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For a while, Martin Arrowsmith, the hero of Sinclair Lewis's 1925 eponymous novel[1] – written in close collaboration with the scientist turned writer, Paul de Kruif – became the iconic image of a medical researcher, and a source of inspiration for generations of American medical students and young doctors.[2] One of the central elements of the plot is a dramatic account of a trial of an anti-plague prophylactic during an epidemic on a Caribbean island. In all probability, the description of such a trial in an important novel (Lewis was awarded the Pulitzer Prize for *Arrowsmith*, although he declined it) favoured the diffusion of the concept of scientific testing of putative preventive and therapeutic interventions. It also popularized the idea of controlled clinical experimentation, while depicting it as a dramatic endeavour. Physician-scientists, Lewis's book proposed, need to overcome the natural tendency of physicians to try to provide immediate succour to sufferers seeking their help, and yet to be willing to expose the few to unknown risks for the greater benefit of mankind.[3,4] *Arrowsmith* is an iconic image of scientist as hero, and the field trial an iconic display of his heroism.[5]

Arrowsmith: a 'coming-of-age' novel (*bildungsroman*)

Sinclair Lewis's novel describes his hero's education and his gradual transformation into a true scientist. At medical school, Martin Arrowsmith came under the influence of an eminent German scientist, Dr Max Gottlieb, a model of commitment to the ideal of science (Lewis wanted at first to call his novel *In the shadow of Max Gottlieb*).

> *'[Arrowsmith] had learned from Gottlieb the trick of using the word "control" in reference to the person or animal or chemical left untreated during an experiment, as a standard for comparison; and there is no trick more infuriating. When a physician boasted of his success with this drug or that electric cabinet, Gottlieb always snorted, "Where was your control? How many cases did you have under identical conditions, and how many of them did not get the treatment?" Now Martin began to mouth it – control, control, control, where's your control? where's your control? – till most of his fellows and a few of his instructors desired to lynch him. He was particularly tedious in materia medica.*
>
> *'The professor of materia medica, Dr. Lloyd Davidson, would have been an illustrious shopkeeper. He was very popular. From him a future physician could learn that most important of all things: the proper drugs to give a patient, particularly when you cannot discover what is the matter with him. His classes listened with zeal, and memorized the sacred hundred and fifty favorite prescriptions. (He was proud that this was fifty more than his predecessor had required.)*
>
> *'But Martin was rebellious. He inquired, and publicly, "Dr. Davidson, how do they know ichthyol is good for erysipelas? Isn't it just rotten fossil fish – isn't it like the mummy-dust and puppyear stuff they used to give in the olden days?"*
>
> *"How do they know? Why, my critical young friend, because thousands of physicians have used it for years and found their patients getting better, and that's how they know!"*
>
> *"But honest, Doctor, wouldn't the patients maybe have gotten better anyway? Wasn't it maybe a post hoc, propter hoc? Have they ever experimented on a whole slew of patients together, with controls?"*
>
> *"Probably not – and until some genius like yourself, Arrowsmith, can herd together a few hundred people with exactly identical cases of*

erysipelas, it probably never will be tried! Meanwhile I trust that you other gentlemen, who perhaps lack Mr. Arrowsmith's profound scientific attainments and the power to use such handy technical terms as 'control,' will, merely on my feeble advice, continue to use ichthyol!"

'But Martin insisted, "Please, Dr. Davidson, what's the use of getting all these prescriptions by heart, anyway? We'll forget most of 'em, and besides, we can always look 'em up in the book."

'Davidson pressed his lips together, then:

"Arrowsmith, with a man of your age I hate to answer you as I would a three-year-old boy, but apparently I must. Therefore, you will learn the properties of drugs and the contents of prescriptions BECAUSE I TELL YOU TO! If I did not hesitate to waste the time of the other members of this class, I would try to convince you that my statements may be accepted, not on my humble authority, but because they are the conclusions of wise men – men wiser or certainly a little older than you, my friend – through many ages. But as I have no desire to indulge in fancy flights of rhetoric and eloquence, I shall merely say that you will accept, and you will study, and you will memorize, because I tell you to!"

