***'MY LOVE WHOM I LOATHE':***

*TECHNOLOGY and the EVOLUTION of ATTITUDES toward 'ETHICAL PHARMACEUTICALS'*

**NOTE**

While academic rigor lets me lay the following sins of omission and commission at the feet of the global pharmaceutical industry, personal honesty makes me add that without many of their products, from bronchodilators and anaesthetics to ESWL lithotriptors, I should hardly be alive to write this paper. One might say of the large integrated pharmaceutical companies with global reach (collectively termed 'Big Pharma') what Winston Churchill said of democracy: that it is the worst possible system save all the others.

However, this does not permit the sins reported here to be swept beneath the carpet. 'Not Quite As Bad As It Could Be' is rarely good enough. Hence my title, taken from an Alfred Bester novel*.* For me it encapsulates the ambivalence of current attitudes toward Big Pharma.

***INTRODUCTION:***

**AGE OF THE PERFESSER**

T

o alcohol!" toasted Homer in a *Simpson's* episode. "Cause of, and solution to, all life's problems!" (1)

Homer's apostrophe to ethanol (like tobacco a grandfathered organic psychotropic) also applies to our vast modern array of pharmaceutical compounds, both synthesized and naturally occurring. Professionals or laity, manufacturers or salespeople, representatives or regulators: all of us love drugs, yet loathe them. As a society we are so hooked on pharmaceuticals that millions of us meet a working definition of an addict, *viz*. anyone whose principal relationship is with a chemical (2). Even as we mistrust drug makers, we clamor for their formulas so strongly that we continue to enrich them.

Scientifically, most drug action occurs in an epistemic near-vacuum. Modern medicine seldom commands exhaustive knowledge of how individual drugs work *in vivo*; its ignorance becomes boundless as soon as two or more drugs interact. True, such ignorance was greater in the past. Few drugs pre-1900 were 'efficient' (*i.e.* consistently showing desirable outcomes on the laboratory bench) let alone 'effective' (*i.e.* demonstrably ameliorating disease in real-world patients). For mild pain, medicine had acetylsalicylic acid, brewed from the bark of willow trees. For severe pain there was poppy sap (opium) and its chemical derivatives, initially morphine and later heroin (3). Ipecac (from the South American tree *Cephaelis ipecacuanha*) was an emetic; digitalis from the foxglove plant was a cardiostimulant. The medical community commanded little else. Even so constrained a pharmacopaeia often became impotent or even actively harmful through inconsistent formulation, packaging, storage, prescription, and quality control. Yesterday as nowadays, every drug carried a risk.

Throughout the 19th century the standard pharmacological responses to acute and chronic illness used popular nostrums repurposed from traditional botanical remedies, whose effectiveness often exceeded that of standard Western medicines (4). Remedies purportedly from the Seminoles, a Florida

(1) *The Simpsons* Season 8 Episode 18: 'H. Simpson *vs*. the 18th Amendment' [Conclusion]

(2) I have been unable to trace the source of this excellent definition.

(3) So named because it was felt to be 'heroically' less addictive than opium and morphine.

(4) When suffering childhood asthma I could either visit a hospital for an injection of norepinephrine, or else stay at home and burn Jimson weed (*Stramonium*), an Amerind folk remedy that worked every time. Also see Note 21 below

folk society still technically at war with the United States c.1900, were especially valued.

The 19th century was the age of the *Perfesser*, a prototypical commercial traveller in patent medicines who appeared in popular venues from Walt Kelly's comic strip *Pogo* (whose nostrum drummer Seminole Sam is a fast-talking fox [5]) to Al Capp's *Li'l Abner* (whose Hairless Joe and Lonesome Polecat brew Kickapoo Joy Juice by "adding dead mules for body"). The type was widely reflected in contemporary literature and survived into the 20th century through such characters as Ross Lockridge's Jerusalem W. Stiles (6). Contemned as charlatan and mountebank but continually sought for his apocryphal simples purported to cure all ills and make all wallflowers into fertile brides, the Perfesser for over a century crisscrossed North America by Shank's mare, buggy, train, and Model T.

As the 1800s ended, supposedly modern wares crept into the Perfesser's pharmacopaeia. c.1890 the Supreme Electric Belt, powered by sal ammoniac dry-cell batteries, was advertised as a sovereign cure for impotence. A surviving print flyer for the quack device shows a moustached gentleman looking confidently into the distance above the block-capital headline *I AM A MAN ONCE MORE* (7).

Unsurprisingly, this Wild West of unprovable medical claims frequently went beyond client disappointment to client injury and even loss of life. Oliver Wendell Holmes Sr., then Dean of Harvard Medical School, fulminated in a public lecture -

I firmly believe that if the whole MATERIA MEDICA [*i.e.* set of all drugs] could be sunk to the bottom of the sea, it would be all the better for mankind, and all the worse for the fishes (8).

As Holmes implied, the problem of drugs extended beyond the uselessness or outright perniciousness of many medicines to an irrepressible demand for miracle solutions by a clientele at once gullible, ignorant, and desperate.

(5) *e.g.* Seminole Sam advertises a toothbrush with a handguard that "prevents the *hand* from slipping into the *oral cavity* and being *cruelly* *bitten*, or perhaps *am*putated" [*Pogo* *Papers* 47]

(6) In *Raintree County* (New York: Doubleday, 1948). To illustrate the ambivalence of the honorific Perfesser, Lockridge recounts an apocryphal tale about a Southern Democratic senator encountering the great Afro-American plant scientist George Washington Carver at the White House. "I was invited by the President to lunch. Imagine my shock when I saw a [*racist slur*] standing next to him. What could I do? I couldn’t call the [*racist slur*] a [*racist slur*] because he stood next to the President. I couldn't call the [*racist slur*] Sir because he was a [*racist slur*]. So I compromised and called him Perfesser." Lockridge, R. (*attributed*)

(7) Zavitz 66f

(8) Quoted in Avorn 40

***'ETHICAL' PHARMACEUTICALS***

A measured response to this situation emerged from a new political movement in the early 20th century: the United States Progressive Party. As Avorn notes -

Responding to the travesties of a completely unfettered marketplace, the Progressive movement . . . called for the establishment of minimum standards to regulate the quality of foods and drugs that Americans consume. The Pure Food and Drug Act of 1906 marked the first [U.S.] official recognition that the wholesomeness of what people put into their bodies was too important to be left exclusively to the haphazard control of unregulated commerce (9).

Avorn then adduces a principal attitude of this historical period -

[T]here was still no requirement that . . . drugs needed to *work*. That criterion was resisted for decades by manufacturers who successfully lobbied against the idea, depicting it as unbearably onerous government regulation of the free market (10).

Surprisingly, the 1906 Pure Food and Drug Act was not resisted by the entire US drug industry. The less saurian drug manufacturers realized that the general public might prefer to deal with firms acceding to the new act's mild strictures, thereby giving compliant corporations a competitive advantage - *We, unlike our rivals, will not kill you.* Such enlightened self-interest sufficiently weakened overall industry opposition to let the contentious new bill pass. The compliant firms then termed their products 'ethical' pharmaceuticals to differentiate them from the holus-bolus wares of the Perfessers and, presumably, from those of their noncompliant competitors as well. For one of the few times in history, responsible commerce here proved profitable.

Unfortunately, the Age of the Perfesser did not entirely end in 1906. A generation later over a hundred patients, many of them children, died after taking a sulfanilamide product that was supposedly antibacterial. To make its syrup pleasant-tasting S.E. Massengill Company, the manufacturer of the deadly drug, mixed its bitter compound with an organic solvent called diethylene glycol. This substance tastes sweet but is deadly poison; its most prevalent use today is antifreeze, which when drained from engines and left unattended frequently kills pets. During the 1936 coroner's inquest, however, Massengill chemists consistently testified they had no idea of diethylene glycol's mammalian toxicity. The company's CEO never apologized, and was neither fined nor jailed. He said his conscience was clear, as his company had used the best scientific information then available (11).

