In which wretched part of the world? A glimpse into western drug- and device-makers (and others) behaving badly

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Abstract

A bioethics colleague wrote of the efforts of those in India "who struggle each and every day in this wretched part of the world" to eliminate corruption from the clinical and research practice of medicine, and from medical education.

Wretchedness is the human condition. Corruption is endemic—and is a pandemic. Both have anchors as firm in the West as anywhere else in the world. The record of wretchedness—whether personal, corporate, institutional, or a combination thereof—is not measured in events, weeks, or months, but in patterns of practice often across decades.

The conditions have no single home, residence, or country of origin. They exist when and where one abets acts or omissions that take advantage of power, or access to it, and adulterate or debase a system—particularly one of governance.

The answer is to identify and share information on the problems and problem-makers, and so cooperate in efforts to increase transparency at all levels of medical research, care, and education. A reasoned first step in this regard would be the institution of a central website at which, inter alia, *questioned research might be identified by journal, article, subject matter, publication date, and authors—and, where appropriate, company; specifics as to questioned data elements and history regarding communication to and with the authors as to the questioned data elements might be set forth; and some resolution of a matter might be posted.*

> *This is the key of modern science and it was the beginning of the true understanding of Nature—this idea to look at the thing, to record the details, and to hope that in the information thus obtained might lie a clue to one or another theoretical interpretation.*
>
> Richard Feynman
> (Nobel Prize Laureate—Physics: 1965) (1)

A bioethics colleague wrote of the efforts of those in India "who struggle each and every day in this wretched part of the world" to weed out corruption from the clinical and research practice of medicine, and from medical education.

TABLE 1: Definitions (2)

Corrupt (adj): perverted into a state of moral weakness or wickedness; tainted by decomposition or rotting; adulterated or debased(2:p 512)

Corruption (n): impairment of integrity, virtue or moral principle; inducement (as of a public official) by means of improper consideration (as bribery) to commit a violation of duty; an agency or influence that corrupts(2:p 512)

Fraud (n): an instance or act of trickery or deceit esp. when involving misrepresentation; an act of deluding; an intentional misrepresentation, concealment or nondisclosure for the purpose of inducing another in reliance upon it to part with something valuable belonging to him.(2:p 904)

Wretched (adj): deeply afflicted, dejected or distressed from want, disease or mental anguish; characterized by or tending to produce misery.(2: p 2640)

Webster's Third New International Dictionary (unabridged), 1981 *(2)*

My colleague's frustration is understandable, and his is not a single voice crying out in the desert for an ethical seachange (3,4). But neither wretchedness nor corruption is defined or constrained geographically.

Wretchedness is the human condition. Corruption is endemic—and a pandemic. Both have anchors as firm in the West as anywhere else in the world. The answer is not to take up a penitent's cave or hermitage. Rather, one must appreciate that the record of wretchedness—whether personal, corporate, institutional, or a combination thereof—is not measured in events, weeks, or months, but in patterns of practice often across decades (5,6).

Consider the following:

- Between January and May 2004, the **Warner-Lambert** subsidiary of United States (US) pharma **Pfizer**—which reported first quarter 2013 net income of $2.75 billion (7,8)—promised to cease illegal promotion of off-label uses of its epilepsy drug Neurontin (9,10). In September 2009, parent **Pfizer** was caught engaged in the practice with Bextra (valdecoxib), the non-steroidal anti-inflammatory drug the company withdrew from the market in 2005 (11–14).