'Martin considered dropping his medical course and specializing in bacteriology.'[1]

Arrowsmith is strongly attracted by scientific research, but his marriage to the nursing student Leora, obliges him to look for a job. He has a series of unfulfilling occupations: as a rural doctor, as a physician responsible for public health services in a mid-west county, and as a pathologist in a fashionable hospital in Chicago. Arrowsmith never loses his enthusiasm for research, however, and ends up accepting an invitation from Gottlieb to join the prestigious McGurk Institute in New York (a thinly-veiled reference to the Rockefeller Institute, from which de Kruif had been sacked before his collaboration with Lewis).

The McGurk Institute, Arrowsmith finds out, is a less idyllic place than he had believed it to be. Its Trustees claimed to be exclusively committed to the promotion of fundamental biological and medical research, but in fact, they are more interested in fame and prestige than in 'scientific truth'. Nevertheless, the McGurk Institute provides Arrowsmith with a supportive environment in which he is able to dedicate himself to biological investigations.

He rapidly discovers a potentially efficient antibacterial principle, the bacteriophage. Arrowsmith learns from Gottlieb that he is not the first to observe this phenomenon: the French-Canadian microbiologist Félix d'Herelle had already published a paper on the same subject (the novel makes many references to real life bacteriologists and immunologists). However, Arrowsmith is still the first to describe a practical application of the phage – the prevention and treatment of plague.[6] An epidemic on the (fictional) Caribbean island of St Hubert provides him with an opportunity to test the efficacy of his preparation, and he sails to the island, together with his wife and a famous expert on tropical diseases, Gustaf Sondelius. Before leaving for St Hubert, Arrowsmith makes a formal promise to Gottlieb that he will conduct a rigorous experiment with the phage, whatever the circumstances might be.

When Sinclair Lewis began collaborating with Paul de Kruif, the episode of plague on a tropical island was the only solid element in the plot of the future book. De Kruif and Lewis embarked on a freighter cruise to West Indies to assimilate the atmosphere of life in the Caribbean islands; to educate Lewis about bacteriology, epidemiology and methods of scientific research; and to draft the details of Arrowsmith's field experiment.[2] The principle of this experiment was very simple: half the population of an isolated community, St Swithins, were to receive the phage, while the other half were to be denied it – or any other – putative prophylactic.

'The plague had only begun to invade St. Swithin's, but it was unquestionably coming, and Martin, with his power as official medical officer of the parish, was able to make plans. He divided the population into two equal parts. One of them, driven in by Twyford, was injected with plague phage, the other half was left without. "He began to succeed. He saw far-off India, with its annual four hundred thousand deaths from plague, saved by his efforts. He heard Max Gottlieb saying, "Martin, you haf done your experiment. I am very glat!" The pest attacked the unphaged half of the parish much more heavily than those who had been treated. There did appear a case or two among those who had the phage, but among the others there were ten, then twenty, then thirty daily victims. These unfortunate cases he treated, giving the phage to alternate

patients, in the somewhat barren almshouse of the parish, a whitewashed cabin the meaner against its vaulting background of banyans and breadfruit trees.'[1]

The main characteristic of the St Hubert experiment was thus that the phage should be given to 'half of the population'. Lewis does not mention attempts at randomization or efforts to verify that the experimental and control groups were similar. It is true that, at the time that Lewis was writing *Arrowsmith*, such efforts were rare, but some examples existed.