(9) Avorn 40

(10) Avorn 40f [Italics mine]. I cannot refrain from adding that greed wrapped up in ideology is nothing new

(11) Avorn 44

In response to mass outrage over what the North American media dubbed the 'Massengill Massacre' the Democratic President Franklin D. Roosevelt then strengthened the 1906 US legislation with an addendum termed the Food, Drug and Cosmetic Act. This Act, passed by Congress in the teeth of intense industry opposition, for the first time made it a criminal offence to sell poisonous drugs.

The farthest-reaching provision of FDR's 1938 bill was to create a federal agency to oversee industry compliance with these novel public protections. This was the Food and Drug Administration, the famous (and occasionally infamous) FDA. Despite its later travails, the FDA proved to be the ideal agency at the ideal time. Less than forty months after its creation the United States entered WWII, whereupon the pressure to invent, discover, prove, manufacture, and distribute efficient new pharmaceuticals became extreme. Through the FDA, the U.S. rose to the occasion (12).

***BEYOND QUININE:* WWII PHARMACEUTICALS**

The expansion into Hong Kong and Manchuria of the Greater East Asian Co-Prosperity Sphere cut off the Western Hemisphere's supply of quinine, a botanical extract that till 1941 was the only readily available compound known to combat the malaria plasmodium. In response the Allies were compelled to mass-produce synthetic compounds of equivalent efficacy (13). Attempts had been made as early as 1833 (14) to synthesize quinine. But while the chemical process had been demonstrated on the benchtop, no company had achieved simultaneous quality and quantity production (15). It was not until 1930 that even small amounts of the synthetic antimalarial compound Atabrine were isolated by the Swedish-American scientist Alfred Sherndal (16).

(12) "The United States generally ends by doing the right thing, after first having explored all possible alternatives" [W.S. Churchill (*attributed*)]

(13) Avorn 51, 64; Mahoney 206f

(14) By the corporate precursor of Merck Pharmaceuticals

(15) Malaria was truly global in scope; in 1920, c.3500 tonnes of organic quinine had to be isolated and processed to treat the world's fifty million malaria patients. Even Washington DC, a lowlying riparian region, was listed as a hardship outpost by the British Foreign Service as recently as the 1930s because of its prevalence of malaria.

(16) Mahoney 206

The Second World War accelerated these efforts, as it did other technologies including explosives, aeronautics, electronics, automated fire control, field (emergency) and restorative (plastic) surgery, and new materials. Of all these new technologies, those involving medicine arguably made the greatest advances (17). van der Vat notes that in the Pacific theatre tropical illnesses, including viruses, bacteria, and parasites, caused more US casualties than the total dead and wounded from all combat operations (18).

The response by the US medical-industrial complex to these demands remains astounding:

The problems in the production of Atabrine were the development of a process of manufacturing truly enormous quantities of chemical compounds not previously made in the United States. The 1940 estimated requirement of 240 million tablets, or almost 60,000 pounds of Atabrine, was increased to 450 million [tablets] . . . in 1942, and the requirement was met and exceeded. By the end of that year [1942] . . . the [production] schedule had been increased to 2 500 000 000 tablets . . . [and] 3 500 000 000 tablets were turned out in 1944. The price meanwhile was dropped from the original $66 a thousand to $3 [per thousand tablets] (19).

It is worth noting that these life-saving pharmaceuticals, as well as undergoing 2200% simple cost deflation over 48 months, were throughout WWII licensed by their manufacturer and patent holder (Sterling Winthrop) for generic manufacture free of royalty charges. Given such patriotic forbearance expressed as voluntary profit reduction, it is unsurprising that the North American public, beginning with military personnel and their families, quickly came to see the pharmaceutical industry as a benefactor of messianic stature.

Other medicines followed the antimalarials. After earlier leads both in isolated medical research and in folklore, penicillin (20) was serendipitously rediscovered by Alexander (later *Sir* Alexander) Fleming when he noticed that cultures on his benchtop Petri dishes were decimated by what he correctly concluded were airborne spores of a bacterially antagonistic microőrganism (21).

(17) van der Vat *passim*

(18) van der Vat, Dan: Private (email) communications, 2012 May-June-July

(19) Mahoney 206

(20) Despite its discovery and theoretical elucidation more than a decade before WWII, penicillin did not enter mass production until the second half of the 1940s. This remains an unaccountable and tragic delay. Public figures as important as Arline Feynman, the wife of future Nobel laureate Richard Feynman, wasted and died of tuberculosis as recently as June 1945. Two 5-mL syringes of purified penicillin would have saved her [*cf.* Gleick 200ff]

(21) STS scholars later used this fact to explain the traditional use of bread mold as a topical remedy for cuts and abrasions

Scientists soon applied neoDarwinian theory to elucidate and exploit the billion-year war between prokaryotic (bacterial) and eukaryotic (fungal and mammalian) cells, a struggle continuously waged in econiches ranging from forest topsoil to the human body. Researchers analyzed soil samples from around the world to uncover antibiotics such as streptomycin and tetracycline, and anticarcinomals such as chloromycetin. The antibiotic aureomycin, extolled in such authoritative media as the British publication *The Lancet* (22) began simply as *Sample 67, Columbia, Mo., Plot #23; Timothy Field, no fertilization; silt loam, Sanborn Field, University of Missouri* (23). This unprepossessing agent nonetheless proved sudden death to pathogens as diverse as rickets, Rocky Mountain spotted fever, and syphilis. Introduced in 1948, aureomycin was soon considered " 'God's Gift to Doctors' . . . [and] became the [world's] most frequently prescribed drug" (24).

Thus the decade following WWII transformed not only the pharmaceutical industry but also, through it, the entire scope and paradigm of Western medicine. There were two components to this revolution, both of which are strongly felt today: research and development, and marketing.

**R&D**

Research of unprecedented intensity, duration, and precision by the drug manufacturers became necessary to accommodate FDA requirements, both immediately after 1938 and on subsequent occasions when US federal regulations were extended, tightened, or more strictly interpreted. Research was, however, an expense the pharmas were glad to pay. Patent protection assured any US company with an approved new drug a monopoly market for up to six years, an interval renewable under certain conditions (25). Despite the immense advantages of such patents, the drug companies who hold them have consistently taken pains to advertise that the resultant earnings are not excessive, but are rather necessary to support new R&D. The industry mantra runs: *Today's profits finance tomorrow's cures.*

(22) "The increasing range of efficacy of these agents against infectious processes, the ease with which they can be administered, and the certainty of their beneficial action have completely altered the medical, social, and economic aspects of infectious diseases . . .[*e.g.*] the costs of hospital and other medical care often are avoided." (Dr Perrin Long in *The Lancet*: quoted in Mahoney 13f)

(23) Mahoney 176

(24) Mahoney 177ff

(25) Mahoney 178 [citing de Kruif]: The apparently laudable provisos of US patent law have led to so many abuses by Big Pharma that a measure is currently before the U.S. Congress (2013 August) to curtail them. Big Pharma constantly launches frivolous and vexatious lawsuits against any generic drug company that attempts the legal manufacture of *any* medicine whose patent has expired. As generic product manufacture is suspended pending outcome of proceedings, Big Pharma for under one per cent of an average year's profits extends its *de facto* patent protection for the additional time (3-5 years) the lawsuit takes to creep through the courts. This lets the pharma not only recoup its R&D costs but also give its =>

Two reasons initially underlie the application of pharma earnings to new research. First is the mind-boggling complexity of any synthetic biologically active compounds (conventionally termed 'small molecules') that a typical new drug comprises. The formal name for the commonplace antibiotic aureomycin, for example, is 'D-threo-2-dichloroacetetamido-1-p-nitro-phenyl-1,3 propenadiol.' The tranquilizer meprobomate is '2-methyl-2-n-propyl-1, 3-propenadioldicarbamate '(27).Second: to such static intricacy must be added the vastly greater dynamic complexity of drug action, both on the bench (*efficiency*) and in real-world use among larger populations (*effectiveness*). Despite these complexities, a pharma that plows back any revenue into new R&D achieves a far greater long-term benefit, *viz.* occupation of the moral high ground. Beginning c.1943, the more forward-looking pharmas deliberately fostered a popular image of themselves (and, just as vitally, a self-image that soothed the consciences of its own employees) as miracle workers whose disinterested love of the public good exceeded that of the G.P. or even specialists such as surgeons. In so doing, the media-savvy pharmas laid a solid foundation on which they would subsequently raise the structure of high drug prices. As a public-relations strategy this position was inspired; six decades later, it remains the effective motto of the pharma lobby - *We overcharge because we care*.

