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Facts: Medicine Then and Now

Forty-two years ago, when I was an intern in internal medicine, we practiced (by today's standards) terrible and unsafe medicine. I cite a few examples.

Heart attack patients languished on our wards for a month. We simply observed them and hoped that they would not suffer cardiac arrests as they gradually advanced from lying in bed to sitting, to limited walking and finally discharge. We also routinely confronted patients in great pain with crippling rheumatoid arthritis, barely able to move from deformed joints. Primitive surgical procedures to repair degenerated hips required long convalescence times, and knee replacements did not exist. Most patients hobbling about with degenerative arthritis were therefore forced to live a life of limited physical activity, which predisposed them to obesity and its many complications. A diagnosis of leukemia was an automatic death sentence. Blood sugar monitoring of patients with diabetes was difficult, rendering its control nearly impossible, and complications arose with certainty.

Today, treatments for all of these ailments – heart disease, arthritis, leukemia, diabetes - are radically different, not because physicians are more "ethical" or better regulated, but because of the tools (drugs, diagnostics and devices) they have at their disposal.

Heart disease mortality has declined by over 50% in the last 50 years, thanks to interventions like drugs that dissolve clots in obstructed arteries and stents that prop them open. Most of these procedures, done safely thanks to technologies that constantly monitor the patient's status, do not require more than a few days of hospitalization. Other drugs (like statins) are available to lower "bad" cholesterol safely and with excellent tolerability or reduce blood pressure with few minimal side effects – preventing heart attacks and strokes for millions of patients worldwide. Still others prevent blood clotting responsible for heart attacks and strokes.

Table I partial list, in no particular order, of valuable medical products industry has provided since I completed my medical internship in 1967.

Product	*Conditions Addressed*
Hepatitis B vaccine	Prevention of liver failure and liver cancer
Interferons	Treatment of hepatitis, multiple sclerosis, cancers
Erythropoietin	Anemias
Proton pump inhibitors	Stomach ulcers, reflux esophagitis
ACE inhibitors	High blood pressure, heart & kidney failure
Azole drugs	Fungus infections
Anti-TNF	Rheumatoid arthritis, other autoimmune diseases
Anti-CD20	Lymphomas, autoimmune diseases
Bisphosphonates	Osteoporosis, bone fractures
Clotting factors	Hemophilia, other bleeding disorders
Anti-CD4	Diagnosis of AIDS
Anti-hepatitis B,C, -HIV	Diagnostics to prevent transfusion-transmission
Rotavirus vaccine	Infantile diarrhea

Coronary stents	Heart attacks
Fluoroquinolones	Severe bacterial infections
MRI and CT scanning	Imaging of internal organs
Anti-HIV retrovirals	Treatment of AIDS
Anti-Gp2b/3a	Heart attacks
Statins	High LDL cholesterol, heart attacks, strokes
ADP receptor blockers	Heart attacks, strokes
Factor 10a inhibitors	Prevent and treat blood clots
HPV vaccine	Cervical cancer
Femoral head implants	Hip degeneration
Aromatase inhibitors	Breast cancer
Porcine valves	Heart valve degeneration
PDE5 blockers	Erectile dysfunction
Knee & other implants	Joint degeneration
Imitinab	Chronic myelogenous leukemia, GI stromal tumors
Enzymes	Inborn metabolic deficiencies
SSRIs	Depression and other mental disorders
5HT3 blockers	Chemotherapy-induced nausea & vomiting
CMV antivirals	Cytomegalovirus infection
H. flu vaccine	Haemophilus influenza infection
Inhaled corticosteroids	Asthma
Calcium channel blockers	High blood pressure
Cyclosporine/Tacrolimus	Organ transplant rejection
Cisplatin	Cancers
Anti-Veg F	Macular degeneration
Colonoscopes	Colonic polyps, cancer diagnosis
Endoscopes	Minimally invasive surgery
Portable defibrillators	Cardiac arrest
Long-acting bronchodilators	Asthma
Leukotriene receptor blockers	Asthma
Biguanides, insulin analogs	Diabetes

The tools listed above came from private industry, informed and assisted by entrepreneurial physicians and scientists in academic health centers.

Private investment in product development by companies reflects the worldwide exponential run up in health care costs (1). This growth rate, and corporate research expenditures began to exceed public (mainly National Institutes of Health-NIH) support of research in the late 1980s, and the gap between them has risen to almost two-fold (2).