Arrowsmith's experiment fails in the end. His wife Leora dies from accidental contamination with the plague bacillus, and Arrowsmith, depressed and disoriented by his wife's death, opens a dispensary, where he distributes the phage to everybody, including people in the St Swithin's control group who come to his dispensary. The experiment is partially saved through the devotion of Arrowsmith's local collaborators, who continue to distribute the phage selectively and collect data. After several months the plague disappears from St Hubert, but Arrowsmith is not sure if the reason was distribution of the phage, killing of rats by Sondelius, a natural cycle of the disease, or all of the above. He is nevertheless hailed as the 'victor of the plague'.[1]

The director of the McGurk Institute persuades Arrowsmith not to publish his real (and imperfect) statistical data about his experiment with the phage, and instead, to issue a research report with an ambiguous summary. The McGurk Institute receives all the credit for developing a 'miracle drug', and Arrowsmith is covered with honours.[1]

At first Arrowsmith accepts these pressures and plaudits, but later decides to turn his back on what he sees as a travesty of true science. By the end of the novel, he has left his rich second wife, resigned from his prestigious position at the McGurk Institute, and joined his colleague Terry Wicket (who left the Institute before him) to pursue independent research on bio-physical chemistry in a small private laboratory they had established in the woods of Vermont.

Lewis presents Arrowsmith's failure at St Hubert as resulting from an unavoidable conflict between doctor as healer and doctor as scientist, that is, between the physician's obligation to his patients here and now, and his obligation to all future patients, which continues to be presented as a dilemma today (see, for example, Epstein[7] and Barbot[8]).

Why weren't alternative experimental designs used in the novel?

Some of de Kruif's and Lewis's contemporaries were not persuaded by Arrowsmith's 'meticulous experiment'. The Harvard bacteriologist and epidemiologist Hans Zinsser explained in 1934 that Lewis produced a sentimentalized and simplified image of epidemiology, and added that 'if an epidemiologist responsible for a plague study talked and behaved in the manner of the hero of *Arrowsmith* he would not only be useless, but would be regarded as something of a yellow ass and a nuisance by his associates'.[9]

The book does not provide any justification (for example, scarcity of the phage, or fear of its undesirable effects) for withholding a potentially valuable prophylactic intervention from half of the population during a deadly epidemic.[1] Arrowsmith was expected to prove his commitment to the ideal of science through resistance to pressures to distribute the phage to people who were not entitled to receive it in the framework of his experiment.[1]

Could Lewis have discussed alternative designs for Arrowsmith's scientific experiment? One possibility is indirectly evoked in the book: a comparison between Arrowsmith's phage and alternative therapies such as 'Haffkine's prophylactic' and 'Yersin's serum' (anti-plague vaccine and antiserum, treatments developed by real life scientists in late 19th and early 20th century, respectively). Sondelius proposed to use all the available methods at the same time. Arrowsmith strongly objected to such approach and insisted on testing his phage, and his phage alone.

'Sondelius wanted to exterminate all the rodents in St. Hubert, to enforce a quarantine, to use Yersin's serum and Haffkine's prophylactic, and to give Martin's phage to everybody in St. Hubert, all at once, all with everybody.

'Martin protested. For the moment it might have been Gottlieb speaking. He knew, he flung at them, that humanitarian feeling would make it impossible to use the poor devils of sufferers as mere objects of

experiment, but he must have at least a few real test cases, and he was damned, even before the Trustees he was damned, if he would have his experiment so mucked up by multiple treatment that they could never tell whether the cures were due to Yersin or Haffkine or phage or none of them.'[1]

The McGurk Institute's Trustees were in favour of experiment using only the phage:

'after all, while they desired to save humanity, wasn't it better to have it saved by a McGurk representative than by Yersin, or Haffkine or the outlandish Sondelius.'[1]

The aspiration to increase the fame of their institution was typical of representatives of a brand of science more interested in limelights than in rigorous experimentation. But why did Martin Arrowsmith and his mentor Gottlieb insist on testing only the phage? Why not an experiment which compared the phage – a treatment which looked promising in the laboratory but had never been tested in field conditions – with Haffkine's or Yersin's preparations, which had already been tested during epidemics, although, at least in retrospect, found to have modest effects only?[10–12]

One reason Lewis did not elect this arrangement might have been the structure of the plot. A comparison of several treatments would not provide the novel with the same level of emotional charge as the 'phage or nothing' experimental design. Distribution of a placebo would also have spoiled this dramatic effect. Arrowsmith's 'scientific heroism' was grounded in his ability to deny people potential prophylaxis, and his willingness to face their wrath. Without this, the dilemmas of the doctor who denies potential protection to desperate people in order to obtain reliable scientific knowledge would not have been highlighted so effectively.