Pharmas big and small have come under fire in the last ten years for overplaying their R&D card, justifying high prices because "they pay for the drugs that will save the lives of those yet unborn." Of course this position carries a lightly veiled threat to withhold tomorrow's discoveries, should populist demagogues threaten profit margins in the slightest degree. Such corporate arrogance is overwhelming; unfortunately the facts partially bear it out. Restricting prices does seem to restrict pharmaceutical advances, at least when one's analytical index is quantity of national patents applied for or obtained per unit time. Avorn, otherwise no friend of Big Pharma, grudgingly admits that countries like the USA whose regulatory régimes permit higher prices, and which delay the sale of generic substitutes, show a proportional increase in pharmaceutical innovation. Avorn is a sharp critic of Big Pharma ethics, particularly its continual instances of slippery and self-serving clinical data; but he is industry's reluctant ally in this regard: bitter medicine indeed (28).

=> shareholders a vastly higher return on investment. See *Wall Street Journal* article by Kendall, Brent: *U.S. Court rejects generic delays* [Reprinted in Toronto *Globe and Mail* 2013 June 18 (*Report on Business* p. B10)]. Congress is resisting industry lobbying against curtailing this; see *Big Pharma cutting costs to compete* (*Report on Business* 2013 July 31).

(27) Mahoney 38, 68

(28) Avorn's praise is highly qualified. "We have acknowledged that many of the companies do sponsor important scientific work . . . Yet we've also seen data that suggest the industry's commitment to sales and marketing is much greater . . . [C]ompanies reported employing 86,226 people in marketing, compared to only 51,588 in research and development." The ratio of the given employment figures is 5:3, year not stated (Avorn 305)

**PERFESSER *REDUX:* THE DETAIL MAN**

The pharmas' new offerings, soon after their introduction labeled 'wonder drugs' by the popular media, reinforced the awe in which most North American laity held the medical profession c.1943-63. This proved an ideal time for the North American drug industry to take the long-retired Perfesser down from storage, press his clothes, improve his manners, and send him back out to flog product. Now, however, he (overwhelmingly *he*) was more than a commercial traveller in folk simples. As conceived by a rapidly evolving Big Pharma, this new type of drug salesman was better educated, dressed, spoken, and briefed on all aspects of the medicines he sold. At his fingertips were each drug's origin, bench efficiency, effectiveness *in vivo*, possible contraindications, recommended dosage, and above all price. The Perfesser *redux* would not just push pills, but provide a service. He would be a co-producer of wellness, a learned ally to the prescribing M.D.

Not that the new drug salesman would presume to be the M.D.'s colleague. Pharmas were explicit, even prolix, in training their sales forces to present themselves as eager, pleasant, *junior* associates to doctors. When volunteering information or venturing suggestions, they would do so with a self-effacing blush. Always helpful, never threatening, they would provide details on the welter of newly available medicines. These were the self-styled 'detail men', who in the last seven decades have revolutionized (some would say undermined) the entire practice of medicine in North America (29).

Despite the pains taken by the drug industry to reinvent the Perfesser in this way, acceptance of detail men by the medical community was initially rocky. Incidents were reported of M.D.s greeting detail men with a cordial handshake, chatting amiably as they led them down a hall, gesturing them through a door, and evicting them into an alleyway (30). There was widespread disbelief that someone who was neither clinician, specialist, nor researcher could say anything to the almighty M.D. (31)

Yet the pharmaceutical industry persisted: the financial stakes were too great for it to abandon its sales campaign. Instructional and training literature produced by the drug industry for its detail men

(29) Greene *passim*

(30) McQuillan 1963:61 (cited in Greene 5)

(31) In a 1950s joke a recently deceased man joins a miles-long line for admittance to Heaven. As he at last approaches the pearly gates a big fellow in a lab coat, carrying a black satchel and wearing a stethoscope, shoves past the front of the line and shoulders his way into Heaven. Who's the doctor? asks the man indignantly. Oh! That's not a doctor, St Peter says. That's God. He only *thinks* he's a doctor.

c.1943-55 gave broad classifications of the types of M.D. they might meet. Some were easy sells and some hard; and some were impossible. The worst client type was the affable, apparently egalitarian doctor who would pick a detail man's brains for drug information, promise an imminent order, and never come through (32). The industry stayed the course till its campaign paid off. On the supply side it was well supported: every month brought more drugs onto the market, an inexorable glacier of product that overwhelmed most doctors' abilities to stay abreast of their relevant pharmacopaeia. As time went on, while the average doctor's experience increased, the relevance of his or her education decreased in lockstep. Scientific and technical knowledge, it seemed, had a half life (33).

Further, to the rising tide of detail men -- industry's present aim, generally attained, is *seven visits per doctor per day* from detail men in the United States alone (34) -- the drug industry embraced cutting-edge marketing techniques in areas that began with, but ultimately extended far beyond, face-to-face contact. Product samples were widely dispersed. Ashtrays (at least until statistics linked smoking with cancer, first correlatively and then causatively), coffee mugs, notepads, and other miscellaneous swag accumulated in doctors' offices (35).

Drug firms also began to underwrite many of the re-education courses mandated by most federal, state, and provincial laws so that doctors could stay abreast of emerging clinical technology. As instantiated by the pharmas, these 're-eds' soon began to cluster in destination resorts with good golf courses. At the same time, M.D.s were inundated with sophisticated print material -- a costly investment made necessary, according to a 1950s drug executive, because M.D.s were so well educated and so aesthetically discriminating (36). By such means the large and growing pharmas increased their influence: first on M.D.s who wrote prescriptions, then at the level of regulators and legislators, and finally throughout the North American health system. Yet at least in the USA, detail

(32) Greene *passim*. The response appears in other cultures: *cf.* the unconquerable Japanese *politesse* that defeats all door-to-door salespeople. Nod, smile, sign an order, and rescind it by telephone next morning.

(33) The term *half life* comes from atomic physics and describes the time taken by half a sample of a given element to decompose into one or more lighter elements. Rolodex lists and reputations display a similar decay.

(34) Greider 157f

(35) I was given an ashtray from my allergist c.1960 that he had received from a detail man: white plastic molded into a graceful shape. Its circumference read in elegant letters *NEVRO-TRASENTIN: AD DIEM SINE PERTVRBATIONE DVM SOMNVM PROFVNDVM*. This swag shilled a sleeping pill.

(36) Mahoney 27. Quoted in full below (p.19)

men were only an opening gambit. The game changer, although in the 1960s three decades in the future, was direct-to-consumer advertising (37).

**THE KEFAUVER BILL**

Nineteen sixty-three brought a pause in Big Pharma's march of conquest. In that year, a generation after the FDA emerged, the North American public was forced to reconsider its faith that all new medicines were good. Five years earlier a published encomium to Big Pharma had announced:

In late 1956, SKF [Smith Kline French Laboratories, a corporate forerunner of today's amalgamated GlaxoSmithKline] followed Thorazine's success with Compazine, a chemical relative of Thorazine, which is recommended for "mild to moderate" cases of depression, agitation, and emotional upheavals. Curiously, both Compazine and Thorazine are also tremendously effective against nausea and vomiting. In 1957 a Boston physician [unnamed] reported more than 90 per cent success against "morning sickness" through Compazine (38).