The 1970s saw the establishment of the biotechnology industry driven by leading scientists, including Nobel Laureates, who had ushered in the watershed use of genetics to discover rare but potent components of body function, to make these components in quantities suitable for therapeutic use. Some, like erythropoietin that stimulates red blood cell production enabled patients with kidney failure and severe anemia to avoid needing blood transfusions. Others block toxins such as inflammation-causing substances responsible for rheumatoid arthritis.

The expansion of medical product development also created opportunities for physicians to participate in clinical trials testing product efficacy and safety. Because of their proximity to daily patient care, the physicians involved were in the best position to advise

companies developing the products as they navigated the risks and unknowns inherent in complex biology. The same physicians were also well suited to familiarizing practicing physicians with new products as they emerged on the market.

Opposition to Profit in Medicine and Regulatory Reactions.

The substantive benefits of corporate money in medicine are almost too well documented to ignore – but they are ignored. At face value, a profound animus against such money is difficult to understand.

Prior to the late 1980s physician and researcher interaction with industry was almost completely unregulated. Suddenly, however, a rising tide of criticism poured out of the medical journals attacking physicians and academic scientists for consorting with corporations. The outburst included articles and editorials in medical journals and books. The code word for the animus against companies and those who associate with them was "conflict of interest (3-12)."

"Conflict of interest" is only a meaningful term in terms of regulatory implications in the context of self-dealing by persons in positions of political or judicial power – and physicians and researchers do not come even close to having such influence. Therefore, the intent of the phrase in the context of medicine is a ploy, used since the beginning of recorded history, of adversaries to invoke allegedly evil motives of an opponent – such as greed -- as a weapon in an argument they cannot win on substance (13).

The assault on money in medicine has been two-pronged, claiming, on the one hand that conflict of interest is detrimental to medical innovation and medical care in practical ways, and, on the other, that it is fundamentally inimical to accepted canons of medical ethics. Both attacks hinge on the fundamental assumption that money – profit, especially profit above some arbitrarily defined limit – is obligatorily corrupting and inconsistent with medical professionalism.

The practical arguments against industry encroachment into medicine vary in stridency. At the extreme, they claim that most medical innovation derives from publicly funded academic research (through the National Institutes of Health or other mechanisms), and that after appropriating it, companies rig the evaluation of subsequent developed products in their favor. They exaggerate the difficulties of product development to inflate prices. Every adverse outcome is the result of malign intentions rather than inadvertent error. The extreme critics aver that if industry simply diverted resources from marketing to research, breakthrough products would automatically appear.

Even those with seemingly more moderate attitudes that pay some tribute to the contribution of industry to medical innovation and to the difficulties of translational product development, however, ally with the extremists by advancing the proposition that in their ruthless pursuit of profit corporations obligatorily deviate from accepted standards of scientific rigor in the execution of studies to evaluate their products, in the reporting of those studies and in the marketing of approved products to physicians.

The crescendo of attacks on conflict of interest have elicited waves of regulatory actions. Initially focused on research, academic health centers enacted rules inhibiting researchers from receiving corporate sponsorship for their work, in some cases even laboratory research, if they had above a defined minimal amount of equity or fees from

the sponsoring company. The institutions required faculty to disclose their financial relationships with companies to university authorities empowered to “manage” or prohibit such relationships.

After newspaper reports alleged extensive irregularities in disclosure of corporate relationships by researchers at the NIH intramural program, the NIH banned all paid consulting to industry by such researchers. This action took place despite the number of violations analyzed by subsequent investigation being few and no damages having occurred. Just as profit supposedly causes corporations to misbehave, the underlying assumption enabling these academic rules is that arbitrarily definable profits or prospects of profits determine an unacceptable risk of corruption of faculty in their research work.

The next tier of regulatory escalation directed itself against overt product marketing and what it interpreted as marketing in the guise of corporate subsidies for CME activities. To eliminate what was presented as, yet again, the damaging influence of profit-motivated corporate misrepresentation of scientific evidence on patient care, recommendations, enacted in some academic health centers, have emerged, with great fanfare, to curtail the provision of product samples to physicians by company sales representatives and, and, especially, the conferral of small gifts and meals to compensate physicians for their time devoted to learning about new products. Corporations and their trade groups embraced these measures, somewhat disingenuously, since they all save marketing costs (14, 15).

