"Frankly, My Dear, I Don't Give a Damn"

Franchement, ma chère, je m'en fous

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Abstract

Four years ago, Michelle Holmes, Wendy Chen and collegues reported a significant negative correlation between aspirin use and breast cancer (Holmes et al. 2010). This summer, they noted that no randomized trials have been initiated that test this potentially important association. Why not? Pharmaceutical companies fund most drug research; there is no profit in aspirin. This explanation is incomplete. The deeper issue is a mismatch between the public interest in advancing research, and the interests of the institutions that governments subsidize in different ways for that purpose. In addition to patent protection, governments directly fund public granting agencies and provide the tax relief offered by private charities. Like pharmaceutical companies, these have their own "stakeholders" and objectives. Nobody, it appears, is interested in aspirin.

Résumé

Il y a quatre ans, Michelle Holmes, Wendy Chen ses collègues faisaient état d'une importante corrélation négative entre l'utilisation de l'aspirine et le cancer du sein (Holmes et al. 2010). Cet été, elles notaient qu'aucun essai aléatoire n'avait encore été amorcé pour tester ce lien important. Pourquoi? Ce sont les sociétés pharmaceutiques qui financent la plupart des recherches sur les médicaments; or, il n'y a aucun profit à tirer avec l'aspirine. Cette explication est incomplète. L'enjeu central est un décalage entre l'intérêt public pour la recherche avancée et les intérêts des institutions que les gouvernements subventionnent à cette fin, de diverses façons. En plus de la protection des brevets, les gouvernements financent directement des organismes subventionnaires publics et offrent un allègement fiscal grâce au statut d'organisme de bienfaisance. Tout comme les sociétés pharmaceutiques, ces organismes ont leurs propres « parties prenantes » et leurs propres objectifs. Il semble bien que personne ne s'intéresse à l'aspirine.

Amazing stuff, this willow bark. Its pain-killing properties have been known since ancient times – do the chimpanzees also know about it? More recently, it has been found to be protective against heart attack. For a time, the research evidence pointed towards significant benefits from taking a quarter tablet (80 mg) daily. Later work refined this recommendation to suggest that the benefits are found only among those who have already shown indications of heart disease; the rest of us can pass up the baby aspirin for now. But we are still advised to chew a tablet while calling 911 if we feel a heart attack coming on.

Hangovers, Heart Disease and … Breast Cancer?

But wait! There's more. In an op-ed piece in the *New York Times* this past May, Michelle Holmes and Wendy Chen (2014) state: "We believe that it might be possible to treat breast cancer … with … Aspirin." The authors – physicians and faculty members at the Harvard Medical School – have some basis for their belief: "In 2010, we published an observational study in the *Journal of Clinical Oncology* showing that women with breast cancer who took aspirin at least once a week for various reasons were 50 percent less likely to die of breast cancer." That's big stuff. Holmes and Chen then note that a subsequent British study assembling results from a number of clinical trials of aspirin to prevent heart disease found that aspirin was also associated with a significantly lower risk of breast cancer death.

So far, so good. But observational studies are not randomized controlled trials (RCTs). And there are those who believe, or at least act as if they do, that there is no truth without trial. Everything short of the RCT gold standard is just speculation. So where are the RCTs?

The Root of All Evil … Again

Where indeed? Breast cancer is not exactly a minor threat. In Canada it is (excluding skin cancers), by far, the leading form of cancer among females (Canadian Cancer Society's Advisory Committee on Cancer Statistics 2014). The age-standardized (female) incidence rate in 2014 is estimated to be 99.2 per 100,000 population, more than double the 47.7 rate for lung cancer at #2. (Lung cancer is, however, much more lethal, with an estimated female mortality rate in 2014 of 35.6 per 100,000 population, double the 18.4 for breast cancer.) The prospect of a highly effective treatment, with minimal side effects and costing literally pennies, should have stimulated an immediate mobilization of research to confirm the benefits of aspirin treatment, map out their scope and limitations, figure out the most effective ways of structuring the therapy, and perhaps (but less importantly) determine how and why it works. (If it does work.) That is not happening.

The authors' explanation is a simple one, and surely correct, though incomplete: "Clinical trials are typically conducted on drugs developed by labs seeking huge profits. No one stands to make money off aspirin …" (Holmes and Chen 2014). You cannot patent willow bark, and the German patents on acetylsalicylic acid (ASA) were given up as part of the Treaty of Versailles.

The implication that it is all the fault of Big Pharma drew a rather huffy response in a letter to the NYT from a certain John L. LaMattina of Stonington, Connecticut (helpfully identified by the *Times* as the former president of Pfizer Global Research and Development): "I was dismayed to read Michelle Holmes and Wendy Chen's assertion that part of the blame for not pursuing aspirin as a potential breast cancer treatment rests at the feet of the companies." Their remarks about the role of labs seeking huge profits "perpetuate the belief that pharmaceutical companies alone should be pursuing this line of research" (LaMattina 2014).