Feeding powerful antischizophrenic tranquilizers to pregnant women was thus viewed as a breakthrough not only in pharmaceutical marketing, but also in public health.

In 1962-64, startling new data undercut this assumption. Compazine, Thorazine, and their molecular colleagues (including a European formulation trade-named Thalidomide) proved to work miracles indeed: only malevolent ones. The greater miracle, *viz*. the exquisitely orchestrated natural processes of human conception and gestation, had been compromised by a set of untried synthetic organics prescribed for nothing more than symptom relief of first-trimester nausea (39). If the typical user of so-called 'ethical pharmaceuticals' was convinced c.1943-63 that the new drugs appearing on the market were indeed wondrous, his or her uncritical appreciation of them stopped abruptly with the unmasking of Thalidomide. Legislation that had already been proposed by US Senator Estes Kefauver to expand the FDA’s powers was headed for Congressional defeat before the Thalidomide crisis. Once the news broke, the legislation passed handily.

(37) Also see below 19f

(38) Mahoney 35

(39) Today's emerging discipline of evolutionary psychology plausibly posits first-trimester nausea [FTN] as an adaptive response to new pregnancy, forcing mothers-to-be to screen closely everything that they ingest. If this be true, then treating FTN as an undesirable symptom and medicating it out of existence, even absent Thalidomidic phoquism, seems like shutting one's eyes to avoid the stress of seeing a predator. In fact the breezy casualness of Big Pharma in pushing pills for the pregnant makes for sobering historical reading, *e.g.* Mahoney 38: "Amusing [*sic*] items in the broadened Wyeth [tranquilizer] line are their multicoloured pills striped like Neapolitan ice cream, which permit an expectant mother to take her medicine blue side up if she wants a boy or pink side up if she hopes for a girl." No commentary seems adequate here.

Unfortunately the Kefauver bill, however well-meaning, continues to instantiate the principle of unintended consequences. The legislation institutionalized M.D.s as sole dispensers of drug prescriptions in the United States, and elsewhere through legislative example. From 1963 through the present day, the doctor has been the First World’s uncontested pharmaceutical adjudicator. While this state of affairs may have been workable in 1963 when the typical M.D. was regarded (and regarded himself) as an untouchably independent scholar-prince (39a), it has since handed Big Pharma a golden bridge through which to access markets, control supply, and maximize sales for a product line not all items of which are benign (39b).

**COSTS**

Drug cost, so critical an issue today, was considered trivial as recently as 1970, when the American Enterprise Institute published an economic analysis reassuring Americans that drug costs were not just stable but sinking. The study claimed that despite a thirty-year flood of new medications, pharmaceutical pricing was deflationary. True, average prescription costs had doubled from under $2 in 1949 to a record high of nearly $4 two decades later (a figure incomprehensibly low by current standards); but even that apparent increase was nullified when a corresponding increase in average dosages over the same timespan was factored in (40). With mid-1961 price averages arbitrarily indexed at 100, prices nine years later averaged out at 92, *i.e.* eight percent lower (41).

Looking back from 2013, however, the Enterprise Institute's 1970 data display the first unwitting indications of the massive price hikes to come. For example: over the period examined [1961-69] relative demand declined for both analgesics (-12.5%) and antihistamines (-29.6%). Demand for sulfa drugs, increasingly eclipsed by the new antibiotics, fell by nearly 60%. But over the same time frame, demand for hormones (mostly birth-control pills) rose by 22%. For tranquilizers the increase was 62.8%; for cardiovascular medications, 87.9%; and for anti-arthritics, 124%. The net statistics show medical technology changing First World health care almost month by month (42). These data induced a second critical change. By the early 1970s, Big Pharma realized that their best hope of growth lay in medications that a patient can be convinced to take for years, perhaps for life. As Firestone puts it:

(39a) Greene’s term

(39b) I am indebted to Richard Jarrell of York University for this datum.

(40) Firestone *passim.* All price figures US$

(41) Firestone 16 (Chart 1)

(42) Firestone 13 (Table 6 *ipse*). Italics mine

"The categories that have shown the greatest relative growth [1949-69] are those *used as* *maintenance drugs, primarily by the elderly*" (43).

The construal of medicine as preventer-maintainer rather than curer was revolutionary. It perfectly suited, and still suits, Big Pharma’s commercial goals. People with arthritis, stress, and circulatory conditions meet Swift's definition of the perfect patient: they neither improve nor die (44). By c.1980 the drug industry correctly foresaw a financial future based more on long-term symptom management than on fast, conclusive therapy.

Not coincidentally, at this point Big Pharma changed its view of those who took its products. No longer were they 'patients': henceforth they were 'consumers.' This shift was a masterstroke of marketing reconceptualization; it was revolutionary rather than evolutionary: it remains as central as a Kuhnian paradigm change within a scientific discipline. A *patient* may be approached only through a physician; a *consumer*, whether of cars or corticosteroids, may be directly accessed and persuaded till he or she arrives in an M.D.'s office with detailed knowledge of one or more pharmaceuticals -- knowledge that has been compiled, spun, and conveyed by Big Pharma with a professional effectiveness that is (depending on your viewpoint) horrendously fascistic or brilliantly monetizing (45). Drug consumers wooed by Big Pharma display a thirst for manufacturer-promoted prescriptions that ranges from ineluctable determination (forcing the M.D. to accede or else lose patients) down to slight but nonnegligible positive inclination (still highly significant in terms of overall sales). Further, patients are grateful for every pronouncement from their medical scholar-princes; consumers may listen to advice but reserve the final decision. Patients are commanded, consumers command; patients are humble, consumers are not. A consumer is a customer, and thus (according to the adage) always right. Most importantly to Big Pharma's marketing experts is that patients may get better, and so cease to be patients. Consumers, however, are for life.

Big Pharma's paradigmatic shift in how it treats those who use its products has spawned corresponding attitudinal changes among medical technoscience's other subgroups. While some M.D.s (*e.g.* specialists, surgeons, Nobel-caliber researchers, Harvard clinicians) occasionally retain the aura of the scholar-prince, the general practitioner and family doctor have seen that lofty state take on a half life of roughly a decade (30).

(43) Firestone 13 (Table 6 commentary). Italics mine

(44) Swift, Jonathan (*attributed c.1740*); see also Bartlett 390a. Swift was speaking of skin ailments

(45) See below 14ff [*Botox*]

Thus the patient *manqué,* now transformed into a 'medical services consumer', enters today’s consulting room armed with data and attitudes expertly conveyed (and as regards content and ‘spin’ virtually predetermined) by Big Pharma. This demotes the line general practitioner from arbiter of life to the means by which consumers obtain their fix. In 2013, the average M.D. is a sales clerk. He or she has been replaced as supreme medical authority by Big Pharma and its bioactive molecules.

Other pressures have acted to diminish the status of the average M.D. In the past, one of the strongest forces resisting socialized medicine in the US was the individual doctor's self-image as untouchably independent, swayed only by scientific truth and responsible no one but the governing medical association (46). That ironclad concept precluded any business model but self-employment. Scholar-princes give orders; they do not take them.

Bit by bit, however, North American M.D.s have been absorbed into the greater *lumpenproletariat* of undifferentiated labour supply. This shift is of tectonic magnitude, though still largely unacknowledged. Many US doctors who still consider themselves 'free of government interference' function *de facto* as wholly-owned employees of health maintenance organizations (HMOs), many of which are privately owned and relentlessly operated for profit. In the USA at least, today's typical M.D. has ceded his scholar-prince's crown to a faceless shareholder.

