Neurological literature: a clinical trial

Clinical trials are an integral part of neurology. Many neurologists have been involved in their conduct, and all will apply their outcomes to clinical practice. A working knowledge of the methodology of clinical trials is fundamental to their evaluation, and hence a learning objective for neurological trainees.

Sir Charles Lewis (1858-1951) was the first American winner of the Nobel Prize for Literature, in 1930, following a series of acclaimed novels published in the 1920s. In one of these, Arrowsmith (1925), the protagonist, Martin Arrowsmith, is a doctor (as was Sinclair Lewis’s father), whose medical career the novel charts, from medical student, to country doctor, to public health official, to research scientist. In the latter context, a description of a clinical trial is to be found.

Narrative
Aged 31 (p. 322), and hence, from internal evidence, in about 1917, Martin discovers the "X Principle" which destroys staphylococci, but the novelty of his finding is short-lived as his scientist mentor Max Gottlieb finds a report from D’Herelle of the same phenomena, described as bacteriophage (p. 327). Martin’s subsequent researches focus on the possibility of curing bubonic plague with phage (p. 357). Aged 37 (p. 384), and hence around 1929, the opportunity arises to put this laboratory discovery into clinical practice.

The scene is the fictional Caribbean island of St Hubert, a "British possession" (p. 355) located in the Lesser Antilles (pp. 352, 355) between Barbados and Trinidad (p. 345) where there is an epidemic outbreak of bubonic plague (p. 348). The plan of Max Gottlieb is "to use the phage with only half [of the] patients and keep the others as controls, under normal hygienic conditions but without the phage" (p. 349), thus permitting "an absolute determination of its value" (p. 349). On departure, he urges Martin: "do not let... your own good heart, spoil your experiment" (p. 354).

Martin’s co-worker on the trip, Gustaf Bonsdorff, wants to give phage to everybody (pp. 349, 351) since "in this crisis mere experimentation was heartless" (p. 350) and on principle twice refuses treatment for himself (pp. 352, 378), but Martin insists on having "real test cases" (p. 349), perhaps a reflection of his training from Gottlieb as a medical student in the importance of controls (p. 40). Martin’s final plan: in a district which was comparatively untouched by the plague... one half injected with phage, one half untreated. In the badly afflicted districts, he might give the phage to everyone, and if the disease slackened unusually, that would be a secondary proof (p. 350).

On St Hubert, both the Governor of the island (pp. 375, 6) and the Board of Health (p. 377) object to the plan of "half to get the phage, half to be sternly deprived" (p. 375) despite Martin’s assertion that "the luckless half would receive as much care as at present" (p. 377).

In the village of Carib, where "every third man was down with plague", Martin gave phage to the entire village (p. 376), following which there is an apparent slackening of the epidemic in the village, observations which Martin hopes will prompt the local bureaucracy to "let me try test conditions" (p. 372). Carib village is then burned in order to kill all the rats, the locals evacuated to a tent village where Martin remains for two days giving them phage (p. 380).

The opportunity for experiment is provided in St Swinfin’s Parish, where, unlike Carib, "the plague had only begun to invade" (p. 386). Martin “divided the population into two equal parts. One of them... was injected with plague phage, the other half was left without” (p. 386). The pest attacked the unphaged half of the parish much more heavily than those who had been treated... Those unfortunate cases he treated, giving the phage to alternate cases” (pp. 386, 7).

However, following a personal bereavement, Martin damns experimentation and “gave the phage to everyone who asked” other than in St Swinfin’s parish where “his experiment was so excellently begun... some remnant of honor [kept] him from distributing the phage universally” (p. 382). Unsurprisingly people from St Swinfin’s are seen in the queue for treatment in the main town of St Hubert, Blackwater (p. 393). Eventually Martin "went back to the most rigid observation of his experiment in Swinfin’s... bloated as it now was by the unphaged portion of the parish going in to Blackwater to receive the phage" (p. 394).

Six months after Martin’s arrival, the "plague had almost vanished" (p. 395). Martin is lionised by the populace as the "saviour of all our lives" but one local doctor reflects that "plagues have been known to slacken without phage" (p. 396). Martin knows that he does "not have complete proof of the value of the phage" (p. 397), that "his experiment had so many loopholes" (p. 400). He plans to take his data to a "biometrician" who may, he notes, "rip ‘em up. Good! What’s left, I’ll publish" (p. 400). Raymond Pearl, the biometrician, “pointed out that his agreeable results in first phaging the whole of Carib village must be questioned, because it was possible that when he began,
the curve of the disease had already passed its peak" (p. 404). It is evident to Martin’s friend, Terry Wickett, that “you bunged it up badly” (p. 405).

Comment

Armstrong has previously attracted attention for his portrayal of contemporary immunology and public health, and I believe I discerned a prior commentary related specifically to the details of the clinical trial. While literary accounts of neurological illness are often to be found, I have not previously encountered a fictional account of a clinical trial.