- Reports emerged in late 2010 that the United Kingdom's **GlaxoSmithKline** (GSK) (15,16) had marketed tainted pharmaceutical products (17,18). Fifty-three weeks later, the company again made headlines for, *inter alia*, illegal marketing practices of the diabetes drug Avandia—including, according to *The New York Times* reports, that "the company had paid doctors and manipulated medical research to promote the drug"(19–21). Notably, this was the same drug the safety of which University of North Carolina professor of medicine, Dr John Buse, questioned in 1999. (According to a US Senate inquiry, GSK executives then hinted at legal action against Buse in complaints made to his supervisor (22, 23)).
- US medical research and academic powerhouse **Duke University** (North Carolina, USA) was stung in July 2010 by reports that its "high-profile cancer researcher," Anil Potti, "claimed in multiple grant applications that he had been a Rhodes scholar, when, in fact, the Rhodes Trust state[d] flatly that he was not" (24). Then the news got worse (25):

  —Of some 40 papers "that had original data that were generated at Duke" and published by Potti with 162 co-authors in journals such as *The New England Journal of Medicine, Nature Medicine, The Lancet Oncology* and *The Journal of Clinical Oncology*, about two-thirds were to be retracted in whole or part (26).

  —Potti et al failed to obtain the appropriate authorisation—an investigational drug exception—from the US Food and Drug Administration (FDA) for use of so-called Lung Metagene Study (LMS) predictors that were not standard of care and were used alongside invasive biopsy procedures in the clinical trials undertaken by him and his colleagues (26).

  —When several participants in the clinical trials under the Potti rubric sued Duke University, Potti, and others, *The Cancer Letter* reported that the university "appointed Nancy Andrews, dean of the School of Medicine, and Victor Dzau, chancellor for health affairs and CEO of the Duke University Health System, to oversee the internal review. Court documents point[ed] out that Andrews [was] married to Bernard Mathey-Prevot, 'a Duke researcher whose career [was] closely tied with [Potti mentor and co-researcher Joseph] Nevins and Potti'" (27).

  —An inquiry by the Institute of Medicine (IoM) focused also on conflicts of interest that appeared to permeate the Potti research: "According to IoM member Thomas Fleming, professor of statistics and biostatistics at the University of Washington, the informed consent forms for the Lung Metagene Study—CALGB30506—did not acknowledge that study chair David Harpole,… vice chief of the division of surgical services at the Duke University Health System, had applied for a patent on the LMS predictor for lung cancer occurrence only four months earlier" (26).

  —In July 2010, Duke suspended Potti and terminated the cancer research in which he had been involved (28,29). Potti resigned in November 2010 (30).

There was no indication of action by the university against Harpole and no reference on his university website as to an ownership interest in the LMS predictor, though the site indicates a "research interest" (31). Notwithstanding the damage left in his wake, Potti resurfaced at the Cancer Center of North Dakota/Grand Forks (USA) in May 2012. Reports of his arrival and practice were published in late summer 2012, along with a claim by his new supervisor, Dr William Noyes, that "[Potti] walked on water. I've never heard so many compliments."(32).

- In May 2009 a jury found Swiss giant **Novartis** (15, 33) liable for sex discrimination in the workplace (34). Four months later, Novartis and its US subsidiary Novartis Pharmaceuticals were compelled to settle multiple charges by the US government regarding off-label marketing of Trileptal (for neuropathic pain and bipolar disease), Diovan (for hypertension), Sandostatin (for growth hormone disorder), Exforge (for hypertension), Tekturna (for blood pressure) and Zelnorm (for irritable bowel syndrome, constipation). The company later withdrew Zelnorm from the US market (35). In April 2013, US prosecutors twice sued Novartis for alleged kickback schemes (15,36,37).The journal *BLOOD* published in its May 2013 issue an editorial decrying the company's increase in charges for Gleevec (imatinib mesylate) (38) its drug for treatment of chronic myeloid leukemia (CML), from nearly $30,000 per year in 2001 to $92,000 per year in 2012 (39,40).
- **AstraZeneca** (the United Kingdom) for a decade paid doctors to test, often on the vulnerable, its anti-psychotic Seroquel—with annual sales of $5.3 billion (41,42). There were marketing and non-disclosure issues (43—45) as well as a horrific suicide during a university-associated clinical research trial of the drug (46). There were additional problems with, *inter alia*, AstraZeneca's anti-reflux drug Nexium, an acid-suppressive medication the use of which "was associated with 30% increased odds of hospital-acquired pneumonia, and this result was significant for proton-pump inhibitor use" (47, 48).

One comes to wonder: What is it about these institutions—and the people driving their actions—that engenders these events?