**MEDICALIZATION**

The drug industry's targeted advertising campaigns have not simply persuaded the patient- turned-consumer to demand drugs; they have conditioned him or her to accede to unlimited further persuasion. The consequence of Big Pharma's reverse takeover by its own marketing arm thus extends well beyond a commensurate loss of transparency, accountability, and public good (47).

(46) God also, perhaps. This self-attitude is paradigmically instantiated by the 23-day Saskatchewan doctors' strike of 1962. Facing imminent provincial legislation that was the first in North America to establish universal state-supported insurance for health care, Saskatchewan doctors with the strong support of both the AMA and CMA withdrew their services. The strike was negotiated to a quick end when the then Saskatchewan premier, T.C. Douglas, demonstrated to the striking doctors that his proposed legislation actually acted to their advantage by eliminating payment default by impoverished patients. Douglas was recently chosen the greatest Canadian in a national poll; one wishes his *geist* would enter the United States' present *zeit*.

(47) For an illustrative example, see discussion of OxyContin below (25f)

One of Big Pharma's most successful marketing innovations is 'medicalization.' In this technique, static or changing conditions previously accepted as an inescapable part of the human condition are relabeled as debilities or diseases for which, fortuitously, Big Pharma sells a molecular solution. Libido, for example, has long been known to diminish almost universally in both genders with age. Big Pharma now represents this diminution not as inevitable or even desirable (48) but as an unnatural condition to be pharmaceutically rectified.

Medicalization is especially intense in psychotropics. A US psychiatrist charged earlier this year:

The business model of the pharmaceutical industry depends on extending the realm of illness -- using creative marketing to expand the pool of customers by convincing the probably well that they are at least mildly sick . . . Falling short of complete happiness or failing to have a worry-free life is too often translated into mental illness (49).

More troubling than such general cases is psychotropic medicalization's saturation of North American educational practice. K-12 educators increasingly demand as normative student behaviour that is physiologically and neurologically more characteristic of girls than of boys – *e.g.* ready obedience to authority, long attention spans, extended periods of silence, less need for continual smooth-muscle exercise, and greater tendency toward group co-operation. Rather than re-examine its systemic pro-feminine bias, however, the educational establishment labels its more energetic boys "troublemakers" and chemically castrates them -- the words are precise -- with brain-neurotransmitter antagonists. In the United States, one high-school boy in eight (!) is so medicated.

One observer writes -

ADHD [Attention deficit / hyperactivity deficit] drugs are a gold mine for the [pharmaceutical] industry. These drugs are marketed heavily to doctors (and, in the United States, directly to families) . . . [N]ew diagnostic guidelines have loosened the [prescribing] criteria so much that some doctors are now writing prescriptions for patients in diapers. We are medicating millions of kids for the malady of childhood (50).

Just as disturbing are new research results indicating that nonwhite children are half as likely as schoolkids from prosperous white families to be medicated for ADHD. These data are, however, being

(48) Demosthenes famously compared the loss of sexual desire to escape from a cruel tyrant (3rd Olynthiac sect. 20)

(49) Frances, Allen: *Saving Normal* [New York: Morrow, 2013]. Quoted in *Globe & Mail* 2013 June 15, p.F2

(50) Wente, Margaret: column, *Globe & Mail*, 2013 June 18, p.A15

clinically interpreted not to show not that ADHD is one more example of middle-class one-upmanship (*my children will outperform yours; I can afford health care that is better than yours)* but that there exists a "comparative [psychotropic] underdiagnosis for minority populations" (51).The latest entry to the long list of minority deprivations, it seems, is the right to be overmedicated.

**BOTOX**

Medicalization, like all successful marketing, first creates a problem and then proffers a solution. Wrinkles are as much a sign of age as waning libido: years of exposure to wind, dust, and solar UV-B radiation systematically deteriorate human skin's elasticity and its ability to retain moisture. Until a decade ago this process, while not particularly welcome, was accepted as inevitable. In 2002, however, the FDA approved a virulent natural poison, botulinum-A, to act as an anti-wrinkle cosmetic via subcutaneous injection.

Botulinum-A is the most toxic substance known: two nanograms per kilogram of human weight, *i.e.* 100 parts per billion for an average 50-kilogram adult, is invariably fatal (52). Botulism, the medical term for this disease, comes etymologically from the Latin work for sausage, a food that often harbours the pathogen *Clostridium botulinum*. Botulinum-A, that bacterium's most potent metabolite, is a neurotoxin (53) that blocks acetylcholine transmission between the synapses of adjacent motor neurons. The result is the interdiction of nerve signals that would otherwise order muscles to tense up. A person with severe botulism first exhibits a smooth, almost shiny face as *C. botulinum* attacks his or her cranial nerves; when respiratory nerves are subsequently neutralized, death soon follows.

Smooth faces! Big Pharma saw an opportunity and now markets Botox (= ***Bo***tulinum ***tox***in), a poison repackaged as a cosmetic drug that smoothes out wrinkles by selectively paralyzing facial muscles. Four million, six hundred thousand Botox treatments (c.10 000 000 subcutaneous injections) were administered in 2007 in the USA alone; estimates for annual worldwide use in 2013 approach 12 million treatments (54).

(51) Morgan, Paul (Pennsylvania State University). Quoted by Reuters International reporter Genevra Pittman. In *Globe & Mail* 2013 June 25, p.L8

(52) Van Nostrand 344

(53) Produced not by the bacterium *per se* but rather by an invading virus called a bacteriophage (Van Nostrand 345)

(54) Montecucco C, Molgó J (2005). "Botulinal neurotoxins: revival of an old killer". *Current Opinion in Pharmacology* **5**

(3): 274–279

In fairness, the medicinal repurposing of poisons has a long history. A century ago Oregon dentists stopped oral bleeding with a drop of full-strength rattlesnake venom, a rapid and powerful hemocoagulant (55). Dilute botulinum toxin has also been occasionally used since 1975 to treat rare medical conditions such as uncontrollable muscle spasms and excessive sweating. Botox, however, addresses not need but vanity (56). The face smoothing from Botox is impermanent; injections must be repeated every 3-4 months. Further, botulinum-A remains a neural poison of appalling virulence. Despite this, and despite Botox's interdiction not simply of wrinkles but also of the face's ability to continuously convey subtle nonverbal information through micromuscular motility, Big Pharma's marketing continues to generate vast demand. Botox injections are now the most frequently administered cosmetic procedure in North America, far surpassing plastic surgery (54).

Botox is a classic instantiation of Big Pharma's ability to attain market share for its products by first obtaining potential consumers' mindshare. In a 2013 interview York University (Schulich School of Business) marketing professor Markus Giesler notes with professional admiration that -

the meanings of new medical drugs . . . and other radical innovations. . . evolve in . . . the course of emotional contestations between the positive brand image promoted by the innovator and doppelganger [counter-] brand images . . . Botox's market success was continually undermined by negative stories in the press. We heard about it being a deadly poison. We heard about rumours of frozen faces, mutilation and even addiction. Nevertheless, through multiple changes in its brand delivery, Botox still managed to become broadly accepted (57).

As a parallel case, Giesler references another positive rebranding: The patent medicine Listerine, originally sold by Lambert Pharmaceutical as an industrial-strength disinfectant for floors, sinks, and public toilets, yet subsequently repositioned as a mouthwash. To achieve this, Giesler says, Lambert -

had to redefine an entire complex of human social interaction rituals (dating, dancing, socializing, talking *etc*.) down to the gesture level to convince people that . . . (Listerine) could really make them more successful in finding a

(55) Atkinson, A.H., personal (oral) communication c.1955. Interestingly, Paracelsus noted <1550 (SOLA DOSIS FACIT VENENVM, 'a substance is poisonous by dose alone') that almost any substance could be toxic in excess (athletes have died from ingesting too much water) or, conversely, that many poisons might prove beneficial at milder concentrations.

