The first intravenous anaesthetic: how well was it managed and its potential realized?

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Summary. Our speciality commonly traces its origin to a demonstration of the inhalation of ether by a patient undergoing surgery in Boston in 1846. Less well known is the demonstration of the i.v. injection of opium with alcohol into a dog in Oxford in 1656, leading to anaesthesia followed by full long-term recovery. After gaining i.v. access, a mixture of opium and alcohol was injected, resulting in a brief period of anaesthesia. After a period during which the dog was kept moving to assist recovery, a full recovery was made. Details from this momentous experiment allow us to compare the technique used with modern management. It is important to consider why there was a failure to translate the results into clinical practice and nearly 200 yr of potentially pain-free surgery. Possible factors include lack of equipment for i.v. access, lack of understanding of dose–response effects, and a climate of scientific discovery rather than clinical application. Given the current interest in total i.v. anaesthesia, it seems appropriate to identify its origins well before those of inhalation anaesthesia.

Keywords: anaesthesia; anaesthetic techniques; history; i.v.; TIVA

Background

Robert Boyle was a wealthy aristocrat who decided to set up in lodgings in central Oxford in the winter of 1655–6 in an area dense with apothecaries, providing resources for alchemical experimentation.1–4 He chose accommodation with John Crosse in Deep Hall at 88 High Street, now on the site of University College. Crosse appears to have combined business as an apothecary with that of providing lodgings, giving Boyle the opportunity to live and work on the same site, a location depicted in a recent painting by Rita Greer (Fig. 1),1 and often associated with experimentation with an ‘air’ (or rather vacuum) pump depicted in this painting.

Oliver Cromwell had taken the City of Oxford in 1646 after its period as Charles I’s centre of power. It is striking that, after the victorious Parliament’s purging of the academe in the late 1640s, Oxford in the 1650s soon became home to many of the individuals interested in the new forms of natural philosophy that were to lead to major advances in the experimental sciences in the three decades after 1650. No less significant was the tendency of these men to gather together in clubs for the purpose of conducting witnessed experiments and discussing results. The famous club centred around Wadham College was more interested in mathematics and mechanics, whereas the groups meeting at the various apothecaries favoured medical and chemical experimentation.5 6

Preceding research

In the mid-1650s, Boyle completed a piece entitled ‘An Essay of Turning Poisons into Medicines’, which was never published in full.7 His fascination included how much the ‘noxious efficacy’ of ‘some Indian Poysons’ depended upon the extent to which ‘the slight hurt made by the points of Arrows, infected with them, did open a capillary, or larger Vein’,8 and how the risk associated with vipers and spiders depended upon the mode of exposure. Pharmacodynamics and kinetics were seen to be in need of comparisons of oral and i.v. administrations of ‘Poysons’:

... we could wish Physicians were more diligent to make tryals of them, not onely by giving Beasts poysons at the mouth, but also by making external applications of them, especially in those parts where the Vessels that convey Blood more approach the surface of the Body, and also by dexterously wound- ing determinate Veins with Instruments dipt in Poysons (especially moist or liquid ones) that being carried by the circu- lated Blood to the Heart and Head, it may be found whether their strength be that way more uninfringed, and their operation more speedy (or otherwise differing) then if they were taken in at the mouth.8

The possibility of transport via ‘circulated Blood’, originating with Harvey, was first published in Latin 1628 and then in English in 1653. During Boyle’s only discussion with Harvey, which occurred shortly before he died in 1657, the topic...
was circulation of the blood. Although opium had been known for centuries to relieve pain and provide some surgical analgesia, Boyle focused on it as poison, perhaps because his interest was more chemical than medical, and because opium was known to kill: ‘we have more than once given to a Dog, without much harming him, such a quantity of Opium, as would probably have suffic’d to have kill’d several Men’. Several pages of his essay were dedicated to the question of how opium might best be formulated and prepared with alcohol to form various kinds of laudenum, some including saffron and vinegar.