A look back into the history of the US pharmaceutical firm **Merck & Co, Inc** (49, 50),might offer insight.

Present-day Merck began as a German firm in 1668, which crossed the Atlantic to open a US subsidiary in 1891. During World War I, the US assets of the firm were seized by the United States government, ending the corporate relationship with the German parent. The US Merck merged with Sharp & Dohme (Philadelphia, Pennsylvania, USA) in 1953. After the 1971 merger of Schering AG (Germany) with Plough, Inc (Memphis, Tennessee, USA), Merck and Schering-Plough began in 2000 to undertake joint ventures. This was followed first by the merger of Schering-Plough with Netherlands-based Organon in 2007 and, finally, by the merger of Schering-Plough into Merck & Co, Inc, in 2009 (49).

TABLE II: Board members, Merck & Co, Inc (49)			
Name	**Position**	**Legacy/Year became Merck Director**	**Background**
Kenneth C Frazier	Chair of the Board, President, CEO— Merck & Co., Inc.	(None)—1/1/2011	Attorney
Leslie A Brun	Chair, CEO, Sarr Group LLC	Merck—7/22/2008	Investments
Thomas R Cech, PhD	Investigator—HHMI, Faculty—University of Colorado	Merck—5/27/2009	Chemistry, Nobel Prize (1989)
Thomas H Glocer	CEO (Retired)— Thomson Reuters	Merck—11/27/2007	Publishing
William B Harrison, Jr	Chair of the Board (Retired)—JP Morgan Chase & Co.	Merck—12/21/1999	Finance
C Robert Kidder	Chair, CEO (former)—3Stone Advisors LLC	S-P—12/5/2005	Investments
Rochelle B Lazarus	Chair—Ogilvy & Mather Worldwide	Merck—10/26/2004	Marketing
Carlos E.Represas	Chair (Retired) — Nestlé/Group Mexico	Merck—2/24/2009	Food Sales
Patricia F Russo	CEO (former)— Alcatel-Lucent	S-P—9/1/1995	Community Equipment manufacturing
Craig B Thompson, M.D.	President, CEO— Memorial Sloan-Kettering Cancer Center	S-P—1/2/2008	Medicine/ Research
Wendell P Weeks	President, Chair, CEO—Corning Incorporated	Merck—2/24/2004	Advanced Materials
Peter C Wendell	Managing Director— Sierra Ventures	Merck—9/23/2003	Venture Capital/MBA

The board of directors of the present-day Merck & Co is composed of members who are identified by the company website (49) as:

- Merck "legacy" members,
- Schering-Plough (S-P) "legacy" members, and
- Members appointed since the November 3, 2009, merger.

They are identified in Table II(49).

A look back at Merck, its history and the composition of its board provides a view into the performance of **Merck & Co, Inc** (and its subsidiary Merck Sharpe & Dohme Corp, also known as MSD) (49) which, over the past two decades, may well be one of the two most disappointing examples of US-based pharmaceutical corporate performance in modern times—the other being Johnson & Johnson, discussed below (51,52).

After a decade of deception involving Vioxx—which Merck had to withdraw from the market in 2004 "because evidence showed that it posed a substantial heart risk"—Merck, as MSD, "agreed to pay $950 million and … pleaded guilty to a criminal charge over the marketing and sales" of the drug in 2011 and in 2012 (53,54).

The company's settlement of government charges came after it paid $4.85 billion in 2007 to settle thousands of civil lawsuits (55). In between those events, what also came to light were reports that Merck paid scientists to write articles in support of Vioxx (56) and paid a publishing company to:

> *… produce several volumes of a publication that had the look of a peer-reviewed medical journal, but contained only reprinted or summarized articles—most of which presented data favorable to Merck products—that appeared to act solely as marketing tools with no disclosure of company sponsorship* (57).

