"Good pharma" is possible!

AMIT SENGUPTA

Donald W Light, Antonio F Maturo. *Good pharma: the public-health model of the Mario Negri Institute* New York: Palgrave Macmillan, 2015. 288 pp. Hardback $ 95, ISBN 9781137388339.

The world of innovation remains divorced from the world of clinical practice and the two intersect only when clinical practice, primed by the pharmaceutical industry's publicity machinery, uncritically laps up all that "big pharma" has to offer. Seldom is clinical research guided by clinical practice and its requirements. New medicines target illusory surrogate end points that might have little to add in terms of actual therapeutic value.

Ben Goldacre's influential book titled *Bad pharma: how drug companies mislead doctors and harm* (Harper Collins, 2012) detailed the relationship between the pharmaceutical industry and the medical profession, and the extent to which the former controls academic research. The book spoke of the dominant paradigm of clinical research and argued that "the whole edifice of medicine is broken" because the evidence on which it is based is systematically distorted by the pharmaceutical industry.

Good pharma: the public-health model of the Mario Negri Institute by Donald W Light and Antonio F Maturo, is in many senses the antithesis of *Bad pharma* and shows us vignettes of an alternative world where clinical research and practice are intertwined, and where medical ethics drive both. It would appear to be a fantasy world, except that the vignettes are real, rooted in the over five decade old praxis of the Mario Negri Institute in Milan, Italy. The saga of the Mario Negri Institute is used as a backdrop to construct the vision of "what could be" if clinical research were to be freed of the shackles of big pharma's greed and chicanery. The authors weave the story of the Mario Negri Institute into a narrative about what "good pharma" should look like.

An idea takes shape

It is also a story of the remarkable journey of Silvio Garattini. Brimming with idealistic notions about research, biomedical researcher Silvio Garattini returned to Italy in 1957, but resented the cloistered environment for science in Europe compared to the open environment he had been used to in the United States during his studies. The book is also a commentary on the fatally flawed vision of science based on patent rights and how the environment for research in the US moved from its open and collaborative roots in the 1950s to the confines of patent-based research by the 1980s. The Bayh Dole Act, enacted in the US in 1980, effectively handed over the reins of fundamental research conducted through public-funded institutions into the hands of the pharmaceutical industry.

Garattini's serendipitous meeting with millionaire philanthropist Mario Negri changed the course of his life. Garattini was seized with the idea of setting up a pharmacological research institute that would avoid the "strictures and meddling of Italian universities and public bureaucracies". Impressed by young Garattini's zeal and idealism, Mario Negri took him under his wing and bequeathed him his fortune to establish a "foundation dedicated to the health of people and pharmacological research, which will be named Istituto di Ricerche Farmacologiche Mario Negri". Thus, at the age of 33, Silvio Garattini gave up his career at the University of Milan as deputy chair of the Department of Pharmacology, to live his dream of setting up a model institute for pharmaceutical research.

Founding principles of "open science"

The Mario Negri Institute commenced operations in 1963 in a working class area of Milan. The founding principles of the institute, worth emulating in a range of settings, included provisions such as:

- No patents will be sought, because patenting distorts research, creates corrupting dependencies, and builds silos of secrecy.
- No contract grant will be accepted for work not already of interest to the research staff and in their areas of competence.
- Researchers control their data, its analysis, and its publication.
- To maintain independence, no funding from any source will exceed ten percent of the institute's income.