**Date**

I.V. injections became widely trialled soon after our index case. A suggestion that it may have occurred as late as 1659 seems laid to rest by the correspondence noted by Frank and Jardine from Christopher Wren to William Petty in Ireland in June 1656, putting the injection of opium, wine, and ale all in the recent past. The constraint for the earliest date would appear to be Boyle’s move to Oxford leading soon to his conversation with John Wilkins and Christopher Wren at which Wren explained that ‘he thought he could easily contrive a way to convey any liquid poison immediately into the mass of blood’. Frank suggests a date of ‘about March 1656’.

**Location**

Boyle’s account does not directly locate the event, although the associated circumstances suggest that it took place in his lodgings at Deep Hall. The comments by Henry Stubbe in 1670, in a criticism of inaccuracies in a book praising the Royal Society published in 1668 by Joseph Glanvill, state ‘I saw my self in those days the Dog into whose veins there was injected a Solution of Opium, at the Lodgings of the Honourable Robert Boyle, of which he makes mention in his second discourse of the Usefulness of Natural Philosophy’. Stubbe is often thought of as an antagonist of the new science, yet here his desire to discredit the priority of the Royal Society causes him to champion the precedence of the interregnum clubs. Frank interprets Stubbe’s encounter with the dog as suggesting that he witnessed the injection of opium into a dog during or after 1658, when there was renewed activity of this kind. A more direct reading is that Stubbe saw the dog used in the original injection of opium in 1656, alive and well living in the locale where the injection took place.

Deep Hall itself was at that time a property owned by Christ Church, one of the Oxford colleges. The Hall contained seven chambers and two habitable garrets. Boyle may have lodged in the one which overlooked the garden, which may have later been used as a kind of ‘recovery area’. The building was demolished in 1809. The site of Deep Hall and its demolition are represented in Turner’s View of Oxford High Street.
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(1810) held at the Ashmolean Museum in Oxford (Supplementary Fig. S1). Although painted a century and a half after the events described, it shows immediately next to University College a gateway leading via the abutting lane to the garden well away from the Street,19 then the three-storey Deep Hall, with bay windows on the upper floor. The site is currently most clearly identified from the street by a plaque shown in Supplementary Figure S2.

Subject selection, preanaesthetic assessment, and preparation

Boyle provided a large dog. The need for a lean subject, to facilitate venous access, was clear from the report of 1665 attributed to Oldenburg in the first issue of Philosophical Transactions.20 A team approach was adopted: the 24-yr-old Wren was to be assisted by ‘some eminent Physicians, and other learned Men’ using the four corners of a table to fasten ‘very strongly’ the four feet of the dog. Equipment had been manufactured or acquired in advance. The basic requirements for an experiment involving vivisection of a dog were probably becoming well known at the time.

Boyle seems to have regarded dogs encountered accidentally as fair game for performing experiments. As he recalled of an experiment concerning poison,

I have been induced to suspect upon this Experiment; That dissecting some live Vipers, there came in accidentally a strange Dog, to whom I gave the Head, Tail, and Gall (which are the parts supposed to contain the Poison) of one of them, and the Head and Gall of another, wrapped up in meat; after which, I locked the little Dog up in my own Chamber, and watched him, but found not that he was sick, or offered to vomit at all, but onely lap’d up greedily some drink which he espyd in the Room; nor was he alone very jocund, for divers hours that I kept him in, but liked his entertainment so well, that he would afterwards, when he met me in the Street, leave those that kept him to fawn on and follow me.8

The account suggests a willingness to allow into his accommodation dogs belonging to others, as we note too for our index case.

The vivisection of dogs was well established by the 1650s. William Harvey had vivisected many animals, including dogs. Boyle’s friend and collaborator Nathaniel Highmore published accounts of vivisections using dogs too. There had been some famous experiments in Paris involving dogs carried out by Jean Pecquet. His Experimenta Nova Anatomica (Paris, 1651) was published in English as New Anatomical Experiments, 1653. The second and third chapters describe his vivisection of a ‘great hound’ and then a second dog. The French edition included a graphic illustration of one of Pecquet’s dogs, fastened down supine with its muzzle and legs bound. Pecquet was much discussed by English physicians and experimentalists in the early 1650s.21