That information was but part of revelations in reporting by *The Australian* of trial testimony on claims by more than a thousand Australians against the company for injuries resulting from their use of Vioxx:

> *The Federal Court [in Australia] has heard that Merck & Co "prepared and gathered" doctors and academics to write the company's own research on Vioxx, which was then published in prestigious medical journals as independent studies.*
>
> *The drug company also allegedly produced an entire journal—called The Australasian Journal of Bone and Joint Medicine—and passed it off as an independent peer review publication* (56).

In addition Merck had environmental issues that—while not criminal matters—nonetheless require the company's ongoing compliance with specified programmes of "Corrective Measures Implementation."[1]

As revealed at Merck's website (49), of the 12 members of the Merck board:

- Only two—Cech and Thompson—have a biology/chemical sciences/medical background;

- Four—Brun, Harrison, Kidder and Wendell—come from the finance and investment industries;
- Two—Russo and Weeks—have backgrounds in equipment and materials manufacturing, respectively;
- One each—Glocer, Lazarus, Represas and Frazier—comes from the fields of publishing, advertising/marketing, food sales and law, respectively.

One must find it disquieting that:

- Only two of the 12 Merck board members—16.67% of its membership—possess the foundational expertise to focus on the company's core medical/biological research functions.
- The primary focus—four of 12, or 33.3%—of its membership is in finance/investment.
- Merck's webpage suggests that three of its present board members have service dates that appear to include the periods of the Vioxx matter or publication of the fake medical journals (through 2004) (49).

There also is the fact that the third-largest pharmaceutical company in the world (by 2011 prescription pharmaceutical sales), second-largest in the US (58), is, or has to be governed by an attorney with a political science background rather than a science professional with a pharmacology, biology, chemistry, or medical background. That condition could be viewed as pointing to Merck's need for damage control for a history of questionable activity—and a lack of a corporate health-science vision.

(This more recent Merck history might be contrasted with that told in "A forgotten pioneer of vaccines"(59).)

Then there is Johnson & Johnson (J&J).

J&J once was the consumer-confidence and industry-good-governance touchstone for its subsidiary McNeil Consumer Healthcare's handling[2] of the 1982 Tylenol poisonings (60). Depending on one's yardstick, J&J is the world's largest pharmaceutical company when sales of all products are included (61), or the eighth-largest company in the world or third-largest in the US, by 2011 prescription pharmaceutical sales (58). Yet J&J was the subject of a *Bloomberg/Businessweek* cover story, "Johnson & Johnson's Recall Rap Sheet," (62) that reviewed the "50-plus recalls in 15 months" which had the company "fighting to clear its once-trusted name" (52,63–67).

Among other "events" uncovered, US government inquiries concluded that "Johnson & Johnson hired subcontractor WIS to buy up products from store shelves without notifying consumers of the potential problems" in a "phantom recall" effort (68).

Yet *The Wall Street Journal* estimated that, notwithstanding a dismal record of corporate leadership as the CEO of J&J from 2002 through April 2012—a record that accorded him among the five "Worst CEOs of 2011" (69)—William Weldon walked out the door as CEO (though he remained as company Chair until the end of 2012) (70,71) taking with him, once he actually retired from J&J, "pension benefits and deferred compensation currently valued at $143.5 million" (72).

Thus, in recent years, Pfizer and its component parts paid out at least $2.81 billion in fines and penalties; Glaxo $3.75 billion in fines, penalties and settlements; and Merck $5.8 billion in fines, penalties and settlements. As for J&J, there is no indication as yet of the costs for faulty artificial hips, recalls of over-the-counter products, its other missteps (51, 63–66, 73–75) or any downsides of its $21.3 billion acquisition in 2011 of Swiss-American bone implants and surgical tools manufacturer Synthes (76). What is known is that J&J settled for $158 million a Texas lawsuit (67,77) and for $181 million the claims of the District of Columbia and 36 states (78), all regarding J&J's marketing of the antipsychotic Risperdal, and the company was hit with a $1.2 billion fine in Arkansas for minimising or concealing the risks associated with the drug (67). Then there are the matters of the $482 million patent-infringement judgment (plus $111.4 million in interest) entered against J&J at trial in Texas (79) and its US settlement of charges of bribery of doctors in Greece (80).

