The Illusion of Evidenced-Based Medicine, by Jon Jureidini and Leemon B. McHenry,
Book Report and Comment by David G. Schwartz, M.D.
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Following up on Dr. Peter GØtzsche's scathing report last month on the pharmaceutical industry's criminal activities, this book details how and why the corrupt business of Big Pharma falsifies and manipulates data from research and has control and influence over how research is done, what gets published, and over the FDA's approval process.

First I will include the introductory paragraph of a short paper I wrote (in the archives) entitled "Is Medical Science Scientific or Even Credible?" In it, Dr. Marcia Angell criticizes the corrupt ties between the pharmaceutical industry and physicians, medical schools, and medical journals. Dr. Angell faults the medical profession and medical schools for accepting funding from Big Pharma.

Dr. Marcia Angell, former editor of the New England Journal of Medicine wrote an essay Jan 15, 2009 in the New York Review of Books, entitled, "Drug Companies and Doctors, a Story of Corruption," regarding three books: Side Effects: A Prosecutor, a Whistleblower, and a Bestselling Antidepressant on Trial by Alison Bass, Our Daily Meds: How the Pharmaceutical Companies Transformed Themselves into Slick Marketing Machines and Hooked the Nation on Prescription Drugs, by Melody Petersen, and Shyness: How Normal Behavior Became a Sickness, by Christopher Lane. Refer to the archives in December 2015 for the rest of this article that briefly summarizes many of the points that Jureidini and McHenry later flushed out in detail in this book.

Dr. McHenry recently spoke on the Joe and Terri Graedon's People's Pharmacy radio show. In that, he recommended that patients refuse to take any drug that has been on the marked for less than 20 years, as a safety precaution, because many of these drugs are not proven safe and effective, even though approved by the FDA.

Jon Jureidini is Professor of Psychiatry and Pediatrics at U. of Adelaide, Australia. Dr. Leemon B. McHenry is Emeritus Lecturer in Philosophy at CA State U. Together they exposed scientific misconduct in two infamous trials of antidepressants in pediatric and adolescent depression, Study 329 of paroxetine, and Study CIT-MD-18 of citalopram. Their findings helped result in billions of $'s in payouts by the pharmaceutical industry in settlement of litigation. In fact, much of their findings could be unearthed *only* through litigation. Their study was not limited to these 2 trials. They assert that these were not aberrations, but symptoms of systemic corruption and misconduct throughout the medical research community.

Corruption is widespread and endemic in clinical research, reporting of research and publication, medical education of physicians, academic medical universities, distorted research priorities, and failure of government regulation. They recognize books already published on this topic by Peter Gøtzsche, Marcia Angell, David Healy, and Ben Goldacre.

The authors recognize that "profit-driven corporations have little interest in the discovery of truth or the exposure of scientific misconduct, and that data from clinical trials is manipulated by the manufacturers of pharmaceuticals, and evidence-based medicine is an illusion."

Besides the studies on paroxetine and citalopram, other striking examples are refecoxib (Vioxx), which was removed from the market after 40,000-60,000 fatal cardiovascular events, Fen-Hen, also withdrawn from the market after life threatening valvular heart disease, Prem-pro related to breast

cancer, rosiglitazone (Avandia), withdrawn from the market in Europe after an increase in myocardial infarction, and the Sackler family's promotion of OxyContin as having little risk of addiction, but drove the opiate addiction epidemic in North America with $635 million in fines paid, yet none of the Sackler family in prison, and the epidemic still rages on. All as a result of the fierce industry competition that results in a race to the ethical bottom. Bayer's Cutter Laboratories made a deliberate decision to sell HIV contaminated Factor VIII and IX antihemophilic factors to 3rd World countries in the 1980's, and Gűnenthal continued to market thalidomide to pregnant women, keeping secret the reports of severely malformed infants.

The authors contend that the marriage of medical science and the profit motive of the free market cannot provide the relevant research for the benefits to humanity. The free market is supposed to be self-correcting, but the harm to public health has shown that the marketplace is too slow or inept when it comes to medicine.

The authors go into great detail about the 2 studies in which they unearthed a lot of scientific misconduct and corruption. I won't go into the weeds in the plethora of data, but the evidence is there if you want to read about it in the book. They conclude that there is nothing exceptional about those 2 studies. "The unreliability of a vast majority of clinical trial reports creates a crisis of credibility, whereby clinicians might regress to the pre-evidenced-based medicine paradigm, making decisions based on unsystematic clinical experience and pathologic rational. In this respect the evidence-based hierarchy is reversed: The least trusted evidence is the randomized clinical trial and the most trusted evidence is the clinician's own prescribing experience."