Another regulatory thrust has been to exact extensive public disclosure of payments from private companies to physicians and researchers. Laws mandating such public information in the interests of “transparency” have passed in several states and are under consideration nationally. In anticipation of such legislation, pharmaceutical companies have begun to disclose such payments on their websites.

A central battleground concerning eliminating conflict of interest is corporate support for CME, presently over half of a $ billion enterprise encompassing a diverse range of educational activities. Some academic health centers have started down the elimination pathway by prohibiting physicians from giving educational talks to other physicians when corporations pay the lecturers. The slogan categorizing such lecturing is “speakers’ bureaus.”

Once again, the central assumption justifying purging CME of corporate funding is that such subsidy must on balance result in biased educational content. An additional presumption is that commissioning a cadre of educators with no interests in particular products will provide better education because it is more “objective.”

Where’s the Evidence of Corruption?

Examining the data on which the anti-commercial critics base their allegations, analyses by the NIH and by the Congressional Research Office, and, especially, an in-depth review of the development history of the 35 most widely prescribed drugs or drug classes uniformly attest that pharmaceutical companies have made major contributions to innovation and that they markedly increase the value of academic research results (16-18).

Almost every reason put forward for how conflict of interest supposedly compromises medical research, especially that it promotes research misconduct, is, when subject to factual analysis, untrue (19). Similarly, scholarly assessments of the amount of research that moves into product development or of the risks of failure and the costs of that process are inconsistent with critics' claims of exaggerated risks or of price gouging (20-23).

The *New York Times* editorialized that "none of the steps yet contemplated by industry or professional groups would completely sever the medical profession and many individual doctors from their far more disturbing ties to the drug industry," and that "the medical profession needs to wean itself entirely from its pervasive dependence on industry money (24)."

What are these "disturbing ties" and "pervasive dependence?" According to statistics compiled by The Association of University Technology Managers, American universities, hospitals and research institutions receive over five times more research support from the NIH than from industry sources – hardly "pervasive dependence (25)." And while surveys reveal that nearly all American physicians have received something of monetary value from industry, in most cases it is in the form of the small sums associated with marketing activities (26). A minority of physicians and academic researchers receive larger and even very large monies for participation in clinical trials or for research and development consulting. The fundamentally important question bearing on whether or not these ties are "disturbing" is their *value*.

Do the allegations concerning the parasitic and devious aspects of the medical products industry survive analytical scrutiny to justify concluding that conflict of interest degrades medical integrity? They do not. Their principal flaws are that they only address *risk*, not benefit, generalize by extrapolating from anecdotes, confuse value and merit and, most importantly, they lack rigorous empiric support.

One striking fact is the relative paucity of adverse outcomes blamed on financial conflict of interest. Table II lists a compilation of such events taken from the large number of journal articles, books and newspaper accounts that have covered this area over the past 20 years.

Table II. Specific Adverse Outcomes Ascribed to Financial Conflicts Since 1967

Case	*Allegations or Events*
Tseng (Mass. Eye and Ear Infirmary) case	Insider trading, IRB violations
Dong (UCSF) case	Publication suppression by sponsor
Kahn (UCSF) case	Suppression of data access
Olivieri (University of Toronto) case	Researcher intimidation
Gelsinger (University of Pennsylvania) case	Death of research subject & lack of financial disclosure
Zimmer settlement	Payments for device use
CLASS publication	Publication of incomplete results
Neurontin settlement & guilty plea	Off-label promotion
TAP settlement	Kickbacks to physicians
Paxil settlement	Non –reporting of efficacy lack & possible side effects

Cephalon settlement	Off-label promotion
Lilly Zyprexa settlement & plea	Off-label promotion
Pfizer Bextra settlement	Off-label promotion
23 drug recalls & device recalls	

The events listed in Table II, some not necessarily ascribable to venal financial motivation, pale before the amount of benefit summarized in Table I. Indeed, the literature output exceeds the substance that it describes; the same stories are simply retold over and over again.

The foregoing is not to argue that the occurrences of Table II, some unearthed by numerous legal monitoring mechanisms, are not undesirable or even reprehensible. Rather it is to ask whether, in the context of total events, they warrant piling more vigilante activity on top of current oversight mechanisms that include the FDA, The Office of the Inspector General, and whistleblower lawsuits or a justify a radical restructuring of financial relationships between the medical products industry, physicians and medical researchers.