(Duke University, a private institution, need not disclose the costs of, *inter alia*, the Potti et al affair.)

With nearly $15.4 billion in fines, penalties and settlements paid and judgments due in the past three years, one would think that the pharmas have gotten their comeuppance in the US.

If one did, one would be very wrong. By the pharmaceutical industry's own numbers:

- the top fifty 50 drug-/device-makers (2012 rankings scored on the basis of 2011 global sales (58) sold $610 billion in human prescription pharmaceuticals in that year alone (58);
- the top 10 of those companies accounted for more than $360 billion—roughly 60% of the industry's global sales—in the most recent year (see TABLE III) (58);and
- those same top 10 companies collectively paid from 2009 to mid-2012 about $20 billion in criminal fines and penalties for violations that stretched across more than a decade. (3-13, 27-35, 39-47, 51-56, 61-66).

Viewed another way, *the top 10 pharmaceutical companies by prescription-pharmaceutical sales[3] paid a penalty of less than 5.6% of one year's sales for their decade of misdeeds.* When "depreciated" in a flat line across a decade, that is an annual cost of less than 0.56% of sales.

There has been no punishment for the individuals involved. Rather, they have been paid handsomely to go into retirement or remain on board—and they have kept silent.

My colleague decried the wretchedness and corruption—and in particular, those conditions in his native India. But those conditions have no single home, no single residence or country of origin, and they may include, but certainly do not require, fake medical journals.

TABLE III
(Top 10 companies by sales of prescription pharmaceuticals (58)

Pfizer	(1st: $57.7 billon) (US)
Novartis	(2nd: $54 billion) (CH)
Merck & Co.(49)	(3rd: $41.3 billion) (US)
Sanofi	(4th: $37 billion) (FR)
Roche	(5th: $34.9 billion) (CH)
GlaxoSmithKline (GSK)	(6th: $34.4 billion) (UK)
AstraZeneca	(7th: $33.6 billion) (UK)
Johnson & Johnson (J&J)	(8th: $24.4 billion) (US)
Abbott	(9th: $22.4 billion) (US)
Eli Lilly	(10th: $21.9 billion) (US)

These conditions exist wherever and whenever one uses the vulnerable as if they were research "cordwood"; or offers or accepts payments to sign-off as an author on articles the signatory had no hand in researching and writing; or markets products for uses for which they are not approved; or hides adverse research results and post-marketing experiential findings. These conditions exist wherever one abets acts or omissions that take advantage of power, or access to it, in order to adulterate or debase a system—particularly one of governance and of patient and research-subject protection.

My colleague's frustration is understandable. The answer to that frustration is to identify and share information on the problems and problem-makers, and so cooperate in efforts to increase transparency at all levels of medical research, care and education (81–84).

There is the argument that:

> *[s]tronger remedies are needed, perhaps including higher civil penalties for each fraudulent transaction and criminal prosecutions of the company officials responsible. The government might also consider the exclusion of specific drugs or of the offending company from participation in Medicare and Medicaid after a criminal settlement (15).* (Emphasis supplied.)

A reasoned first step in would be the institution of a central website at which, *inter alia*:

- questioned research might be identified by journal, article, subject matter, publication date, and authors—and, where appropriate, company;
- specifics as to questioned data elements might be set forth;
- a history regarding communication to and with the authors as to the questioned data elements might be set forth; and
- a resolution of the matter might be posted.

As Richard Feynman observed "… record the details." (1) (Emphasis supplied)

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Endnotes

[1]Merck was involved in corrective actions required because of contaminants—including benzene, chlorobenzene, chloroform, methylene chloride, naphthalene, trichloroethene, vinyl chloride, and vanadium—in groundwater Stonewall Facility. The facility site is in northwestern Virginia (USA), approximately 2 miles southwest of Elkton and within the Shenandoah Valley, just south east of the South Fork of the Shenandoah River. The facility occupies approximately 1300 acres. The constituents of concern in surface and subsurface soils include several volatile organic compounds (VOCs) and semivolatile organic compounds (SVOCs): *US Environmental Protection Agency (EPA)*. (May 2011). Available from: http://www.epa.gov/reg3wcmd/ca/va/webpages/vad001705110.html.