(56) *Cf*. belladonna, a floral toxin used in Italy at least since the *quattrocento*, which received its name via its cosmetic use. One of belladonna's effects is to dilate the pupils, simulating the drug taker's interest in whomever he or she might be regarding. Many modern restaurants lower ambient lighting to achieve the same effect. Evidently a key criterion of attractiveness is interest in oneself; beauty is in the eye of the beheld. (*Bella donna =*  'lovely lady')

(57) YORKU Magazine, Summer 2013 - 30f

partner and succeed[ing] in life . . . "In extreme terms, innovators not only create solutions [says Giesler] but they must also *create the problem that will cause their product to then be viewed as indispensable*"(58)

I have elsewhere documented (59) a similar transformation c.1930-1950 by various chemical and pharmaceutical manufacturers (*viz.* Reckitt Benckiser and others) to repurpose Lysol, an industrial disinfectant even more caustic than Listerine, as a vaginal douche. Lysol's makeup has changed over the years, with various formulations encompassing benzalkonium chloride, potassium hydroxide, and alkyl C12-C18 dimethylbenzyl ammonium chloride; some formulations added cresols and chlorophenol. It would seem self-evident that subjecting the human vagina's exquisitely delicate, self-cleansing, self-maintaining microfaunal-microfloral ecology to an agent so vitriolic it kills fish at a concentration of 280 ppb seems breathtakingly irresponsible. Nonetheless, Big Pharma sustained multimillion-dollar douche sales of Lysol for more than thirty years (60).

If medicalization and repurposing are two major consequences of marketing's dominance of Big Pharma, advertising is a third. Drug companies learned early on that M.D.s respond positively to sophisticated promotions. In 1959, for example, a pharma booster wrote -

To introduce Aureomycin, Lederle Laboratories mailed ten [rail]car loads of samples, worth around $2 million, to 142,000 physicians. As these [M.D.s] receive a heavy volume of mail, only something outstandingly attractive is likely to gain attention . . . The mailings of many [drug] companies are masterpieces of color printing. This is necessary, explains . . . [a pharma] vice-president in charge of advertising, because physicians are "highly educated and artistically discriminating" (61)

While such encomia do typify the North American public's admiration of Big Pharma a half-century ago, they stand in need of updating. Not only is the net present value of $2 million c.1959 more than an order of magnitude greater; in the intervening half-century Big Pharma has increased its overall marketing and advertising budget ten thousandfold, so that its 2012 marketing outlay was tens of billions of dollars per month. Notwithstanding such enormous cost escalation, resultant revenues more than repay it. For Big Pharma, drug marketing and advertising are not expenses but consistently lucrative investments (62) (72).

(58) YORKU Magazine, Summer 2013 - 30 (Italics mine)

(59) Atkinson 100ff

(60) De Lee 319

(61) Mahoney 27. Also see Note 37 above

(62) Greiser esp. Chs.IV, VI

**GLOBALIZATION**

Globalization is the tendency of capitalism to look beyond a commercial base that is intranational, or at most intra-First World, toward a worldwide base (63). The West has long sourced raw materials globally. Europe's great exploratory-colonialist expansion, which began in the 15th century, was powered by the demand of its growing population for spices, tobacco, and other exotic products (64). 21st-century globalization has extended this established trend beyond raw materials to labour, first unskilled and then skilled, and most recently to the mass purchase of consumer goods. Communications technology enables this process by uniting the world: telemarketers cold-calling North American suburbanites may work in Rajistan or Mumbai (65). Globalization lets the West's medium-to-large industries outsource jobs to locales whose hourly labour costs are lower by up to two orders of magnitude and whose labour climate tends to exclude unions (66).

One effect of globalization is the transfer of wealth from the First World to developing nations; a second, less evident effect is to broaden the global consumer pool. The newly monied of BRIC (Brazil-Russia-India-China) and other cheap-labour pools often use their pay to buy the very products they help make, and here the drug industry has profited from globalization as much as any other economic sector. Yet while Big Pharma's initial benefits came by overseas transfer of drug production and afterwards R&D, greater profits have come from outsourcing the clinical trials that (after marketing) are its single biggest source of overhead. Developing countries offer two key advantages in clinical trials: a virtually limitless source of subjects who can be found, used, and retained for little money; and a comfortable legal and geographical distance from any regulatory agency based in the First World (67). Such insulating distance is especially useful in disaster. If American, Canadian, or European subjects are injured by a new drug's side effects, their societies can offer swift and rigorous access to competent treatment, prognoses, tests, analyses, and (if necessary) legal redress (68).

(63) My suggested definition

(64) Using 'exotic' in its literal meaning of 'extraterritorial'

(65) Formerly 'Bombay'

(66) Globalization has exported jobs from the First to the Second and Third Worlds, to the overall benefit of the latter (more jobs, more earned revenue) and to some extent the former (lower inflation). However, events such as the May 2013 collapse of a garment sweatshop in Bangladesh continue to put Western capitalists in a moral and ethical spotlight for which they often prove ill-prepared.

(67) See Epstein *in toto*; Le Carré, Afterword (in which Le Carré accuses Big Pharma of greater atrocities even than those he dramatizes)

(68) One group is excepted from the First World's generally high state of individual rights, *i.e.* prisoners. These may be regarded as the anti-citizens of a Third World intrasociety.

The Third World victim of an untested drug, assuming he or she survives, may be bought off with a few dollars' worth of *weregeld* (69). Further, wherever clinical trials are conducted, many data reported by Big Pharma are full of troubling contradictions. Outlier points are routinely ignored as inconvenient anomalies, rather than as useful alarms that qualify or disprove comfortable assumptions; studies that oppose marketing aims are routinely filed away and unreported, even if rigorously performed and analyzed; field data are cherrypicked to support Big Pharma's marketing-based preconceptions (70).

Unfortunately, the effect of globalization on attitudes to Big Pharma by regulators, the medical community, and patients is nugatory: it signifies no more than comfortable ignorance. *Why be concerned?* Say we in the First World. *Are these foreigners known to us? No. What would their lives have been like otherwise? Dismal and dead-end. What were they likely to achieve by participating in this clinical trial? Financial benefits. What have they achieved, even in death? Betterment of humanity*. 'But that was in another country; and besides, the wench is dead' (71).

***FDA*: DECLINE & FALL**

As noted, the US Food and Drug Administration emerged in response to the so-called Massengill Massacre, a slaughter of the innocents that was the direct result of regulatory inattention to industry processes. Hence the FDA was born with a primary mandate to protect the public: its client was the citizen and no one else. That situation *ab origine* has changed. Big Pharma has lobbied so consistently and so effectively that the agency created to control it is virtually its lapdog (72).

According to the FDA, for example, any new drug need demonstrate improvement not over existing medications but only over placebo, a loophole that Big Pharma consistently exploits.

(69) *Weregeld* (lit. 'man-gold'): an Old English term for a monetary fine legally assessed for homicide.

(70) Healey *passim.* A *Globe and Mail* review calls Healey’s despairing view of Big Pharma “a slow boat to hell”

(71) Marlowe, Christopher: *The Jew of Malta* IV.i (Cited Bartlett 212b)

(72) In many regulatory areas Canada ties its regulations (*e.g.* emissions by internal combustion engines of atmospheric pollutants CO and NOx) so closely to the US as to follow in lockstep. But while many FDA regulations apply to Canada (*e.g.* Canada accepts data from US clinical trials as developed internally) one area in which Canada departs from FDA strictures is in direct-to-patient advertisements of prescription drugs. Direct-to-patient (consumer) advertisements of over the counter (non-prescription) medications (*e.g.* Reactine) are permitted in both countries. Some mass-media advertising is also allowed in Canada (*e.g.* Viagra, Cialis) but even then product function cannot be stated explicitly. This has led to some wonderful comedic spoofs in the mass media: *e.g.* the CBC’s "We Took Too Many, My Friend" (riffing on a Cialis ad using the Queen song "We Are the Champions") in which males overdosing on erectile pharmaceuticals attempt to copulate with utility poles, fire hydrants, and pets.