They make a brief synopsis of what real scientific endeavor would look like. They cite philosopher Karl Popper's work from 1945, <u>The Open Society and It's Enemies</u>, and hold up his philosophy of science as a framework for preserving scientific integrity in medicine. This demands a structure that values open, critical debate, and that it has to be supported by a political structure. An open society tolerates a diversity of views and uncertainties about fundamental questions. It values the freedom to propose ideas and to have them rigorously criticized. Scientific solutions can never be more than provisional and are always subject to improvement. Popper thinks that science is the most respectable form of human inquiry when it is done right, because it is self-correcting. We must be fully prepared to correct mistakes Rather than to wait for errors to reveal themselves, we should consciously and deliberately seek them out.

Ideology advances some cherished idea. Science is not in the business of selling ideas but rather testing ideas and abandoning those that fail testing. Not enthusiasm but criticism is what we honor in a scientist in our determination to get at the truth. A genuine scientist must embrace the prospect of proving a hypothesis wrong, (which Popper calls "falsification"), by an experiment. To protect a hypothesis by modifications after a negative test or by designing an experiment that makes it immune from refutation lowers the status of this approach to pseudoscience. Of course there can be a valid false negative result, but this should be infrequent, and overwhelmed by many positive results in order to dismiss it as invalid. Popper's methodology rejects the idea that science confirms a hypothesis or proves it right. Rather he argues that satisfactory explanations have to be testable and falsifiable. Rigor is achieved in science by proposing hypotheses and then actively seeking out critical testing that can potentially refute the ideas. On the other hand, pseudoscience fails to put itself at serious risk of being proved false. Every scientific statement must remain *tentative forever.* A theory is "corroborated" if it has withstood genuine attempts at falsification, but it is never more than a working hypothesis, never demonstrated true, but practically usable until or unless it is disproven.

In the scientific basis of medicine, we do not have anything close to Popper's concept of scientific rigor. The role that corporate interest plays in government and in the control of academic medicine stifles real freedom in the marketplace of ideas. With ideologues, marketing executives, and key opinion leaders compromised by industry consulting, practitioners of "science" seldom abandon hypotheses and theories when confronted with scientific evidence.

Popper says that science does not proceed in a vacuum, but it is a social enterprise that requires checks on the system, to ensure that others would come to the same conclusion if testing the same hypothesis.

The pharmaceutical industry enacts scientific pursuit in a vacuum, in secrecy, with group-think and a commitment to positive outcomes. Instead of inviting criticism, it suppresses it. Potential critics are "neutralized" by public relations campaigns conducted by marketing departments.

So "industry science" is an oxymoron because commercial interests override Popper's requirement of disinterest in the outcomes of testing.

So the pharmaceutical industry creates the appearance of science with clinical trials, medical journal articles, scientific posters, speakers at conferences, etc. Studies appearing in medical journals overwhelmingly report positive results. So patients will be harmed, lawsuits will reveal the corruption, and the industry will suffer harm to its reputation. But in spite of public apologies and financial settlements, very little ever changes because the financial incentives to corrupt science is just too strong.

A comical effect of circular logic pops up in trials showing that drug A beats drug B, drug B beats drug C, and drug C beats drug A, in head-to-head comparisons.

The following is a list of methods used by the industry to get the results they want in research:

Conduct a trial of a study drug against a treatment already known to be inferior.
Do a trial with the study drug against too low a dose of a competitor drug.
Test a study drug against too high a dose of a competitor drug, showing lower toxicity of the study drug.
Use multiple end points and select for publication only those that give favorable results.
Do multi-center trials and publish results only from the centers with favorable reports.
Conduct subgroup analysis and publish only the favorable ones.
Present results that are most likely to impress, like relative risk instead of absolute risk.
Conduct trials on subjects who are unrepresentative of the general patient population.
Conduct a trial of study drug against a "fauxcebo" instead of a real placebo.
Add post hoc endpoints not specified in the study protocol in exchange for negative endpoints in the protocol.
Conflate primary and secondary endpoints.
Conceal unblinded patients and include them in efficacy analysis.
Exclude placebo responders in the washout phase of the trial.
Delay publication of negative trial results until positive trial results are published.
Conceal negative trial results, publishing only positive trial results.
Overstate efficacy and safety results in the abstract that are unsupported in the body of the paper.
Fail to distinguish clinical from statistical significance

So Popper says that rigorous science needs to be protected by law, and progress depends on political institutions that safeguard the freedom of thought, and on democracy.

The paradigm of evidence-based medicine, in its uncorrupted state, is at present the best system we would have for assessing whether treatments work, and stands among the great accomplishments of medicine. Popper's philosophy provides a foundation required to protect the integrity of evidence-based medicine. But alas, we see that that integrity is demolished by the financial pressures of the pharmaceutical industry.

So not only the research is corrupted, but also the communication of the research findings, along with compromised academic independence, perverse research priorities, and poor regulation.

