no fights between stakeholders.

This book is therefore important reading, and can be strongly recommended for pharmaceutical industry executives, Ministry of Health and health insurance officials, development agencies' staff, and international consultants and health professionals interested to help get us out of the current pharmaceutical crisis.

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Medicines: The emergence of constructive criticism

Anatomy of an Epidemic: Magic Bullets, Psychiatric Drugs and the Astonishing Rise of Mental Illness in America, Robert Whitaker (Crown Publishers, New York, USA), 2010, US$ 17.80.

The Risks of Prescription Drugs, Donald Light (Editor) (2010): (Columbia University Press), 2010, US$ 15.

However one looks at it, the world of pharmaceuticals and drug prescribing is not at present a particularly attractive place in which to find oneself; to put it mildly, it is a deal less inspiring than it was half century ago. Many of us are old enough to have lived through an era in which true therapeutic breakthroughs enriched society in every decade and at times in almost every single year. The pioneering antibiotics radically met one challenge after another posed by infectious disease; inflammation succumbed to the corticosteroids; the seemingly innocuous benzodiazepines assumed the role once played by the addictive barbiturates; the mercurial diuretics gave way to the far safer thiazides, just as the treatment of hypertension with rauwolfia faded with the advent of the beta-blockers; the hormonal contraceptives changed the face of family planning. It seemed indeed that the age of pharmaceutical plenty had dawned and that from now onwards progress towards the conquest of every form of disease and disorder would be unstoppable. The onward march of drug therapy also appeared to be in large measure the fruit of industrial research. And then, quite suddenly, disillusionment seemed to set in.

In retrospect it would seem that the disappointments began to pile up in the 'sixties and certainly during the decade that followed. The thalidomide disaster of 1961 brought home to the world the fact that some new drugs might do a great deal more harm than good. At the very least they might prove to be no better than their predecessors yet a great deal more costly. The rich promises with which new treatments were heralded sometimes proved to be quite unsubstantiated. And then, in the early nineties, came the sort of data that seemed to confirm the dying of the dream; by 2001 people like Achilladelis and Antonakis were advancing alarming figures pointing to the virtual collapse of innovative research in the field.[3]

Whenever society appears to experience a dramatic turnaround for the worse in its fortunes, it is necessary to be objective about it. It may be popular and even profitable at such times to play the role of a Jeremiah, but it is not necessarily very helpful. In an area as vital as that of medical therapy, the commentator needs to be very sure of his facts, he must strive for a balanced assessment and he must attempt to develop realistic proposals for reform. Above all he must avoid hasty generalizations; pharmaceutical companies are not all bad or all good, nor are their innovative capabilities, which tend unpredictably to go up and down. In the course of only a few years firms once as renowned as Smith, Kline & French, Searle, Wyeth, Allen & Hanburys, Schering-Plough, Beecham, Pharmacia, Organon, Brocades, Wellcome, Upjohn and Warner Lambert have disappeared into the larger empires built by Pfizer, Merck or Glaxo; some of the companies that succumbed had suffered a period of relatively poor performance; some had certainly fallen into error, be it ethical or scientific. Nor, however, had the empires that acquired them always lived with a clear conscience; the Vioxx^{R} drama involving the suppression by the prestigious Merck Inc. itself of adverse effects detected in clinical studies vividly illustrates that fact. On the evidence to date it would hardly seem that massive mergers provide any guarantee that drugs will in the future be better or safer. If there are to be real advances they may well come from a greater

[3] B. Achilladelis and N. Antinakis, The dynamics of technical innovation; the case of the pharmaceutical industry, *Res Policy* **30** (2001), 535–538.

input from academic research, from small biotechnological units, or from such once unexpected sources of current innovation as China or Iran. One simply does not know.

In the recent past, a remarkable number of books on the pharmaceutical scene have appeared, many of them critical of industrial research, drug promotion or prescribing practice, but their quality too is very uneven and most are unhelpful. Those that take as their starting point an objection in principle to the capitalist approach tend to be disappointingly one-sided in their analyses. Fortunately there are a number of sound studies. Marcia Angell's *The Truth About the Drug Companies*, which is forceful but also calmly constructive, is one such volume.

Robert Whitaker's *Anatomy of an Epidemic* is a puzzling book that deserves careful but critical reading. To quote directly from the publisher's blurb:

> "In this astonishing and startling book...Robert Whitaker investigates a medical mystery. Why has the number of disabled mentally ill in the United States tripled over the last two decades?...What is going on? *Anatomy of an Epidemic* challenge readers to think through that question themselves...Do psychiatric medications fix "chemical imbalances" in the brain or do they, in fact, create them?"

Although Whitaker challenges his readers to think through these matters for themselves, he is prepared to convince them with ready-made and convincingly formulated answers; psychiatric drugs, according to his analysis of the literature, have done very little good but much harm. Recovery rates in schizophrenia are higher in non-medicated than in medicated individuals. An antidepressant may increase the risk that a depression ultimately disables the patient. The long-term outcomes in children with Attention Deficit Hyperactivity Disorder are not improved by stimulant treatment, and the latter puts both the patient and his surroundings at risk.

As was to be expected, Whitaker's analysis has been subjected to a barrage of criticism, especially in the United States, which has generally led the way in the medicalisation of mental disorders, and where the psychiatric profession has long been in an uncomfortably close alliance with the drug makers. He has been accused of propagating half truths and interpreting literature in a manner that serves his purpose. It has been pointed out that antidepressant drugs indeed help many a patient through the worst phase of a depression and that the tranquillizers are similarly of value in acute anxiety. Some impossible little children, whose behaviour has rendered the lives of their parents and teachers a misery, have for some reason become rather more attentive and less excitable in the short term on methylphenidate therapy. It is also a fact that some newly emergent problems can have several valid explanations; the rise of both depression and anxiety, for example, might reflect the stresses of modern society; it is not necessarily attributable to drugs alone. Criticisms such as these seem reasonably well-founded.