Many of the events in Table II are examples of inferior value – apparently intentional devious behavior that could have promoted inappropriate patient care outcomes, although some are only allegations. Nevertheless, the clear-cut instances in the Table contrast with actions critics subjectively deem lacking in merit in the absence of knowledge concerning their ultimate value. Table III lists such cases gleaned from the voluminous conflict of interest literature. Again of note is that the number of examples is not large, especially compared to the volume of pages devoted to describing them.

Table III. "Low-Merit Behavior" Ascribed to Financial Conflict of Interest

Low-Merit Behavior	*Reasons Given for Condemnation*
"Positive" research reports	Negative research results delayed or suppressed
"Speakers' bureaus"	Biased and/or misleading CME
"Seeding" trials	Designed for marketing, not research
"Ghostwriting"	"Honorary" academic authors lend credibility to research they did not do
Conflicted FDA panels & practice guidelines	Biased recommendations for product approval and disease treatment
NIH consulting violations	Rules not followed
Conflict disclosure failures	Erosion of public trust
Gifts to physicians	Inappropriate patient care, increased costs

Overbalancing anecdotes concerning industry's distortion of, delay in or failure to report unfavorable research results are studies documenting that corporate-sponsored clinical trials are of higher quality than most academic trials (27), and examples of the timely publication in high-profile journals of clinical trial results that have had enormous negative economic consequences for the companies that sponsored them (28, 29).

The topics of "speakers' bureaus" and "ghostwriting" exemplify the confusion between merit and value. "Speakers' bureau" is a euphemism for physicians giving educational talks to other physicians concerning specific medical products and for which they receive

payment from the product manufacturer or from some intermediary. The merit criticism is that for physicians to perform "promotional" talks for commercial entities is, by definition, unprofessional.

But the value proposition is whether information conveyed by promotional talks benefits patient care. Speakers and their audiences believe it does, and no evidence supports the opposite conclusion. Critics find distasteful that companies sometimes provide speakers with communication aids such as projection slides. However, companies do this to assure that the information presented complies with FDA regulations (and the speakers have final control of these materials). Advocates opposing promotional speaking have not come close to proving that such speaking lacks value.

If physicians or researchers allow themselves to be designated authors of papers written by professional writers without having participated in the research or contributed in some other way to the article – so-called – "honorary" authorship, low value is manifest, and this practice should be eliminated. Nevertheless, professional writers appropriately acknowledged can help render publications more timely and readable.

If "seeding" trials get published in peer-reviewed journals, as they are, they arguably provide value; a scientifically valid trial is useful irrespective of the motives behind it (30). Internal and external analyses of FDA panel decisions have revealed no effect of financial conflicts (31).

By far the most aggressive criticism that money devalues medicine is in the context of product marketing. The centerpieces of the case against medical product marketing are two articles published in *JAMA, The Journal of the American Medical Association*. The first, entitled "Physicians and the pharmaceutical industry. Is a gift ever just a gift?" appeared in 2000 and is a summary of 29 studies surveying the relationship between practicing physicians and medical product company sales representatives (32). Although, as revealed by the subtitle, the article's author took a dim view of trinkets and meals provided by the salespeople, she compiled a list of outcomes that arguably balanced out in favor of marketing, despite the admission of only one "positive" outcome: "improved ability to identify the treatment for complicated illnesses."

Against this powerful benefit was pitted non-rational prescribing behavior, a conclusion based on a single Dutch study (33). Strangely identified as a "negative" was that physicians acquired a "positive attitude" toward sales representatives. The other "negative" outcomes were rapid and increased prescribing of promoted medications and requests to have them added to formularies – exactly what one might expect new information to cause. The author squarely acknowledged the absence of outcome information to inform whether these prescriptions were inappropriate for patients, and, in fact, evidence exists that undertreatment, such as failure to address high blood pressure, is overall a worse problem than overtreatment (34).

The stated absence of patient outcome data in the Wazana article did not deter the authors of the second *JAMA* paper that came out six years later from exaggerating the actual outcomes by stating,

> *The systematic review of the medical literature on gifting by Wazana found that an overwhelming majority of interactions had negative results on clinical care* (35).

In the same spirit of quantitative declarations based on no evidence they also claimed:

> *Physicians' commitment of altruism, putting the interests of patients first, scientific integrity, and an absence of bias in medical decision making now regularly come up against financial conflicts of interest.*

Despite its errors, most institutional policy preambles cite this paper to justify the need for severe conflict of interest regulation.