The industry targets high-impact prestigious journals for publication, as they are worth millions of dollars in marketing the drugs. Ghostwriting is the key to the deliberate misrepresentation of science, and the number one factor in the crisis of credibility. A company engages a ghostwriter from a medical communications firm to spin the data in favor of the drug, and since the pharmaceutical company owns the data, it controls exactly how the report is written. The title page of the draft has the name of the "ghost" as author, but after revisions, and peer review, the author's name is removed, and for publication, the name of an academic person in a world-class university is put on it to give it credibility. Often the doctor whose name is on the published article doesn't even review it thoroughly, but the honorary author who takes false credit for writing the article gives credibility to the article and makes it more likely to be published. "The job of the ghost, after all, is to remain invisible in order to conceal conflicts of interest with industry and to create the appearance of scientific objectivity." Then in continuing medical education, the article is cited as independent verification of efficacy and safety of the drug. Then the professor, the "honorary author," who is selected by the industry as a potential speaker or key opinion leader, gets publication credit for career enhancement.

Efforts to curtail ghostwriting have failed, even after Congressional investigation. Journals fail to police authorship, due to difficulties in discovering how the manuscript was produced, and of course there is little incentive because of large ad revenue from the industry. The industry prohibits ghostwriting, then with clever semantics, it argues that what goes on is *not* ghostwriting. The physicians who lend their names to these articles are betraying ethical responsibility and are committing academic dishonesty. As an example of harm to patients, the Vioxx scandal came about as a result of ghostwriting, and countless adverse events and fatalities could have been averted, had the clinical trials been honestly reported in the medical journals.

Continuing medical education for physicians is heavily sponsored by the industry, which claims that the funding is "unrestricted" and that care is taken to not promote a particular drug in the educational programs. But the whole presentation is based on bringing more attention to certain diseases, which happen to be treated by their drugs. Speakers are often unaware that they are being used by the industry. In my personal experience, the conferences give very little attention or credibility to non-drug treatments, such lifestyle, nutritional or herbal supplements, homeopathy, etc. That is in itself a bias, a conflict of interest, presented in a very subtle way, though there is no overt references to a particular brand of drug.

Authors of clinical practice guidelines have extensive conflicts of interest with the industry. In one study, 87% had interactions with industry, 58% received financial support, and 38% had been employees of or consultants for industry.

Meta-analyses have been put at the top of the hierarchy of credibility of research, because it includes some unpublished studies, but if many of the studies in the meta-analyses are flawed, how can the outcome be much different?

Universities have long laid claim to being the guardians of truth and the moral conscience of society, but this claim seems empty and they compromise basic academic values when universities engage in collaborations with industry, and take in huge sums of money from the industry. This is especially so when misrepresentations of scientific testing resulting from that collaboration remain uncorrected by university administration responsible for oversight. Not only is there individual conflict of interest, but conflict of interest for the whole university, and faculty cannot be objective and ethical when pressure is for expediency, conformity, and intellectual lethargy from the university, on which they depend for salaries, promotions, space, and tenure. This can lead to demoralization when faculties are led by other than principles of academic excellence. That is profitability in attracting corporate sponsors and outside grant revenue. This makes the university a business. The free market imposes itself where it has no place – education and disinterested scientific research. It eliminates some forms of research that would not be funded by a commercial source, such as pure mathematics, life-saving drugs for rare diseases, etc.

Key opinion leaders are university physicians who happen to like a particular drug, and they are sought after by the industry and are enticed by large sums of money, which is very attractive to those who depend on meager university salaries. They are groomed to speak and promote the industry's product to doctors, who think they are listening to a highly regarded principled academician, and may not be aware of the industry funding. Key opinion leaders, when confronted with accusations of scientific misconduct, blame the excesses of pharmaceutical marketing, and the industry blames the opinion leaders for their greed and entitlement.

Academic critics of the industry, however, face irrelevant rejections and legal threats, and criticism can be dangerous to one's career. Drug companies hire public relations firms to get revenge on critics with smear campaigns and attempts to ruin their academic reputations, stalking them when giving talks and maliciously maligning their scientific work, and with hospitals charging them with unprofessional conduct.

The industry has distorted research priorities, ignoring essential research into treatments for major diseases worldwide, malaria, tuberculosis, etc., and "disease mongering," turning normal behavior into diseases, marketing drugs for shyness, a variety of mood disorders, because they can turn a huge profit from treatments of basically healthy people, marketing them on TV. Screening for depression has not proven valuable, and many times misleading, depending on how the wording is done, and has considerable false positives.