Mr. LaMattina does have a point. Holmes and Chen are of course perfectly correct that clinical trials are typically carried out by labs seeking (hoping for) huge profits. And they did not in fact say such research should be carried out by pharmaceutical companies alone – quite the contrary – although, as Willie Sutton famously said of banks, "That's where the money is." Nevertheless, we cannot be too often reminded that pharmaceutical companies are not "eleemosynary outfits." They are strictly for-profit corporations, responsible to their shareholders for maximizing "enterprise value" – a polite term for profit. That rules out spending even small numbers of millions of dollars on research that has little or no prospect of returning a profit. Not our department – let George do it, with someone else's money.

This response does, however, raise a deeper issue. The pharmaceutical industry enjoys the enormous privilege of delegated state authority to suppress normal market competition for its patented products. The industry's corresponding exceptional profits arise from the extraordinary prices, relative to costs of production, that drug patents make possible. These prices, in turn, support not only research, but also – in equal or greater measure – exceptional marketing expenses, including political activities to protect the industry's privileges.

The justification for this extraordinary privilege is the presumed public benefit that flows from the innovative activities of the industry. Patents are intended to induce the industry to "do well by doing good." The public benefits from pharmaceutical innovation are certainly real, although typically greatly overstated by the industry's marketing and public relations. The proportion of true "therapeutic breakthrough" drugs is surprisingly low, compared with the much more extensive activity devoted to "new" products – "me too" molecule manipulation or new combinations of existing drugs, or line extensions, to maintain and extend market position.

While the value of incentives to innovation may be accepted, a number of commentators have pointed out that there could be other ways of inducing innovation that would provide a better balance of public and private benefits. A different mix of policy instruments might result in the industry's doing more good while doing less well (at public expense). One could, for example, scale the degree of market protection to the therapeutic significance of the innovation. Joseph Stiglitz (2012) has suggested a system of prizes, potentially very large for the true therapeutic breakthroughs. Either of these approaches might steer research resources more towards greater benefits for patients rather than for shareholders of Big Pharma. The determination with which the industry has fought off any such proposals for modifying the patent system is testament to how the industry views the current balance of benefits.

But this is a larger topic. The point to note here is that Mr. LaMattina seems perfectly comfortable dismissing the notion that pharmaceutical companies have any social responsibility over and above their duty to their shareholders. If he has any sense that the highly profitable privileges conferred on these companies might carry a corresponding obligation to support research in the public interest, it does not show in his letter.

Now, of course, pharmaceutical firms operate within an extensive web of rules, of legislation and regulation, that impose obligations upon them over and above their duty to their shareholders. This framework is in principle intended to protect public interests that are not necessarily parallel with those of shareholders (or of senior management). But pharmaceutical companies have on numerous occasions not merely ignored the public interest; they have actively flouted it – doing well by doing bad. Pfizer, the company in which Mr. LaMattina was formerly a senior executive, has a long history of criminal convictions for violations of American law in particular, and currently holds the record, $2.3 billion, for fines and penalties arising from these convictions (Harris 2009). But, as in the case of the American banking system, no individuals have been held responsible for what the courts have clearly found to be criminal behaviour. No one goes to jail. So criminal behaviour will persist whenever it is profitable enough to cover any resulting financial penalties and associated legal expenses. Those are just part of the cost of doing business.

La trahison des experts

In this context, it is not hard to understand why there are no company-funded trials of aspirin for breast cancer. Big (and little) Pharma is in the business of producing profits, not knowledge. (Or even of producing drugs. Drugs are simply means to the ultimate end.) That focus is required by the rigorous laws of the market under which companies must operate; if we do not like the result, then we must change those rules. Any attempt to do so, however, will run into fierce opposition from the industry, which rather likes the very favourable regulatory rules they have succeeded in embedding in national laws and international trade agreements.

But what about national governments themselves? There is a view that democratically elected governments, at least, are supposed to act in the general public interest. Sometimes, in fact, they do. Governments channel large amounts of public money directly into medical research, over and above the huge indirect benefits they provide for private pharmaceutical firms. It seems obvious that if aspirin really could significantly improve cancer outcomes, the savings in "blood and treasure" – reductions in mortality, morbidity and health expenditure – could be very large indeed. The case for public funding of a research trial to find out seems compelling, even overwhelming. But it is not happening.

The explanation may lie in the discrepancy between the public interest and the private incentives that drive biomedical researchers and the public agencies over which they exercise substantial influence. Of course, everyone wants to "find a cure for cancer," but Holmes and Chen suggest that there is a strong professional bias towards finding the *right sort* of cure: "[G]eneric drugs, particularly ones as old and familiar as aspirin, just aren't sexy."