[2]See also the announcement of the death of James E Burke, the former chair and CEO of J&J, who led the company through the Tylenol-poisoning events: *FirstCall,* "James E Burke, former chairman and CEO of Johnson & Johnson, dies at 87," *The New York Times.* (October 1, 2012). Available from: http://www.nytimes.com/2012/10/02/business/james-e-burke-ex-johnson-johnson-chief-dies-at-87.html?_r=0.

[3] It is important to note that the sales numbers used here are for prescription-pharmaceutical sales. While the prescription-pharmaceutical sales reported by *Pharmaceutical Executive* for J&J are $24.4 billion, for example, the company's total sales reported January 24, 2012, for 2011 totaled $65 billion. http://www.investor.jnj.com/releasedetail.cfm?releaseid=641760.

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Bioethics and corruption: a personal struggle

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Abstract

The author attempts to give a general picture of corruption, especially in the area of healthcare. Corruption ranges from fraud, through deceit, bribery and dehumanisation, to immeasurable moral decay.

As a bioethicist who has challenged corruption in various ways, the author approaches this worldwide plague mainly on the basis of his personal experience. He does not offer a recipe for successfully combating corruption, but tries to provide some ways and means to fight immorality without self-defeat. Bioethics is not a discipline whose task is to investigate, expose, or punish corrupt people. A number of agencies exist for this "noble" job. Nevertheless, an ethics teacher should not be completely indifferent to obvious and harmful immoral behaviour, regardless of his/her personal compulsions. It is not the "patient rights" that threaten the prestige of the medical profession; it is rather the bad apples that infiltrate the moral mission of this esteemed work.

It seems that the hardest challenges in the struggle against corruption are bad laws—laws that provide loopholes and immunity to immoral dealings. In a stable, strong democracy, morally unfounded laws can, and will be changed. Where real democracy exists, they would not even have come into effect.

Facing corruption: a personal account

"Where are all the bioethicists when you need them?" asks the title of an interesting article by Subrata Chattopadhyay and his colleagues (1). They refer to the fight against corruption in healthcare. Well, here I am, one of the few. I finished the study of law and then worked at a medical university where quite accidentally, I became a teacher of Marxist ethics, then medical ethics, and finally bioethics. At that time, in the 1980s, no one in Hungary knew what bioethics was. I consider bioethics simply as a discipline of ethics in healthcare and medicine. Robert Baker, a prominent bioethicist from New York, answers the question: "What is bioethics? in this way:

> *I take bioethics to be a multidisciplinary field whose members include administrators, clinicians and health professionals of all sorts, historians, lawyers, literary scholars, nurses, philosophers, physicians, policy analysts and policy makers, psychologists, religion scholars, scientists, social scientists, theologians and others united by the common purpose of analyzing, consulting, researching, studying and attempting to address, mediate and offer ethical solutions or resolutions to actual or potential ethical problems arising in biomedicine, biomedical science and healthcare (*2).

Way back in the pioneering times in Hungary, in the early 1980s, medical ethics was the exclusive domain of medical doctors. Their main topics were: Hippocrates, the doctor as the ship's captain, and the so-called "tips" (*parasolvencia*, bribes, under-the-counter payments, etc.) given to doctors secretly for various favours.

Due to the birth of bioethics and its subsequent advances, I too felt the need to deal with issues connected with patient rights; and instead of a one-sided approach, I initiated professional and public debates on genuine ethical questions such as, death and dying, euthanasia, human experimentation, confidentiality, and the like. At the same time, I strongly felt the need to challenge immoral behaviour within the healthcare system. This "atypical heroism" might have come from my own feelings of intolerance towards the prevailing widespread corruption and immorality, and my deep sympathy for the "underdog". A famous Hungarian writer and poet said something like this: "Guilty (is he) who is silent among corrupt and unjust people" (Mihaly Babits, 1883–1941). I just did not want to be a silent