Thus if Company X has a big-selling over-the-counter antihistamine that has outlived its patent protection, and if its means of deferring generic manufacture of this drug have proven ineffective (73), then Company X need merely present to the FDA clinical trial data on some 'new' drug whose metabolic action exactly duplicates that of the old drug. This 'new' drug, once shown to be marginally better than no drug at all, is virtually certain to gain FDA approval. It then goes head-to-head with its generic competitor, which is a reinstantiation of Company X's 'old drug' and previous cash cow. As the 'new' drug is propelled both by the cachet of novelty and by Company X's rich marketing machine, such 'new' formulations have historically achieved a disproportionately high market share (74).

A partial *explanans* for this effect may lie in the federal regulator's specification policy. The FDA's criteria for patent protection define protected drugs via what engineers call exact or 'hard' specification. In the case of medication, 'hard spec' requires the detailed stipulation of molecular formulas and their three-dimensional isomeric configurations. As measured by hard spec, drugs A and B differ only insofar as their difference in chemical makeup. A more logical regulatory specification would be 'soft spec', *i.e.* description of drugs based on their effects. If drugs A and B have the same outcome in the human body, soft spec would view them as identical and most ‘new’ drugs would be correctly seen as not new at all. Big Pharma has successfully lobbied against such a change. The FDC remains bound by hard spec, and considers two drugs performing identically under identical circumstances unique and incommensurable so long as they possess variant chemistry. This lets the FDA distinguish between the non-steroidal antiinflammatory drugs acetylsalicylic acid [Aspirin] and acetaminophen [Tylenol] even though their medical behaviours under nearly all conditions are equivalent. Hard spec lets Big Pharma replace drugs whose patents have expired, and which are thus open to immediate remanufacture at far lower cost by generic drug firms, with patent-protected equivalents. Prices for these 'new' drugs can then be maximized via marketing, using techniques that are themselves sustained via industry lobbying of legislators and regulators (75).

(73) Means of monopoly retention by the drug industry are both legal (patent protection) and illegal (vexatious lawsuits brought at the instant of patent expiry solely to extend patent protection). On 2013 June 17 The US Supreme Court, invoking federal anticompetition laws, enjoined lower courts to scrutinize Big Pharma's use of this technique to boost its profits by delaying lower-cost generic manufacture of patent-expired drugs. See *Wall Street Journal* Tuesday 2013 June 18, reprinted same day in *The Globe and Mail* p.B10. Also see Note 25 above

(74) Avorn 267ff ; alsoXV-XVII *passim*

(75) Epstein provides an exemplary discussion of the profound social effects for some seemingly abstract technoscientific aspects of drug regulation (*See* Bibliography). I have also addressed this issue (essay for YU Prof. D.Durant, STS 2411, 2011 March: available on request).

**BIG & LITTLE PHARMA**

As the global pharmaceutical industry underwent explosive growth post-WWII, it passed through a metamorphosis whose first stage established a few large vertically integrated companies. Merck, Squib, Kline, Glaxo, Smith, Pasteur, and other rapidly growing firms in France, Britain, Germany, and Switzerland adopted a business model first pioneered by Henry Ford between the wars (76). Like the famous vehicle manufacturer, the 'ethical' drug manufacturers sourced raw materials via wholly owned subsidiaries. Out-Fording Ford, however, they also financed expeditions to search remote locations for new pharmacologically active substances (77). A Big Pharma firm would then put (or attempt to put) a lock on key raw materials; import, purify, and process these; incorporate them into drugs; and market and distribute the resultant medicines.

Initially the big firms used university and hospital laboratories mostly for staff recruitment, and did most of their research in-house. Well before the parallel and better-known revolution in information and communications technology (ICT), then, Big Pharma drove the technoscientific-commercial evolution of what has come to be called intellectual property. Drug research also has marketing implications, so that starting in the mid-1950s and continuing through the present day, Big Pharma has constantly extolled its R&D work. In both closed-door lobbying and public relations campaigns, industry's main rationale for high prices is its stated need for revenue to finance the research, development, and clinical trials that result in important new drugs. A rhetorical corollary is that those who seek to reduce drug prices, be they regulators, politicians, or NGO activists, foolishly jeopardize the nascent medicines that will save lives tomorrow.

This last contention may have been true four decades ago when Firestone concluded that drug prices were deflationary. In 1970, however, Big Pharma had not achieved its present pitch of no-holds-barred marketing. It seems no longer true that high prices are necessary to support new drugs. Big Pharma's expenditures on sales and marketing, including its army of detail men, dwarf its total R&D outlays. As noted, moreover, the majority of 'new' drugs are not new at all: they are what have been termed 'me-too' drugs, which are R&D-nonintensive. If a me-too drug has a novel molecular formulation, the FDA does not care if its effects duplicate those of one or more existing products.

(76) At one point Ford owned his own iron mines, steel mills, workers' houses, and manufacturing cities containing workers' houses, churches, shops, and meeting halls (the latter *not* open to unions)

(77) Mahoney 20f

Even falling short of this low bar is no barrier: bettering placebo is the only criterion. Some me-too drugs do not innovate even this far. Examples have been tabled in Congressional investigations of an identical pill being sold as new when its only innovation was a different-coloured coating (78).

As medical science advances it first creates, and then requires, steadily more advanced technologies. Thus c.1990 Big Pharma found it could no longer perform all its own R&D in-house. Each research area, from enzymes to genomics and proteomics, had become too specialized. The industry's vertical-integration model was failing, exactly as it had failed Henry Ford a half-century before. In drug manufacture as in auto manufacture, a full corporate mini-economy had proven too complex to sustain. Hence today's Big Pharma outsources not just raw materials and labour but much of its R&D as well. Sometimes a Third World research contractor is hired, with IP reverting to the big firm paying the bills. In other cases Big Pharma buys out a Little Pharma hotshot to acquire its personnel, physical plant, and interesting proprietary IP. In still other cases, two large firms consolidate into a supergiant such as GlaxoSmithKline. In all cases, the net result is a lessening of competitive forces that might otherwise exert downward or at least stabilizing pressure on drug prices.

**ATTITUDES: STATE OF THE ART**

Attitudes are of two types, external and self. The two are interdependent: rare is the individual whose self-worth stays high when he or she is universally excoriated, or stays low when he or she is universally praised. Attitudes of external groups toward Big Pharma -- M.D.s, patients, regulators, legislators, and insurers -- may therefore be profitably compared with Big Pharma's conception of itself. The latter is invariably positive: Big Pharma presents itself as, and really believes it is, the put-upon 'good guy.' Yes, it says, we comprise companies (not all big) that are, like all corporations, after profit. But profits ensure our companies' continuance. Employees, managers, and shareholders all benefit. Patients - consumers*,* rather - benefit even more.

The self-righteousness in Mahoney's book, many of whose 'facts' seem a compilation of industry puffs presented without source, dispute, or discussion, is a case in point. So is is Mahoney's reincarnation a half-century later in the modern industry described by Avorn, Greider, Finkelstein *et alia*. We are blameless, says Big Pharma. Our attackers are ignorant, malevolent, or both. Besides: if you refuse our fees you thereby curtail all future wonder drugs. We overcharge because we care.

(78) Avorn 55; Greider *passim*

For all Big Pharma's proven benefits, its iron grip on global health care remains troubling. One recent example may suffice. A 2010 M.D. graduate of the University of Toronto, Dr Nav Persaud, became uneasy when attending university-sponsored lectures on the prescription of opioid medications to mitigate chronic pain. The lectures, it turned out, were -

financially supported by the pharmaceutical industry, taught by an outside lecturer from a drug-company speakers' bureau [,] and supplemented by a free reference book paid for by Purdue Pharma, manufacturers of OxyContin (79).