> [E]ven as government funding for research is slashed, the government is still willing to test new cancer drugs pushed by pharmaceutical companies, despite very high failure rates for those drugs. Federal grant review panels have no direct financial interest in the studies they approve for funding, but inevitably they are seduced by the more novel treatments – the scientific equivalent of the latest smartphone. (Holmes and Chen 2014)

Nobody is going to win a Nobel Prize for prescribing aspirin; no heroics here.

There is a further important consideration. Successful research teams are not assembled overnight; they can take months or years to develop. Granting agencies know this. You cannot simply turn off the flow of funds to a team one year and turn it back on the next. The people at the core of the team may be gone. So there is a form of co-dependency between research "stakeholders" and the granting agencies that support them. Research teams like to continue doing what they know how to do and are good at. Consistently successful research teams make the agency itself look good and improve its chances in the overall competition for public funds.

This, in turn, may explain the authors' concern for the expense of an aspirin breast cancer trial. Ten million dollars?! That's peanuts – not just for the US, but for just about any public research organization in the high-income world. But if budgets are static or shrinking, those peanuts have to come from someone else's bag, some established research stakeholder, and then things get nasty.

It gets worse still if research funders want to extend their resources by encouraging or even mandating public–private "partnerships," or evaluating research success by whether or not a new patentable product comes to market (hello, universities). The for-profit incentives that inevitably drive private research then determine the allocation of public research dollars as well. But if profit incentives adequately captured the full range of public interests in health research, why would we need public agencies at all?

Furthermore, although the authors do not mention it, there is an indirect financial interest in the medical community at large. The authors note the exceptional costs of present forms of post-surgical treatment (including drugs) to prevent recurrence, as well as their significant side effects. But it is important to keep in mind that none of the expenditures for cancer treatment are paid out to Martians. Every dollar of cost is income to some individual or organization here on Earth. So if aspirin actually works as suggested, the cost savings will all be income losses to someone, as well as lost opportunities to display professional and technological prowess through more advanced treatments.

In normal markets, cost savings can give an organization a competitive advantage. But despite the fantasies (or even deliberate deceptions) of some economists, healthcare never has been and never will be a normal market.

Cold Charities

There is, however, yet another major source of funding flowing into medical research – private charities. As Holmes and Chen (2014) note, a first RCT of the use of aspirin in cancer treatment is in fact underway in Britain, funded by the non-profit group Cancer Research UK. But this study, of four different cancers, will not be completed until 2025. Many people will die of breast cancer over the next decade. The authors believe that a focused trial of aspirin in breast cancer treatment could be completed in half that time. (Even better, it could be American.)

Significantly, however, a large proportion of the funding that flows through "private" charities is in fact public. Donations to organizations approved by the relevant national taxation authority (such as the Canada Revenue Agency) are offset in part by some form of income tax relief for the donor. The resulting reduction in government revenue (known in public finance as a tax expenditure) means that the state is participating along with the private donor in supporting whichever (state-approved) charity the private donor finds most appealing.

These tax expenditures can be quite substantial. A taxpayer in British Columbia, for example, who donated $1,000 in the 2013 tax year would receive a reduction in income tax of $437 – $290 from the federal government and $147 from the provincial government. In effect, then, the tax credit for charitable donations delegates to individual taxpayers the determination of priorities for a substantial chunk of public spending. A good deal of this donor-directed public money goes to medical charities of various sorts, and cancer societies are among the most prominent.

There are thus parallels among the three possible sources of de facto public funding – patent protection for pharmaceutical firms, public research granting agencies and tax credits for charitable donations. In each case, control over public resources is delegated to more or less arm's-length institutions or individuals, whose objectives presumably (hopefully) overlap with a broader public interest.

The funds transferred appear to be in very different forms. Granting agencies appear explicitly as items in public expenditure budgets. Tax credits represent foregone revenues and do not show in the public accounts, although ministries of finance have pretty accurate estimates of their fiscal impact. The fiscal impacts of patent protection are much more diffuse. They show up, obviously, in the higher prices charged to government programs that pay for drugs. But private employer-paid health insurance coverage is heavily subsidized by governments through tax expenditures, and there is also some tax relief available for individuals with exceptionally large drug bills. So some portion of the higher prices paid by apparently private purchasers comes back indirectly as a charge on the public purse.

The public costs of supporting research through the patent process thus flow through a number of channels, mostly well hidden, but well understood by their corporate beneficiaries.

Come back to the charities themselves. They must depend on individuals and corporations, both for private donations, and for the public money that these draw in their train. That

requires a good deal of imaginative and sophisticated marketing, and that costs money. A (surprisingly?) large share of charitable donations goes to support fundraising and administration. (In this, charities resemble private health insurance, where also a large share of revenues goes to marketing and administrative overhead rather than paying for health services.)