In early 1650s Cambridge, the physician and don Matthew Robinson of St John’s College vivisected dogs in the chambers of interested senior academicians. His account is noteworthy: ‘he was invited by some learned persons in other colleges many years his senior to shew them vividisectons [sic] of dogs and suchlike creatures in their chambers, to whom he shewed the whole history of the circulation, the venae lacteae, the cutting of the recurrent veins in the neck with many experiments novel, to great satisfaction.’122

In 1656, Boyle asked the physician George Joyliffe to remove the spleen of a live dog in his presence, and reported how the dog survived the ordeal:

Dr Joyliffe ... did the last Year, at my request, take out the Spleen of a young Setting-dog I brought him: And that it might not be pretended, the Experiment was unfaithfully or favorably made, I did part of it myself, and held the Spleen (which was the largest in proportion to his Body that ever I saw) in my Hand, whilst he cut assunder the Vessels, reaching to it, that I might be sure there was not the least part of the Spleen left unextirpated, and yet this Puppy, in less then a Fortnight, grew not onely well, but as sportive and as wanton as before: which I need not take pains to make you believe, since you often saw him at your Mothers House, whence at length he was stol’n.21

This vivisection, however, took place in London, but it does suggest that dogs that had lived through such ordeals at the hands of the famous Boyle and his collaborators were seen as animals glamorous enough to be abducted. Indeed, the dog which received the i.v. opium and alcohol in Oxford in the same year suffered the same eventual fate.

I.V. access

I.V. access was by cut-down. Wren made an incision in the skin over large vessels, in a hind limb.8 A distal ligature was then applied to the vessels. A brass plate was used to immobilize the vein. This is described in detail: more than half an inch long and about one-quarter of an inch wide, with sides ‘bending inwards’; it was ‘almost of the shape and bigness of the Nail of a Mans Thumb, but somewhat longer’. It had four holes near the corners for fastening to the vessel by threads, and contained along most of its length a slit through which the ‘Vein’ could be incised with a lancet from the ‘Ligature towards the Heart, great enough to put in at it the slender Pipe of a Syringe’. Piston syringes had been known since Roman times; in the mid-17th century, they were commonly made from pewter and used for rectal administration, the ‘clyster’, not always having a ‘slender pipe’. An apothecary might have been expected to stock a range of sizes, including one suitable for penile irrigation with mercury for venereal disease. It is not known, however, what modification was required for this historic connection. It is noteworthy that the i.v. injection was achieved even though the invention of the syringe connected to a hollow needle suitable for passing through the skin did not occur until the mid-19th century.

Choice of induction agent

Opium had long been combined with alcohol as a ‘tincture of opium’ or ‘laudenam’, due to the better solubility of the active alkaloids in alcohol than in water. Boyle had prepared a ‘warm solution of Opium in Sack’, the latter usually referring to fortified white wine, such as sherry. Alcohol (ethanol) has been used for surgical anaesthesia in many
hundreds of patients. The first use in large numbers of cases was by the pioneering Mexican surgeon Marin as reported in his doctoral thesis in 1929. A later phase of enthusiasm occurred at a time when inhalation agents were seen as highly effective and safe but not suitable for certain procedures, such as heart surgery requiring a heart–lung machine. Interestingly, Mannheimer described the use of i.v. procedures, such as heart surgery requiring a heart–lung machine. Mannheimer described the use of i.v. agents in open heart surgery in 1971, commenting: ‘It is remarkable that in 1970, some 125 years after the discovery of anesthesia, the most advanced surgical procedures are being done with the aid of the two most ancient anesthetic agents known—a derivative of laudanum and alcohol’. I.V. ethanol had adverse sequelae, and total i.v. anaesthesia (TIVA) did not become widely used until the advent of propofol.

Course of the anaesthetic

Boyle recounts that the tincture ‘getting into the mass of Blood… was quickly, by the circular motion of That, carry’d to the Brain, and other parts of the Body. So that we had scarce unty’d the Dog… before the Opium began to disclose its Narcotick Quality, and almost as soon as he was upon his feet, he began to nod with his head, and faulter and reel in his pace, and presently after appear’d so stupifi’d, that there were Wagers offer’d his Life could not be sav’d’. The account suggests a brief period of anaesthesia. A complication was noted regarding the difficulty of avoiding the ‘shedding’ of blood.

