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Abstract

In 1962, Louis Lasagna was one of the central figures in the creation of our current drug regulation systems. His influence on the practice of modern medicine, through a series of unanticipated consequences of these systems, has been profound. In the 1960s, he was one of the most progressive thinkers in medicine. By the 1980s, he had apparently become one of the most reactionary. This article attempts to delineate the dilemmas he believed he was dealing with, dilemmas that stemmed from a system he had helped create, that produced this apparent change in orientation. The problems with which he grappled are ones that remain unresolved and, indeed, have become more acute. The example of how he attempted to remedy what had gone wrong may provide pointers as to how to solve or how not to solve current difficulties.

Keywords

drug evaluations, Food and Drug Administration amendments, Lasagna, patient values, randomized controlled trials

Edward Nik-Khah's article about the pharmaceutical industry's 1970s confrontation with the regulation of their products in the name of free market ideology points to efforts to neutralize regulation through direct resistance and indirect regulatory capture.

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The tensions between these superficially opposed positions and their interface with the practice of medicine are caught extraordinarily in the figure of Louis Lasagna. Our concern is with Lasagna's intentions and actions in the 1960s, before the Conference on the Regulation of the Introduction of New Pharmaceuticals (CRINP) in 1972 that, according to Nik-Khah, culminated Lasagna's purported 'volte-face' to Chicago school neoliberal opposition to regulation.

Nik-Khah downplays Lasagna's role in the 1962 passage of the Kefauver-Harris Amendments to Food and Drug Administration (FDA) regulations. Lasagna had already pioneered the placebo-controlled, randomized trial, and as such was one of the fathers of evidence-based medicine. He pushed drug effectiveness at the Kefauver-Harris hearings, where he was Kefauver's lead scientific adviser. He also introduced an effectiveness criterion based on placebo-controlled trials into the regulations (Lasagna, 1989).

As a result, in 1965 Lasagna was touted as the next head of FDA. Industry feared this. His support of Democratic party platforms and organized labor even led to speculation by friends such as Alvin Feinstein (1966), from Yale, that he might make a suitable vice-presidential running-mate to Hubert Humphrey on the Democratic 1972 ticket (the same year as CRINP). In view of this, and, more importantly, in light of particulars in Lasagna's skirmish with FDA drug evaluation procedures that he himself had helped bring into existence, any narrative suggesting that his call not 'for more reliance on clinical trial data but for *less*' (Nik-Khah, 2014: 498) implies his capture by an emergent neoliberalism needs to be scrutinized.

As Nik-Khah suggests, Lasagna was a media star. But he set, rather than followed, the academic consensus. He spoke out against prevailing opinions. He did so to his cost in 1969 in the Panalba case mentioned by Nik-Khah. He had little regard for the combination antibiotic marketed under that brand name and no stake in defending Upjohn. However, he believed that the FDA had not applied due process in their efforts to ban the drug (Carpenter, 2010). His peers argued that the ends justified the means, and they shunned Lasagna for his resistance.

The Drug Efficacy Study and its Implementation (DESI) program, which began in 1965, was another flashpoint. Perhaps believing the myth that it was the first scientific regulator, the FDA recruited academics to adjudicate on drugs that had been approved before 1962 – without controlled trials. DESI recruits were not informed that in the absence of unequivocal evidence of efficacy from a randomized controlled trial (RCT), an academic consensus that a drug probably worked would not be enough to keep the drug from being removed from the market (Shorter, 2009).

Was this an instance of overweening bureaucratic arrogance that set itself above the domain expertise of medical academics? Or was it an apparent belief in some disinterested rationality manifest in RCTs that allowed non-medical bureaucrats to trump the verdict of seasoned academic clinicians – mechanical objectivity trumping expertise (Porter, 1996)? In either case, we see here bureaucratic versions of the therapeutic reformers, Marks (2000) discusses.