It is not difficult to enumerate the many shortcomings in this clinical trial: no ethics, no planning, no involvement of a statistician from the outset, no patient consent, no blindness of any kind, no randomization, no matching of cases and controls, no clear definition of outcomes, etc. Indeed, this might be better termed a “therapeutic experiment” rather than a clinical trial. Of course, there is no reason why Lewis as author should present the perfect trial, motivated as he was by literary rather than scientific concerns, specifically to illustrate the tension between Martin as a clinician-scientist and clinician-humanitarian. Although the randomized clinical trial as we know it was not to evolve for several more decades, clinical trials characterized by “fair allocation” schedules had been undertaken at least from the time of James Lind.6

Sinclair Lewis was awarded the Pulitzer Prize for fiction for *Arrowsmith*, but he declined it, his previous novels (*Main Street*, *Babbitt*) having been passed over. In the same year, 1925, the surgeon Harvey Cushing (1869-1939) also won a Pulitzer Prize for his biography of Sir William Osler (1849-1919). According to another Osler biographer, Michael Bliss, “Cushing wrote friends that he had nothing but contempt for the spirit of Lewis’s novel, which had mythologized research and denigrated medical practice.” Cushing hoped Osler’s biography would be an antidote to *Arrowsmith*.7 Cushing’s objection may have been to the “literary stereotypes that portrayed surgeons as money-grubbers in novels of the early 20th century.”8 His name appears in the novel (p. 83) in a list of surgeons with exceptional surgical technique. He may also have perhaps baulked at a description of one of Martin Arrowsmith’s medical student chums “reading a Sherlock Holmes story which rested on the powerful volume of Osler’s Medicine which he considered himself to be reading” (p. 61; although Holmes’ creator was, of course, medically qualified and the Holmes oeuvre features some interesting medical material).9 Osler is mentioned elsewhere in *Arrowsmith* as the “god” (p. 82) of the professor of internal medicine and Dean of Arrowsmith’s medical school who is a “fit disciple of Osler” (p. 127), and his treatment of diphtheria is cited (p. 158). Lewis had been “fed inside knowledge” (p. 117) for the novel by the microbiologist Paul de Kruif (1890-1971), later to gain fame with his book *The Microbe Hunters* (1926),10 who is acknowledged at the start of the novel.

**Brush with Greatness**

The year was 1994, and I had just completed my stint in research in Creutzfeldt-Jakob disease (CJD) with Bob Will at the National Surveillance Unit in Edinburgh. Some of the work I had done with the team had been accepted for presentation at a joint ANZACANA conference in San Francisco. I set off proudly, clutching two posters, accompanied by one of the Neuropathologists from the unit – James Ironside. San Francisco was of course the base of Stanley Prusiner, who had proposed the “prion” hypothesis, as the explanation for some of the unique aspects of the spongiform encephalopathies. At the time the theory was still under scrutiny and the subject of much debate (although a few years later Prusiner was partially vindicated by the award of the Nobel prize in Medicine; the same mechanism is now thought to underlie many more possibly all? degenerative disorders affecting the brain associated with abnormal proteins, including (perhaps) Parkinson’s disease). It seemed appropriate that James and I should visit Prusiner in his laboratory, during our visit.

It smacked a little of paying homage, but we were excited by the prospect of meeting this controversial character, and it was simply too good an opportunity to miss.

The conference passed without event, and my posters were accorded the appropriate lack of interest they deserved. Undeterred, James and I set off for Parnassus Heights one October morning, to the UCSF campus there. Prusiner breezed in, a few minutes late, but was polite, genial and dully condescending. We had gone armed with more data from the unit. Variant CJD had not yet appeared, but James, Bob and others were already engaged in an intensive (and ultimately rewarding) surveillance exercise. We showed Prusiner the data we had been collecting, and he listened patiently to us, rather like a kind Montessori teacher. His time was clearly precious, and after half an hour, he indicated that our time was up by looking at his watch very deliberately.

We hastily concluded our chat, and got ready to leave. Prusiner, perhaps feeling a little sorry for us by then, started asking what we planned to do the rest of the day. The conference organizers had arranged various excursions after the meeting, one of which was a walking tour of San Francisco’s famed Chinatown. Our meeting with this famous scientist took a surreal turn at this point, when I explained that I was hoping to join this tour that afternoon. Prusiner responded by asking what time I needed to be at the airport. I looked at him curiously, but also with some bemusement. Did he not know that there was a Chinatown in his own City, and that you didn’t need to fly to get there? Was he really the great man...and, crucially, should he be a Nobel prize contender? It dawned on me that he had not understood my British-Sri Lankan accent, and thought that I was going to visit Chinah. More explanations followed, and we departed, flabbergasted.

Prusiner did receive the Nobel prize in 1997, and many more accolades followed. Our meeting with him took place at a heady time: the world was fascinated by these disorders and the potential impact of Bovine Spongiform Encephalopathy on humans. Neuroscientists too were intrigued by ‘prion’ biology, and the extent to which Prusiner’s theory account for our clinical and laboratory observations. It was a privilege meeting him, seemingly at the height of his career, that day, although from his perspective it was a considerably more pedestrian encounter, I suspect. However peculiar, what made the memory of that meeting indelible for me was a rather embarrassing misunderstanding – one which did make me query, however briefly, his brilliance!