As with other government regulating bodies being influenced by the industries they are charged with regulating ("regulatory capture"), the FDA is also unduly influenced by the drug industry. Former FDA drug reviewer Ronald Kavanagh, who was fired from his position in 2008 for whistleblowing, said that "drug reviewers were clearly told not to question drug companies and that our job was to approve drugs...If we asked questions that could delay or prevent a drug's approval...management would reprimand us, reassign us, hold secret meetings about us...Sometimes we were literally instructed to read a 100-150 page summary and to accept drug company claims without examining the actual data, which on multiple occasions I found directly contradicted the summary document."

The pharmaceutical industry is the largest lobby in Washington D.C. Dr. Marcia Angell, in her book The Truth About Drug Companies, exposes the influence of pharmaceutical lobbying on government and the political networks that maintain the status quo. As a result of Congressional legislation establishing user fees (which in 2020 was 45% of the FDA's total budget), and the FDA Modernization Act, the industry applying for a license is now treated as a client rather than an entity subject to regulation. Peter Gøtzsche notes that the FDA's quick approval process is as absurd as it would be to make demands on air-traffic controllers to land planes more quickly. Also with the revolving door, regulators move back and forth between government and industry. One report on one department showed that 15 of the 26 who left the FDA later worked for or consulted for the biopharmaceutical industry. The FDA is also massively understaffed to rigorously evaluate new drugs and to monitor post-marketing adverse events reports. Direct marketing of drugs to consumers, only allowed in the USA and one other country in the world, misleads consumers about safety and efficacy, and violations of the rules for advertising have no serious consequences.

The research participants are betrayed, as they are often indigent or of low income, and are desperate for the payment they receive, and are likely to overlook the hazards under which they are put. Dr. Peter Gøtzsche notes that a more honest version of the patient consent form should read as: "I agree to participate in this trial, which I understand has no scientific value but will be helpful for the company in marketing their drug. I also understand that if the results do not please the company, they may be manipulated and distorted until they do, and if this also fails, the results may be buried for no one to see outside the company. Finally, I understand and and accept that should there be too many serious harms of the drug, these will either not be published, or they will be called something else in order not to raise concerns in patients or lower sales of the company's drug."

How to fix the problem? The authors present several attempts that have been made to counter this situation, but they all have marginal and temporary effects. Transparency policies require conflict of interest to be reported, but there is no enforcement when non-transparency occurs. Ensuring the accuracy of data: Retractions of papers are rarely announced. Trial registration: The protocols are not available but considered private intellectual properly. The Cochrane Collaboration was supposed to make systematic reviews and increase accuracy of reporting, but many of the reviewers have financial ties to the industry, and if doing a meta-analysis, "garbage in, garbage out," and often unpublished studies are not available. Restrictions on pharmaceutical marketing is a minimally effective intervention, as many ways can be found to circumvent restrictions. Government investigations can lead to consternation about conflicts of interest and corruption, but after the furor, it is back to business as usual. Litigation and punitive damage result in some drugs being withdrawn from the market, long after many patients have already been harmed, but the settlements preserve the confidentiality of the incriminating documents.

So the authors assert that this situation cannot be remedied without a radical restructuring of research, taking it entirely out of the hands of the pharmaceutical industry, having it done by disinterested 3rd parties, funded by government, contained within a national health service, which we do no have in this country. Medical journals would have to refuse industry funding and restrict the role of peer reviewers to determine the interest and newsworthiness of the research and the critical appraisals should be done by paid Health Technology Assessment experts without conflicts of interest, to be retained by and accountable to the journal's editor.

At its basis, the problem is political, the failure to protect the integrity of science from commercial forces. This especially has to be a priority in a capitalist system. Capitalism has to be regulated, and

when it is not, the industry suppresses free critical inquiry and imposes blind loyalty, allowing degeneration into the vices of a closed totalitarian society.

My perspective is that these radical reforms, like many other radical reforms that could make our lives and society better, are not likely to be allowed to take place as long as big money drives politics, and Americans have such a love affair with capitalism, as to avoid looking at its pitfalls and dangers.

Failing these reforms, what can the consumer do? Refuse to take any drug that hasn't been in regular use for at least 20 years. Look at the wisdom and experience of health care practitioners in their choices of treatments, preferred over the data of the clinical trials of new drugs. Keep ourselves healthy so as to need as little medical treatment as possible. Practice healthful lifestyle, make use of nutritional medicine, functional medicine, and of herbal medicine, which has had hundreds of not thousands of years of experience in several cultures simultaneously. Make use of low risk treatments like chiropractic, acupuncture, massage, physical therapy, yoga therapy, etc. Accept conventional medical treatment when it comes to emergencies, necessary surgery, etc.

If a national health service would be provided, like "Medicare for all," (very unlikely to occur in this capitalism-obsessed society), what would be the advantage of providing poor quality care for everyone, based on flawed research? More cost without much benefit. May the buyer beware. Take responsibility for your own health, and choose wisely in the treatments available. It is sad that we are left with this, but for now, we need to be very circumspect and to watch medical treatments with an informed and critical eye.