Within weeks of the 1962 law being signed, Lasagna was faced with the limitations of RCTs for the complexities of drug evaluation. At that time, the only drug that had been through a placebo-controlled RCT prior to marketing, in which it had been shown to be safe and effective, was thalidomide – the sleeping pill that had caused the crisis. The

study had been undertaken by Lasagna himself (Lasagna, 1960). Richardson-Merrell had geared up to market thalidomide in the United States, but the drug was delayed within the FDA. Richardson-Merrell also had produced the very first cholesterol-lowering drug, and although Lasagna had castigated their drug and the idea of cholesterol lowering as a legitimate medical target, on the basis of his thalidomide study, Richardson-Merrell approached him to lobby on their behalf to have thalidomide licensed. After the 1962 regulations were put in place, when the press heard that Lasagna had lobbied for thalidomide, they confronted him. He hastily replied that if Marilyn Monroe had been taking thalidomide rather than a barbiturate, she would still be alive. He repeatedly had to state afterwards that he was not arguing for thalidomide to be licensed.

Lasagna later pointed to the fact that most of the effective drug groups were introduced in the 1950s without having undergone controlled trials en route to licensing, drugs like metformin, the antibiotics, thiazide antihypertensives, antidepressants, and others. By the mid-1960s, Lasagna, along with Bradford Hill and other early advocates of RCTs, could see that, far from being reined in by controlled trials, company salesmen were using trial results to sell their products (Lasagna, 1998).

This perversion of what clinical trials were intended to be has since mushroomed into a full-scale capture of them and the guideline apparatus based on them. Trial publications now give a more complete academic endorsement of products than the testimonials of individual doctors in the pay of industry ever did in the 1950s. As Kotler and Simone argue in their book, *Building Global Biobrand*s, ‘Clinical trials are the most credible and powerful form of marketing in the prelaunch period’ (Healy, 2012; Simon and Kotler, 2003)). Guidelines based on clinical trials now coerce treatment in ways that could not have been imagined in the 1950s. And so, one might ask, were the terms that Lasagna used to describe the new apparatus being imposed on the practice of medicine (‘totalitarian’, ‘Lysenkoism’) (see Nik-Khah, 2014) a symptom of his conversion to an anachronistic Bush-era style neoconservative support of profits over health, or was he presciently sounding an alarm bell that RCTs with their ‘p-value madness’ were becoming a weapon for an even more insidious threat, as later suggested by Lasagna (1998)?

Another skeptic was William Wardell. Wardell arrives in Nik-Khah’s narrative without context, some denizen from a neoliberal coven based at the University of Rochester. As with Lasagna, whatever happened later, in the mid-1960s, Wardell was a pharmacologist working for DESI, where he witnessed the marginalization of traditional pharmacological expertise in drug evaluation under the new epidemiological paradigm that had become de rigueur in the FDA. As with Lasagna, the question is whether his later political views stemmed from this experience with the implementation of the new legislation, rather than from an original ideological commitment to ‘neoliberalism’. After 40 years, both pharmacology (Wardell) and clinical pharmacology (Lasagna) had pretty much disappeared in medical schools.

Today, many argue that the growing crisis in health care stems from conflicts of interest and lack of access to clinical trial data. Our view is that small-print disclosure in academic footnotes and open access to trial data, important though these are, will not solve problems that stem from the notion that clinical trials provide a higher form of knowledge than knowledge borne in a clinical encounter – the realm of the experiential

and the singular. Lasagna recognized this conflict and worked to ensure that experiential knowledge not be devalued.

Lasagna was the first to criticize the use of surrogate outcomes as determinants of effectiveness. Decades later this is accepted wisdom. But aside from this point, there was at the time no coherent critique of RCTs to which he might have appealed and no awareness that clinical trials can systematically hide adverse events.

Finally, it is worth bearing in mind that in the 1960s Ivan Illich and others were more worried about medicalization than pharmaceuticalization. Today, the sheer power of the pharmaceutical industry is manifest; critical pharmaceutical studies, including many published in these pages, demonstrate how medicine's traditional authority in health care has diminished and how the mighty 'reputation and power' of the FDA (Carpenter, 2010) has been captured. Reading the story backwards, a Chicago-School-as-conspiracy hypothesis can look plausible. But this is to miss the context of the times and what Lasagna and others saw as a looming nemesis for one kind of medical practice.