OxyContin is (one may assume uncoincidentally) the very opioid touted in Persaud's supposedly objective classes. In a paper in the 2013 June issue of *Journal of Medical Ethics*, published in London UK, Persaud went on to warn about -

drug-industry influence in undergraduate medical education, where conflict-of-interest standards remain lax. "Doctors should not teach medical students and work for pharmaceutical companies at the same time," says Persaud, now a physician and researcher at St Michael's Hospital in Toronto . . . "This association can be linked with dubious information presented to students and could have a negative impact on patient care. When you go to the doctor, you want to know that you're getting the advice that's best for you and not something that’s based on the marketing plan of a pharmaceutical company" (80).

In other words: *First, do no harm* - an oath that, two and a half millennia after Hippocrates, may need restating. Less than two weeks after publishing his cautionary article, Persaud was hit with 'legal chill' in the form of attack litigation launched by Big Pharma. His response: "If papers like this don't get published and people who share my concerns don't speak up, I won't be surprised if this problem continues" (81).

As noted, public attitudes toward Big Pharma suffered a sharp reversal in 1963. Yet at some point in the half-century 1963-2013, the popular mood changed again to meet one cynic’s definition of a second marriage, *viz*. the triumph of hope over experience (82). Even if not all drugs were all good, most seemed so; and whether leading or following patients' resumption of trust, the medical community agreed. Journal articles announce the imminent eradication of all infectious disease (83).

(79) *Globe and Mail* 2013 June 26 L6

(80) *Globe and Mail* 2013 June 26 L6f

(81) *Globe and Mail* 2013 June 26 p.L6

(82) Johnson, S., quoted by Boswell, J. in *Life of Johnson* (1769 October 26). Cited Bartlett 431a

(83) A prediction that *Scientific American* has accurately called 'hubris'

Powerful antibiotics such as tetracycline continue to be prescribed for nonthreatening conditions such as *acne vulgaris*. Livestock farmers correlate a steady diet of strong antibiotics with better health and faster weight gain among their animals. The medical community, till recently functionally separate from veterinarian science, did not know (or chose to deny) that antibiotics ingested by animals may while still active flow via meat and milk into humans. The entire biomedical community achieved a theoretical denial of how neoDarwinian selection might favour the emergence of drug-resistant pathogens such as MRSA, which plague today's hospitals. Instead, belief in 'miracle medicine' again became absolute. The world ignored that every benefit has costs: that there is no free lunch.

In fairness, while medical professionals have rightly been blamed for sharing the lay public's blinkered belief in drugs' omnipotence, the pressure on them to do so was and is extreme. A clinician pharmaceutically empowered to cure a patient's acute bronchitis with a ten-day course of aureomycin would not in 1970, nor is likely to now, counsel antibiotic abstinence *pro bono publico*. The M.D. still weighs doubt against certainty. In most instances that means giving the patient-consumer immediate relief, downstream public-health consequences be damned.

**SUMMARY & CONCLUSIONS**

The production, regulation, and use of pharmaceutical drugs involves five main stakeholders: Industry, regulators, the medical community, insurers, and patients. These groups are involved in a complex and continuous series of negotiations that influence, and are in turn influenced by, their attitudes vis-à-vis one another and themselves. Despite the intricacy of such negotiations, broad trends appear when this multipartite system is examined dynamically over the last seven decades (84).

Certainly the attitudes of most external stakeholders have changed. Technology embodying new pharmaceutical discoveries convinced patients c.1943-63 that drug manufacturers were literally "The Merchants of Life" (85), a positive external image that was seized on and magnified by Big Pharma through relentless application, and in many cases invention, of brilliant strategies in marketing, sales, lobbying, and public relations. Industry initiatives convinced the medical community, initially resistant to sharing power and authority, first to accept the new drugs as useful tools and then to allow the detail

(84) Even after cigarettes were incontrovertibly outed as a strong carcinogenic risk factor, people kept smoking "because by the time I get cancer they'll have a cure for it." This was actually said to me by a friend who died from non-Hodgkins lymphoma in 2012

(85) Mahoney's book title. *See* Bibliography below

men who sold them to elucidate and advise on their use. Bit by bit, most M.D.s ceased to see the detail man as a drug-drumming Perfesser. They ignored what they had correctly seen as a glaring conflict of interest and accepted industry propaganda as a reliable basis for therapeutic decisions, on a plane with objective research data. In the meantime the FDA, already hamstrung by new U.S. regulations that let Big Pharma pitch directly to patients, internalized the deregulatory *zeitgeist* by working less for patient welfare (financial as well as medical) and more for industry profit margins. Thus in 2013 most stakeholders, including patients themselves, view those who take pharmaceutical drugs not as *patients*, *viz.* people temporarily ill and seeking cures, but as *consumers*: that is, people whose continuing health or very existence depends on endless medication.

Self-attitudes have also evolved in non-patient stakeholders. For example:

* From its establishment the FDA saw itself as representing citizens. Now its self-perceived client is industry;
* The mirrors of many M.D.s no longer reflect scholar-princes, but overworked and underpaid employees of privately held, profit-oriented HMOs.

The sole holdout, the species that remains unevolved, is the drug industry, whose self-image has stayed static. Beginning c.1943 Big Pharma regarded itself as a bringer of universal good: not simply an emissary of health, but rather an instantiation of the reach and beneficence of market capitalism. That self-view still holds. It grants industry a bully pulpit to preach its benefits; to exhibit real or feigned hurt at attacks it represents as unfair and ill-considered; to bask in self-righteousness. Beneath this mask, however, a Big Pharma in thrall to its own marketing arm relentlessly continues to distort clinical-trial data, stonewall generic substitution, and maximize consumption of its products. Avorn notes in something like despair -

A particularly useful exercise was something we called a brown bag session, in which the patient . . . was asked to collect all medications currently being used . . . [T]he drugs [were] layered upon each other like coral on a reef (86).

Breakfast used to be toast and orange juice; now it is a pyramid of pills. Today's typical drug consumer (once a patient) has become a destination resort for pharmaceuticals.

(86) Avorn 126f

Yet in practical terms, why should industry concern itself with self-image? Big Pharma is the most profitable endeavour on earth, over the last six decades consistently outperforming even investment banking. The manufacturing, mining, energy, retail, and nonmedical tech sectors all bow before Big Pharma. To be sure, the drug industry is continually reviled for greed, dishonesty, and callousness. Stories of its sins emerge with metronomic regularity; those touched on above are but a smattering. Big Pharma does not care. A favourite epigram of the Caesar Caligula was *Let them hate, so long as they* *fear* (87). Big Pharma says: *Let them hate, so long as they buy*. And we do buy. At each scandal MV Pharma is briefly tempest-tost (88), then surmounts each transient wave and sails on.

Suggestions for ameliorating the drug industry's enormities have been profuse and various; they continue to be made almost monthly (89). Addressing these requires not another paper so much as a whole new library. We can, it seems, no longer endure Big Pharma's hubris; but neither can we live without its products. Big Pharma is our supplier, the love whom we loathe. As a society, we might examine that.

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(87) *ODERINT DVM METVANT*. Lucius Atticus, from a lost tragedy: quoted in Bartlett 109b (incl. Note 3)

(88) Shakespeare, *Macbeth* I.iii; quoted with modernized spelling by Lazarus, E., in *The New Colussus* (inscription for the Statue of Liberty, New York Harbor)

(89) Consider Finkelstein & Temin, who conclude their book with an impassioned plea to US regulators to duplicate earlier antitrust breakups (AT&T *etc*.) and establish a separate agency for drug R&D. They forget, or else have not heard, that an identical effort (Canada Patents and Development, 1973-9) proved ineffectual. Hope springs eternal.

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