Fundamental research as the only route to effective treatments

Another reason Lewis and de Kruif did not propose that their hero test several treatments may have been linked to their view of therapies. In spite of abundant evidence to the contrary, they believed that treatments work only when they are grounded in understanding of the biological mechanisms of disease and the discovery of the means to disrupt these. They believed that observations made in the laboratory, if grounded in solid physiological and biochemical knowledge, can be directly transferred into clinical practice. This view of therapy is also present in the description of Max Gottlieb's short misadventure at the Hutzinger pharmaceutical plant. Gottlieb was able to 'synthesize antibodies in a test tube', and the factory owner wanted to market this invention immediately, with appropriate publicity. Gottlieb strongly resisted, explaining that he needed more time to be sure, that is, to perform additional experiments and get his equations right. There is no mention of clinical trials or of real-life patients, and no hint whatsoever of possible difficulties during a passage from bench to bedside.[1]

Arrowsmith concludes that the solution to this dilemma is to return to fundamental research which, he believes, holds the promise of the development of truly effective ways of preventing and curing diseases (see Rosenberg[5] and Löwy[13]). Lewis's (and de Kruif's) proposal – through Martin Arrowsmith – that better understanding of the basic mechanisms of life is the precondition for developing effective treatments has its roots in the emergence of scientific medicine in the mid-19th century. The rise of 'therapeutic nihilism' was one of the reasons for the belief that in order to be effective clinical medicine must be grounded in basic science. After several centuries of bleeding and purging, questions were increasingly being asked about the effectiveness of medical practice (see, for example, Forbes[14] and Agnew[15]). Famously, Oliver Wendell Holmes declared:

'I firmly believe that if the whole materia medica, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind – and all the worse for the fishes.'[16]

This attitude was energetically promoted in the middle of the 19th century by the leaders of the Vienna Clinical School, Karl Rokitanski, Joseph Dietl and Joseph Skoda. They claimed – not unreasonably – that nearly all the medical treatments then being used were based on ignorance, and many did more harm than good. It was therefore better to abstain from using them. A doctor's true task was to increase understanding of fundamental physiological and pathological mechanisms in order to make possible the development of truly effective therapy.

Joseph Dietl summed up this attitude:

> *'One should appreciate the physician as nature's investigator, not as an individual dedicated to the act of healing (…) Our strength lies in our knowledge, not in our actions. Therapy will result from our knowledge like a fruit growing from a flower. If the natural sciences blossom, practical medicine, their fruit, will also be established.'*[17]

In 1899, the Polish physician and philosopher of medicine, Edmund Biernacki, who was familiar with the works of Vienna Clinical School, went a step further. He suggested that doctors' wish to decrease the distress of their patients was a major obstacle to the growth of medical science and, ultimately, to permanent alleviation of human suffering.[18] Ideally, Biernacki argued, doctors should observe disease in the same, dispassionate way as a botanist observes a plant. In practice this is impossible, however, and he refers to the 'nightmare of utilitarianism', that is the wish to 'do something, anything' to help the patient, which often hampers the development of promising directions of study in the prevention and treatment of diseases.[18]

Dietl's and Biernacki's point of view has many followers in the 21st century. The abundant historical evidence that information flowed more frequently from clinical practice to the biological laboratory than the other way round did not undermine many scientists' and doctors' belief that only basic research leads to the development of effective cures.[19] For example, in his recent comment on *Arrowsmith*, Howard Merkel, the North American paediatrician and historian of disease, explains that the book's main interrogation is 'who is more important in the conquest of disease: the compassionate, sympathetic healer caring for the sick individual, or the cold, obsessive investigator trying to ascertain the cause of disease and, if successful, render the doctor obsolete'?[3] Arrowsmith, Merkel adds, is the incarnation of the scientific spirit and 'nowhere is this more clearly drawn than during the bubonic plague epidemic raging on the mythical island of St Hubert (….) Martin immerses himself in a meticulous experiment in which half of the island's inhabitants receive bacteriophage and the rest a placebo'.[3] (In fact, placebo is not mentioned in the book.)