Lasagna was the first clinical pharmacologist. He was also a doctor. The bottom line for healing, he believed, cannot come down to anything other than a patient's values. This bewilders many who want regularity or, indeed, equity. The point goes to the heart of the differences between regulating pharmaceuticals and practicing medicine. If we say that the evidence base used to support a license application for a drug should dictate medical practice, we take the practice of medicine away from doctors and patients. As we have since learned, in so doing we hand the practice of medicine over to companies, for whom the rise of treatment-induced death to the status of one of the commonest causes of death is nothing more than the cost of doing business.

We three authors have each argued for the accountability of pharmaceutical marketing in the horrific rise of treatment-induced death. Decades of exposés of drug company manipulations in the academic literature, in the media, and in the courts have failed to catalyze more than cosmetic reform. A trillion-dollar business generates its own political endorsement, permitting it to skirt regulation as easily as it stifles critique – in the form of independent research into the veracity of its claims.

Lasagna supported a science-led regulatory approach first, and then, seeing the problems created by this, apparently sought an alternative. It is easy now to say that he may have swung too far. He believed that industry could be deployed to break the grip on health care of the combined scientific/bureaucratic apparatus, a grip that threatened to subordinate medicine to the regulatory process and distort perceptions of drug efficacy and safety. But this was an error of means, not ideology. Lasagna's fears were ultimately justified, and his classical liberal (rather than neoliberal) instinct that somehow the interface between practicing physicians, a market-disciplined pharmaceutical industry, and an informed and listened-to public might be the best place to seek reform deserves reconsideration.

Lasagna's emphasis on patient values points to a collaboration between subject and healer, rather than a contract between rational egoistic utility maximizers. He was fostering self-reliance, rather than individualism. Under current conditions, the possibility of a relationship-based medicine and a market-disciplined pharmaceutical industry seems a pipe dream. How do we provide space for a situated granular encounter between a healer and patient that delivers textually mediated approaches to the whole person?

When evaluating the safety and utility of drugs, we surely need to take into account the experience of individuals who take them and the doctors and nurses who, in the context of an ongoing clinical encounter, witness noteworthy changes. But at present doctors report well under 5 percent of serious adverse effects, and almost none of the other side effects that may adversely affect lives.

As part of the effort to regulate drugs, the data on the drugs being used are generated through the best system ever invented for hiding the adverse events that treatment can cause, concealing the fact that these events are more common than any benefit that might be expected (Healy, 2012). We have a system in which ever weaker and more costly drugs eliminate better and cheaper drugs – precisely the problem that concerned Lasagna and Kefauver in 1959. The comprehensive implementation of RCTs as the predominant evaluative tool for drug licensing has aggravated, rather than solved, this problem and, even more problematically, has affected the possibility of relationship-based clinical care.

In Nik-Khah's story, a great deal is attributed to a handful of individuals linked to the Chicago School – Friedman, Stigler, Peltzman. His assertions about individual intentions and unwholesome ideologies are not uninteresting, but ironically they divert attention from a system of medical scientific, regulatory, economic, and commercial reasoning and practice whose mechanisms and consequences, whatever the intentions of its original creators, only social science can hope to lay bare, and whose cultural footing, by this point, perhaps only a poet can truly articulate.

This 'Trust in Numbers' story was caught wonderfully when it was unfolding, by George Oppen, a New York poet and member of the communist party, in his 1968 volume *Of Being Numerous*:

Crusoe we say was rescued.
So we have chosen.
Obsessed, bewildered
By the shipwreck of the singular
We have chosen the meaning
Of being numerous.

These lines also capture the shipwreck that disease- and treatment-related adverse events inflict on us. Ironically, the isolation is even greater now than in the 1960s precisely because the triumph of numbers has rendered experience insignificant.

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Author biographies

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