Short- and long-term recovery

The motivation for trying to make sure that the dog recovered was that Boyle ‘was willing to reserve him for further observation’. Recovery was achieved by causing the dog ‘to be whipp’d up and down the Neighboring Garden, whereby being kept awake, and in motion, after some time he began to come to himself again’. The dog was ‘carefully tended, began to grow fat’, and was admired. This experiment and ‘some other tryals’ made the dog famous and long-term observation was limited by the dog being stolen from Boyle, an occurrence we have noted in relation to another of Boyle’s canine subjects. Nevertheless, a period sufficiently long for weight gain and further experiments presumably covered weeks if not months, so fairly long-term recovery was confirmed. It was during this period that Stubbe must have seen the celebrity.

Subsequent technical modifications

The brass plate was found not to be necessary if sufficient surgical dexterity with a finger was used to support the vessel to be opened. A quill was introduced, attached to a ‘bladder’ as ‘somewhat more convenient than a Syringe’. Boyle’s record implies one or more failures in dogs with too small a vein. The surgical challenge of venous access is emphasized by Samuel Pepys’ account in his diary of May 16, 1664, of watching the London surgeon Mr Pierce and injection-enthusiast physician Dr Clarke ‘fail mightily in hitting the vein, and in effect did not do the business after many trials; but with the little they got in, the dogg did presently fall asleep’. An eyewitness account by Thomas Willis first published in 1674–5, of a ‘transfusion’ of ‘about three ounces of the tincture of opium made very strong in Canary wine’ into a dog via the jugular vein appears likely to have arisen from his time with Wren in Oxford. It suggests reproducibility of the original experiment, albeit with a different route of venous access and a delay of ‘a quarter of an hour’ before the dog ‘began to be a little dozed’ and then ‘to fall asleep’ before making a full recovery.

Boyle developed an interest in emetics given i.v., with a dose–response to Crocus metallorum (oxysulphide of antimony, a strong emetic in common use) being obtained. This was the agent later settled upon for a human trial by Wren and Clarke in London reported to Boyle by a visiting foreign ambassador on ‘an inferior Domestic of his that deserv’d to have been hanged’, which luckily escaped completion of the experiment by fainting early in the proceedings.

Failure to translate basic research to clinical benefit

In the frantic atmosphere of experimental investigation, the new technique of injection encompassed not only poisons and their antidotes but also the possibilities of parenteral feeding, diuresis, anatomical tissue preservation, and blood transfusion. A human death from blood transfusion in France around 1667 led rapidly to cessation of attempts at i.v. therapy in patients. When injection of opium or morphine was eventually taken up, it was following the design of an effective syringe and needle by Alexander Wood in 1853, and then initially only via the subcutaneous route for claimed local analgesic effects and then more systemic effects.

So why was the possibility of TIVA with opium and alcohol not developed soon after 1656 for use in human surgery, to the potentially huge benefit of mankind in the two centuries before the introduction of inhalation anaesthesia with nitrous oxide and then ether? We discuss five main factors.

First, there was the challenging problem of venous access. The ‘cut-down’ was invasive and unreliable. The percutaneous cannula for anaesthesia that we now take for granted is a relatively recent luxury. Yet, there is evidence for early relative ease with venous access in humans. In Clysmatica nova of 1665, Elshaltz described many technically successful i.v. injections in dogs and humans. Surgeons familiar with opening veins with a lancet for bleeding patients modified the technique with careful pressure to prevent such bleeding so as to introduce the pipe of a silver syringe into the crural vein of the dog or the ‘inner branch of the crural vein’ or the ‘median vein’ of patients. A fascinating summary suggests relative ease of venous access in patients:

Indeed, the work can be carried out far more easily with human beings. For in dogs the skin must be first cut open and the veins freed from the membranes, which is a tedious task; and further, we are frequently disturbed during the operation by the...
An associated figure illustrating human leg and arm injections shows a three-handed approach using a syringe in what appears close to a percutaneous access.31