Patents are an Italian invention and it is believed that the first patent was granted in Italy in 1421 to the Florentine architect, Filippo Brunelleschi, for a barge with hoisting gear that was used to transport marble along the Arno River. Six centuries on, the Mario Negri Institute has squarely turned its back on a patent-led system of innovation. In 1963, pharmaceutical product patents were not recognised in Italy (very like the 1970 Indian Patents Act), but in 1978, Italy decided to remove the exemption of medicines from its patent law. However, Garattini and the Mario Negri Institute decided not to finance part of their research through patenting new discoveries or

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developments. The Institute argued that morally, they are paid to invent and discover for patients and society, so their inventions should be available to all, like Jonas Salk when he refused to patent his vaccine against polio. A 1990 report of the Institute characterised itself as "a moral institute completely independent of industry, the state and universities, working with maximum freedom, without bureaucratic interference, without political pressures, with the efficiency of a private organization but working for the public. All results are never protected by patents and are available unconditionally to everyone".

Less expensive and more effective

Researchers at the Institute receive no pay beyond their regular, modest salaries and an observer comments that it "feels like a community of graduate students". Yet today, the Institute is engaged in cutting edge research and conducts about 80 clinical trials at any one time, involving about 70,000 patients. It integrates bench research with concerns about patient care and community welfare. Mario Negri trials are clinically more important and less costly than industry trials because a trial is not started until a complete review of all the evidence is carried out and a clear hypothesis is formulated with a strong end point.

An abiding concern manifest in the Mario Negri Institute's approach has been that clinical trials must be designed to test whether a new drug is better for patients, as measured by outcomes that patients rate as important. The Institute opposes the approach that is dominant in the pharmaceutical research industry, whereby surrogate or substitute measures are used as proof of efficacy for a new product. Thus, for example, instead of measuring to what extent a new anti-diabetic drug reduces serious complications such as blindness or amputations, companies may test new drugs (unfortunately approved by regulators later) for their effect on surrogate end points such as blood pressure, lipid levels, albumin excretion, or C-reactive protein. This approach makes trials faster and cheaper, but much less informative about real patient outcomes.

Over the years, the Mario Negri Institute has been responsible for developing many new molecules that provide therapeutic benefits. But its output is not limited to new drug innovations. As Garattini notes, the industry defines innovation in terms of new molecules; but almost half of these do not prove to be clinically superior to the existing medicines. Thus, research at the Institute also focuses on existing clinical practices with a view to improving upon them.

Conducting research that matters

Research at the Institute has been hugely influential in changing clinical practice in a range of disciplines. For example, work at the Institute led to the introduction of ACE inhibitors (hitherto used to treat hypertension) for the treatment of chronic renal failure. The Institute's research also showed the benefit of administering a single large dose of streptokinase as soon as possible following symptoms of acute myocardial infarction – soon to become standard practice in cardiac care centres across the world. Further research in the area contributed to the recommendation that a combination of aspirin and streptokinase should be routinely administered to all myocardial infarction patients. The Institute's research is also about questioning current practices. Scientists from Mario Negri were responsible for showing that standard chemotherapy worked significantly better than high-priced erlotinib, which had looked very effective compared to a placebo.

The Institute is not just a centre for producing new knowledge, but also functions as a repository of knowledge and as a medium for the dissemination of knowledge. Its Rare Diseases Information Center has been gathering information on more than 1000 of the estimated 7000 rare diseases known to humankind. Scientists at the centre respond to hundreds of inquiries from patients, families and physicians about conditions suspected to be related to rare diseases. The Center for Information on Pharmaceuticals provides reliable information to pharmacists, doctors and patients. Every day, scientists at the centre answer people's questions and sometimes, to the callers' surprise, Silvio Garattini himself answers the phone and addresses their concerns.

The institute has never shied away from taking up cudgels in defense of scientific rationality. In a widely publicised case in Italy, the Mario Negri Institute busted claims made by a hugely popular self styled cancer healer, Luigi Di Bella. Di Bella had developed a concoction of different drugs that claimed to shrink tumours or cured cancer. Both he and his therapy became so popular that according to a survey in the mid-1990s, 42% of citizens believed it worked and 53% were unsure, while only 1% thought it was a sham. The Institute's study of cancer patients treated by Di Bella from 1971 to 1997 served to debunk his claims.