More rigorous clinical experimentation was generalized only from the late 1940s on.[20] Nevertheless, there were important early attempts to develop such experimentation (several are described in records and commentaries in the James Lind Library). It may be interesting to note that one such attempt was made by the Russian bacteriologist Waldemar Haffkine, mentioned in *Arrowmith* as the developer of an anti-plague vaccine. During his 1893–1896 tests of cholera vaccine in India, Haffkine compared the incidence of cholera among vaccinated and non-vaccinated members of same households, workers at the same plantation, inmates of the same prisons, and soldiers in the same camp.[21,22] This observational study (the vaccination was voluntary, and was given to all the people who wished to receive it), Haffkine argued, was nearly as valuable as observations made in the laboratory, because he was able to carefully watch the populations he studied, especially those who lived in a well-controlled site such as a prison or a military camp. Studying such captive populations, Haffkine claimed, one could have been reasonably certain that there were no important differences in environment and lifestyle between the vaccinated and non-vaccinated people.[23] Haffkine's studies often involve self-selected groups, but on some occasions at least he used forms of alternation for evaluation of plague prophylaxis[24] and a toxin treatment of plague.[25,26]

When *Arrowsmith* was written, there were no large scale trials of efficacy of bacteriophage to prevent or cure plague. In 1927, D'Herelle conducted a clinical trial in India in which bacteriophage was used to treat and prevent cholera, the first in series of attempts to evaluate the efficacy of this approach. Later, similar trials were conducted to assess the efficacy of the phage in prevention and treatment of plague.[27] Some of these trials, like the one conducted in 1933–1935 in the Campbell Hospital in Calcutta, used strict alternate allocation of this therapy. In the majority of the trials, however, the results were seen as inconclusive because the distribution of the phage was not strictly limited to experimental areas. The Cholera Advisory Committee for Indian Research Fund Association noted in its report for 1936 that they regarded it as 'most unfortunate that this trial was not carried out as a strictly controlled experiment and the use of bacteriophage was not confined to experimental areas only'.[27]

Biernacki suggested in 1902 that clinical medicine would never become a 'true science' because the physiological effects of medication cannot be

dissociated from those of doctor–patient interaction. Ideally, Biernacki claimed, drugs should be administered to two groups of patients, to one together with suggestion and to the other without. But 'how can drugs be administered without suggestion'?[28] Randomized, double-blind clinical trials were devised to try to address this objection. A book written in 1925 could not contain a full description of such a trial as we know it today. However, Lewis's lack of interest in real-life experimentation with drugs and vaccines probably reflects the fact that he was not advised by a clinician but by a basic scientist (de Kruif) who admired the reductionist approach to 'complete understanding' advocated by the real-life model of Max Gottlieb, the experimental biologist Jacques Loeb.[2,29]

Arrowsmith's oft quoted 'prayer of the scientist' pronounced by him when he was hired by the McGurk Institute, ends with the sentence: 'God give me a restlessness whereby I may neither sleep nor accept praise till my observed results equal my calculated results or in a pious glee I discover and assault my error'.[1] In Lewis's and de Kruif's radically reductionist vision of medical science, only basic science could provide 'calculated results' that would need to be confirmed in well-controlled conditions in a research laboratory.[5,30] They judged that there is no place for this kind of accuracy in practice-oriented clinical research. Arrowsmith's final choice to retire to the wilderness of Vermont in order to dedicate himself to pure, mathematically-driven basic research in pure natural surroundings was a logical end of his personal trajectory. It was also presented as the best way to achieve his original goal of producing efficient cures, and an appropriate expiation for sinning against the ideal of science during the St Hubert experiment.

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