But donors do not want to see their donations diverted into overhead and administrative expenses, essential as these may be in the real world of competition for donor dollars. This may be the explanation for the reluctance (refusal) of the Canadian Cancer Society to disclose the salaries of its top executives. *Frank* magazine, a scurrilous, muck-raking periodical (a dirty job, but someone has to do it – there's a lot of muck out there), recently requested this information from the CCS. While the Society is "fully committed to transparency and accountability" (Canadian Cancer Society 2014), that information was not forthcoming. The US Internal Revenue Service, however, requires the filing of this information as a condition of tax-exempt status. (The CRA, politely Canadian, does not.) So *Frank* gleefully published the salary data from the IRS (Kent 2014).

Are these salaries excessive? I don't know, and I see no reason to reproduce them. (Those with a prurient interest can look the article up.) Senior executives in the public and private spheres do earn a lot of money, and their relative incomes have, as we know, been rising steadily over the past three decades. The Canadian Cancer Society is a large and very successful organization, and its senior management may well be worth their pay.

But the key point is that it is a large and successful organization. The Society's annual report for 2012/13, "Life Is Worth Fighting For," shows total revenues of $223.8 million for the year ended January 31, 2013, of which $204.3 million came through various forms of donation. Direct and indirect fundraising expenditures were $90.4 million; along with $7.4 million for administration, these accounted for 43.7% of total revenues. Could $10 million over five years not be found for a study of a possible major breakthrough in cancer treatment? Come to think of it, there is also an American Cancer Society whose budget must be at least ten times that of the CCS. Might they not be interested? Apparently not.

Why not? The reasons may lie in the same limitations that inhibit the public granting agencies. There may appear to be a lot of money in the pot, but it all has some names penciled in beside it. An established stable of distinguished researchers, pursuing the conventionally accepted, most promising lines of inquiry, become agency "stakeholders." None would be pleased to see even $10 million diverted away from their own, very important, research.

Who Needs an RCT, Anyway?

Whatever the reason, the trials are not happening – except glacially in the United Kingdom. But so what? Holmes and Chen are perhaps barking up the wrong willow tree. They are advocating a trial of aspirin as therapy for second- and third-stage breast cancer. But their own study, and the British heart disease study they refer to, does not address therapy for diagnosed disease. Both studies simply show a significant negative association between cancer mortality and a low level of regular aspirin intake – as little as one a week.

The potential weaknesses of associational studies are well understood and not in dispute. But do you need gold-standard evidence before taking action or giving advice? It depends upon who "you" are. If you are an oncologist treating breast cancer patients and relying on experimentally based protocols, you might well want gold-standard evidence before changing your treatment. After all, the fact that breast cancer mortality is so much lower than disease incidence implies that much of treatment is working. (As does the decline in age-standardized mortality by over 40% during the last 20 years [CCS 2014].) It may not be fun, but it keeps a lot of people on the right side of the grass. If you are a woman in the higher-risk age ranges, however, maybe you should be taking a couple of aspirins (with a glass of milk), say, every Sunday morning?

Of course aspirin has risks, including gastrointestinal bleeding, and people who are already taking other blood thinners should perhaps leave it alone. But older males will recall that when we were all being advised to take a baby (one-quarter strength) aspirin a day – or was it every other day? – as protection against heart disease, the side effects were never a major issue.

The dangers of aspirin have been grossly inflated for good commercial reasons. A long and highly successful advertising campaign (with other forms of brainwashing) by Johnson & Johnson has promoted acetaminophen as a safer alternative to aspirin, and their particular branded version, Tylenol®, as *the* drug of choice.

Today, in my local supermarket, 100 standard Tylenol® tablets sell for $9.13; 100 plain aspirin tablets (generic acetylsalicylic acid, or ASA) can be had for $5.39 – if you can find them. They are down on shelf seven, just off the floor, and occupy about four inches of shelf space. Various versions of Tylenol take up about 10 feet of premium space, on the top two shelves. Tucked in among them, less than a foot of space is allocated to generic acetaminophen, at $6.39 per 100.

Now we know that acetaminophen – even good old Tylenol – also has risks. It can seriously damage the kidneys. Well, all drugs have risks. The marketing machine rolls on.

The observations from associational studies, however, raise a very disturbing possibility. Suppose a well-executed RCT showed that regular, low-level aspirin use was to some degree protective against breast cancer? The pro-Tylenol, anti-ASA campaign must surely have significantly reduced the consumption of aspirin over the decades. Has this, then, contributed materially to the incidence of breast cancer?

All the more reason for doing the trial, and doing it soon. While we are waiting for Godot, however, why not advise (hello, CCS) those of the female persuasion to take a couple of aspirins? You are unlikely to do harm, and you might save a few lives.

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