Influencing practices across the world

While the Institute's pioneering work has led to fundamental changes in prescription practices and contributed to the rational use of drugs, it has also led to it being at the receiving end of the pharmaceutical industry's ire. The Institute's Regional Center for Drug Documentation and Information surveyed prescribing practices and found that three-quarters of all the 14,176 pharmaceutical products on the market in Italy were "useless, irrational, or even dangerous". It concluded that only 1398 of the 7812 brand names in the national formulary were based on 352 active ingredients with documented therapeutic value. Ironically, the drugs with the least therapeutic value were being promoted the most extensively under the largest number of brand names. This process led to the development of a formulary of safe, effective drugs in the mid-1970s. The formulary excluded most fixed-dose combinations, a favourite among many manufacturers. In the mid-1990s, further work at Mario Negri led to more stringent tightening of Italian government regulations and the

relegation of over 1000 drugs to the "useless" category. The national expenditure on drugs dropped from the equivalent of 6.5 billion euros to 4.5 billion euros. Pharmaceutical companies were outraged and claimed that such policies would undermine "innovation". Farmindustria, the Italian association of pharmaceutical companies, accused Garattini of having financial ties with some companies whose drugs made the essential list. Many affected companies withdrew their contracts with Mario Negri. A Senate hearing, ordered to settle the issue, ruled in favour of Garattini and the Mario Negri Institute.

In 1975, the director of the division that oversaw drugs and devices at the World Health Organization (WHO), Vittorio Fattorusso, paid a visit to the Institute. Garattini discussed Mario Negri's methods for developing evidence-based formularies with him and explored the idea of a list of "essential drugs" that could be useful for all nations that wanted to promote rational, cost-effective prescribing. Dr Fattorusso liked the idea, developed it further, and in 1977 called the first meeting of the WHO Expert Committee on the Selection of Essential Drugs. Garattini served on the committee, and thus was born the widely known and extremely influential Essential Medicines programme of the WHO and the regular publication of the WHO's Model List of Essential Medicines (EML).

A blueprint for "good pharma"

The authors of *Good pharma* extrapolate the approach of the Mario Negri Institute to propose a blueprint for "good pharma", as opposed to "bad pharma". In 2013, *The Lancet* commented on the continued lack of published or even disclosed evidence concerning the benefits, and especially the risks of harm, of new drugs and vaccines. Drawing on an assessment by Iain Chalmers and Paul Glasziou, *The Lancet* estimated that 85% of the billions spent on commercialised biomedical research is being wasted because of the following four deficiencies:

1. Researchers do not investigate questions relevant to patients and their clinicians because they do not ask them what matters to them.
2. Half the time, no systematic review is made of the existing evidence and studies fail to protect themselves against forms of bias.
3. Disappointing results are underreported and over 50% of researchers do not publish their results in full.
4. Over half the results of planned studies are not reported, and 30% of researchers do not describe interventions in enough detail for them to be useful.

The authors propose that "good pharma" should be about wanting "honest researchers to work together, not separately in high-security labs, and to learn from each other's failures as well as successes while trying any active ingredient that might work, regardless of its patentability". They conclude: "Patents may work in other realms of innovation and technology; but in medicine they have not. Morally, societies exempted medicines from patents for decades because they were regarded as a social, not a commercial, good. Medically, patenting distorts every step of the research process as well as testing, publishing, marketing, and finally prescribing. Making drugs subject to patents has led to the current proliferation of pseudo-innovation and serious risks we have discussed. But the Mario Negri Institute, as an oasis of classic science – independent, transparent, and funded for just the costs of research – represents a classic, alternate model for how to do good science to develop good medicines without any of these distortions."

Good pharma is a fascinating story and a must read for all those who believe that something is not right about the way we incentivise medical research today. Both laypersons and specialists in the field will find something to think about in a book that is full of delectable nuggets of information interspersed in the story of Silvio Garattini and the Mario Negri Institute.

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