Whitaker is however undoubtedly at his best and most credible when he questions the long-term safety of psychiatric drugs, an issue to which the manufacturers have usually devoted scant attention, though encouraging prolonged and even life-long maintenance treatment. The methylphenidate used in ADHD is – pharmacologically though not chemically – a type of amphetamine, prone to lead to dependence and misuse. As to depression, it is entirely correct that its attribution in the 1980's by "biological psychiatrists" to a supposed chemical imbalance in the brain, demanding chemical treatment, has hardly proved credible; Whitaker seems to be right when he adduces evidence that the drugs in question themselves produce a chemical disruption of brain function, that ultimately may impede recovery. He is also entirely correct when he points to the commercial "medicalisation" of some non-pathological states; shyness has become "social anxiety disorder"; merely to feel miserable (perhaps with plenty of justification) is now to be classified as suffering from a depressive state calling for a prescription. And in a host of other situations,

physicians are now persuaded to provide tablets when all that is called for may be a little more rest, a kindly word and some gentle encouragement.

In summary: Robert Whitaker's book is well worth reading, but it must be read critically and carefully, here and there he is rather too sure of himself.

While the Whitaker book concentrates entirely on the mental health scene, Donald Light's team of authors for *The Risks of Prescription Drugs* take the entire field of medicine for their province. This is in no sense a replacement for *Meyler's Side Effects of Drugs* which for more than half a century has soberly and expertly surveyed the adverse reactions scene and which for a generation has been complemented by the *Side Effects Annuals*. Unhappily, the Meyler volumes have in recent years only been available at a price that makes one wonder whether they are ever sold to institutions other than drug companies and a few well-endowed universities. Donald Light's slim volume, little more than an evening's reading, sensibly confines itself to examples and to broad issues so that the reader is provided with a general but well-documented basis on which to form his own opinions. Those opinions are likely to render him reticent to believe much that is said about medicines and even more reticent to swallow the latter lightly.

Light himself opens the volume in a Chapter that among other things advances the concept of a Risk Proliferation Syndrome – a worrying concept but one convincingly backed by the figures and trends. By 1998 there was strong evidence that prescription drugs had become, as the author puts it, "the fourth leading cause of death, behind stroke but beyond pulmonary disease and accidents". The known facts are alarming enough, yet a great more incriminating evidence is obviously hidden; the U.S. authorities themselves admit that only some 1% of adverse events are reported to the authorities.

One might as a reviewer comment that the U.S. system suffers from the fact that adverse reaction reports from physicians to the authorities are largely routed through the manufacturers, providing the latter with an opportunity to filter them; during the hearing of one case that was brought by injured patients in the 1990's the extent to which the manufacturer in question had suppressed inconvenient reports in this way was all too evident. Yet even in European and other environments where reports of suspected adverse reactions are routed directly to government agencies, under-reporting by physicians presents an unmet challenge; as with the proverbial iceberg, the greater part of the problem remains hidden below the surface.

A following chapter cogently defends the thesis that the authority and practice of the U.S. Food and Drug Administration are insufficient to provide adequate protection for the American public from avoidable pharmaceutical risk. The same might well be argued with respect to the situation elsewhere, where the process of drug regulation is all too often one involving a cosy get-together of regulators and companies, working largely on the basis of data provided by the latter and generally to the exclusion of the patient and consumer lobby. The concept of "Cosiness" also comes to mind in a chapter in which Howard Brody examines the overall relationship between prescribers and drug manufacturers, which today is in some respects one of mutual dependence. Reading it, one is inevitably reminded of the paradoxical fact that while the doctor is constantly reminded of the real or supposed virtues of drugs he is hardly reminded from year to year of the virtues and safety of other approaches to treatment, such as physiotherapy, psychotherapy, nutritional measures or social adjustment.

One area in which the persuasive effect of drug promotion wreaked immense harm was that of menopausal and post-menopausal treatment, here examined in detail by Cheryl Stults and Peter Conrad. The recklessly fictional view of the menopausal woman as a "physiological castrate" was developed by the Wilsons in America in the early sixties; tragically, it led within twenty years to an epidemic of endometrial cancer among women treated with oestrogens, many of whom had no need of them. Even in the present young century the harm is still being done, as these authors graphically illustrate.

Donald Light closes the volume himself with a cautious view of the future and some proposals as to what may realistically be done to put society and its prescribers back on track where the safe use of medicines is concerned. As he points out: "employers, taxpayers and patients are now beginning to realize that the rising costs of prescription drugs stem from higher-priced newer drugs that offer few proven advantages over older, cheaper agents, even as they put patients at greater risk of adverse reactions..." He pleads among other things for a stronger FDA, for measures to reduce the pressure on the doctor to prescribe, for reporting of adverse reactions by patients themselves (already practised in a number of countries) and for a new social contract with companies to ensure that a drug may be marketed only if its superiority over other agents has been demonstrated. Any or all of these measures may prove feasible and effective. In view however of society's obsession with money it could well be that in the long run financial measures will prove most effective in putting matters to rights.

This is a sensible, readable and constructive book that could in various respects open the reader's eyes, and then lead him, with his eyes wide open, along the road to a healthier world.

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