Secondly, there is the difficulty of titrating the dose of a drug to effect. Boyle's dog of 1656 appears only briefly to have been narcotized and 'stupified'. Willis had observed an equally, or more, successful experiment, with a defined dose, as noted above.29 By 1665, Elsholtz's detailed account of the consequences of injecting 'an ounce of liquid extractum opii' in a dog that was 'very strong and ferocious' is a model of careful observation and documentation of surgical anaesthesia over 2–3 h, then slow recovery over a further day and a half, and finally a return to the point where he became 'perfectly well'. No such record of surgical anaesthesia in a human from that period is known. With Elsholtz, as others, the preoccupation during human injections was with supposed therapeutic agents for conditions, including a leg ulcer, fever, and 'scorbutic impurity' leading to 'heaviness in the limbs'.32 The animal work suggests that empirical dosing in humans might have been possible, but priorities lay elsewhere.

Thirdly, the primary cause of death from opiate excess, namely ventilatory failure, appears not to have been identified, even though the means for countering it with artificial ventilation using a bellows and a tracheostomy were known to Galen, Vesalius, and Harvey.32 It is fascinating that Boyle's close associate Robert Hooke was so appalled by the suffering of a dog vivisected and undergoing artificial ventilation after thoracotomy in Gresham College in 1664 that he entertained the possibility of improving experimental conditions with opium:

I shall hardly be induc'd to make any further trials of this kind because of the torture of the creature but certainly the inquiry would be very noble if we could any way find a way soe to stupify the creature as that it might not be sensible which I fear there is hardly any opiate will performe.33

Hooke deserves credit for proposing a practical union between narcosis and surgery, even though he then doubted the practicality of it. It is ironic in this connection to consider the argument that Hooke's later journals suggest, as Jardine has discussed in her essay in London's Leonardo, that he later became an obsessive self-doper.34 The Royal Society at large also experimented with 'bangue' or cannabis, which was appreciated for its medical (narcotic, but not surgical) use in some eastern cultures. What a tragedy it was, for both dogs and humans, that extent skills of i.v. anaesthesia were not combined with surgery and artificial ventilation to relieve the suffering of the subjects and the distress of the operators.

Fourthly, it is also important to recognize that the search for mechanical and chemical explanations for aspects of human physiology was not in itself a project its practitioners needed immediately to associate with the business of curing illness. Of course, practical applications might soon have suggested themselves, but the dangers attending upon such invasive experiments were impressed upon both the experimentalists and their observers following the first blood transfusions. Transfusion was initially carried out from the carotid artery of one live dog into the jugular vein of another by Richard Lower in Oxford in 1665; the Parisian Jean-Baptiste Denis then successfully transfused blood from a sheep to two humans in 1667. Later in the year, Lower and Edmund King successfully transfused sheep blood into a human too. It had taken the experimentalists some time not only to find a willing subject but also to overcome some serious ethical objections from within and outside the experimentalist community.35 The next year a subject died in France, and the practice was soon banned in both countries. Transfusion and narcosis are medically distinct, but it is not hard to see that the notion of passing foreign liquids directly into the blood stream was increasingly seen as too dangerous to be attempted on human subjects. There were also growing concerns in the 1660s and 1670s that the new experimentalists were at best wasting time, and at worse engaged in impiety. In 1669, in his oration to mark the opening of the new Sheldonian Theatre, Robert South, public orator of the University of Oxford, denounced the Royal Society of London.36 There were still many doubts about the new science within and outside the academe. Experimenting on live humans may well have struck even the scientifically active as ethically, even religiously, problematic.

Finally, we need to consider that at that time the very concept of anaesthesia, despite Hooke's tantalizing thought about relieving the pain of vivisection using an opiate, was remote. We now take for granted a state of surgical anaesthesia. Although Elsholtz described in detail using increasingly painful needle pricks to the tongue and hind foot of a dog showing a degree of surgical anaesthesia,37 there is little evidence of a wide appreciation that Boyle's 'narcotick' effect of opium could coexist with a state in which dogs or humans might tolerate surgery. The experimenters were hugely busy men in the thick of advancing knowledge over a very wide range: chemistry, physiology, microscopy, mechanics, astronomy, and architecture. In reflecting on this period, it is interesting to ask whether the current emphasis on 'translational medicine' speeds progress in medicine, or tends to distract from the basic science via which medicine ultimately benefits.
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