Cost savings is a reason frequently given to justify such regulation. However, sales of medical products -- drugs and devices – have contributed relatively little to the relentless increases in medical expenditures over time. Currently this contribution is less than 15%. Despite this fact, physicians, hospitals, health insurers, the news media and politicians have disproportionately blamed the industries producing those products for medical costs. This distortion conveniently deflects blames away from the major cost drivers.

Real Costs.

Proving what does not happen is difficult, but venture capitalists, making risky investments in technologies at early development stages, state that they would much prefer to invest when physicians and scientists have financial incentives to devote time and energy to such projects. Anecdotally, academic researchers have been unable to attract investment for startup companies to translate research into products or to license technologies to existing companies.

The ban on paid consulting inflicted on researchers in the NIH intramural program has caused morale, recruitment and retention problems (36). By definition, companies are not obtaining the advice of these researchers.

Burgeoning disclosure regulations divert company resources from research and development to reporting payments, and taxpayers foot the bill for state and national repositories that house the reports. What good these databases will bring is unclear, because surveys reveal that the public in general and patients in particular have almost no concerns about who pays physicians or researchers how much (37-39).

Allegations of financial disclosure failures have received much media attention. Since consultants only disclose fees, equity and royalties, and the companies tend to report all payments such as expense reimbursements, the inconsistencies are most probably unintentional, so that few of these investigations unearth serious disclosure violations, and none have revealed consequential damages. As the volume of public disclosure increases, any theoretical benefits must be weighed against whether it will be used for industrial espionage, or for plaintiffs' attorneys to troll for "failure to warn" litigation opportunities.

Complexity and rapid changes in the medical product environment mean that physicians, especially physicians outside of academic health centers, are hard pressed to familiarize themselves with new developments. Statutory requirements mandate continuing medical education (CME), and CME is a large enterprise substantially subsidized by the medical products industry.

Attacks on the validity of commercial sponsorship of CME have ratcheted up the difficulty community hospitals have in obtaining corporate support for CME events (40). Heeding the call to purge all such support can only eventuate in drastically reduced education, an outcome hardly in the interests of patient care.

Why Criticism and Regulation Succeed.

Why, despite the weakness of the evidence and the opportunity costs, does policy intended to purge conflict of interest from medicine and separate physicians and researchers from their productive partnerships with private industry flourish?

One major cause of physicians' unwillingness to resist may reside in medicine's unique history, the vast majority of which is a chronicle of bad ideas and ignominious failure. For thousands of years medicine was mired in superstition and reasoning by analogy.

Until the birth of the modern era and the modern corporation, doctors could do little to help their patients – and much to hurt them. Bleeding and purging were favored techniques, as was a cornucopia of herbs and potions that were – at best - placebos. Even early in the last century, science had not yet impacted importantly on medical care. Medical research (such as it was) was the pastime of the leisured aristocrat with disdain for craftsmen and merchants and their pursuit of lucre.

The understandable need for traditional medical practitioners to cloak their practical inadequacies with aristocratic and priestly trappings disappeared when science and industry afforded them the ability to provide legitimate and desired services and ever more opportunities to improve those services. Nevertheless, the opprobrium against "business values" persists, cloaked in a one-sided view of "professionalism" that views profit with contempt (41).

The arguments made against commercialism in medicine invoke a dualism epitomized by an oft-repeated mantra that "companies have a fiduciary responsibility to shareholders whereas physicians' fiduciary responsibility is to patients." This opaque platitude implies that business has no social responsibility and that physicians only behave in a venal manner when contaminated by business. In addition to the fundamentally disrespectful position of this binary stance is its prejudicial demonization defining what is to dislike: it is all well and good for industry to interact with physicians and academic institutions – as long as it does not behave like industry – interested in profits.

Infected by medical school ethics instruction with guilt, physicians suffer embarrassment over profiting from failure. Hence, a low profile seems the best course for avoiding attention from critics and the news media.

Conclusion.

Modern medicine extends our lifespan and improves our life quality because of its grounding in rigorous science, its minute specialization and its ability to attract market entrepreneurship. Unfortunately, these very attributes of success have divided and distracted the medical workforce from the ground of their own success – the modern for-profit firm. This consequence has empowered simplistic linear thinking and

unsubstantiated and archaic beliefs to inflict with little accountability or feedback coercive limits on the freedom of medical practitioners and innovators.

History has repeatedly demonstrated that top-down, central planning impedes innovation. Unless we resist the zealots driving conflict of interest regulations, progress will slow – and patients will suffer.

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