

Early Intravenous Anesthesia: An Eyewitness Account

Norman A. Bergman, M.D.*

Descriptions of the earliest iv injections of various substances by individuals who actually witnessed the experiments in 1656 are presented. Of particular interest is an apparently overlooked account of an experiment in which opium was administered intravenously to a dog many years before 1674 as related by the physician and anatomist Thomas Willis. He does not identify the precise date nor the experimenters. However, at the time of this event Willis would have been at Oxford. There he was a very close professional associate of Christopher Wren who originated the practice of iv injection. These eyewitness accounts are worthy of note because the articles usually cited to establish Wren as the first individual to administer a drug intravenously were not written by anyone who actually observed the experiments.

THE EARLIEST IV ADMINISTRATIONS of substances were performed at Oxford University about 1656 and were attributed to Christopher Wren (1632-1723). He injected opium and other substances into dogs. These experiments were designed to help answer some questions that had arisen as a consequence of publication of William Harvey's work on the circulation in 1628.¹ Wren and his associates were interested in such problems as whether substances, even when unmodified by gastrointestinal digestion, could be carried by the circulation to tissues and still exert their characteristic effects and also whether circulatory transport was responsible for such phenomena as the remarkably rapid collapse following bites by venomous snakes. Many subsequent authors who have had occasion to refer to these historic earliest injections have cited two articles in "Philosophical Transactions of the Royal Society" in which the experiments were described.²⁻⁴ However, these communications were written neither by Wren nor by any other individual who witnessed the original experiments.

The first such article appeared in 1665-1666 and was anonymous.⁵ It has been attributed to Henry Oldenburg on the basis of information in the second communication that appeared in 1668. This second article was written by the "Learned and Experienced" Dr. Timothy Clarck and published in Latin.⁶

Henry Oldenburg (1617-1677) was one of the secretaries of the Royal Society. He was not formally educated

in science but became knowledgeable through years of association with many prominent scientific workers. He is remembered for scientific writing, administration, and editing. Correspondence to him, his book reviews, and his accounts of scientific proceedings appeared frequently in "Philosophical Transactions."⁷ Oldenburg was at Oxford for a brief time in 1656-57, but he was not listed among those who witnessed the original experiments on iv injections.⁸

The anonymous 1665-1666 article (attributed to Oldenburg) indicated that there were several reports from foreign countries of attempts to convey liquors into the blood. One purpose of this anonymous article was probably to establish English precedence for iv injection. The real originator of this practice was identified as Christopher Wren who had done this at least 6 yr earlier and who had demonstrated his technique to Robert Boyle and others at Oxford. Oldenburg related some of Wren's ideas on iv medication:

"... he thought, he could easily contrive a way to convey any liquid thing immediately to the mass of blood; videl: by making ligatures on the veins and then opening them on the side of the ligature towards the heart, and by putting into them slender syringes or quills, fastened to bladders (in the manner of clyster-pipes) containing the matter to be injected; performing that operation on pretty big and lean dogges, that the vessels might be large enough and easily accessible."

Dogs given opium were temporarily stupefied but survived. Dogs given an infusion of crocus metallorum, impure antimony sulfoxide used as an emetic in the 17th Century, vomited and died. An account of similar administration of a small quantity of crocus metallorum by iv infusion to a human malefactor with survival was related. Injection experiments were said to have been repeated frequently since that time. Another use suggested for iv injection was to prepare specimens for anatomical dissection.

In the second "Philosophical Transactions" article, Timothy Clarck (or Clarke) (1620-1672) related that Christopher Wren was the first to infuse various liquors into the mass of blood of living animals.⁶ Clarck was in London in 1656 and did not learn of the injection experiments nor begin his own extensive iv infusion trials until discussions with Wren in London during the following year.⁸

There are accounts of the earliest iv injection trials written by individuals known to have participated in or

* Professor of Anesthesiology.

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Address reprint requests to Dr. Bergman: Department of Anesthesiology, Oregon Health Sciences University, 3181 S.W. Sam Jackson Park Road, Portland, Oregon 97201.

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witnessed these events personally. Wren described them to a former Oxford colleague, William Petty, in a letter most likely written in 1656 but which remained unpublished until 1973.⁹

"—But the most considerable [Experiment] I have made of late is this. I have Injected Wine and Ale in a liveing (sic) Dog into the Mass of Blood by a Veine, in good Quantities, till I have made him extremely drunk, but soon after he Pisseth it out: with 2 ounces of Infusion of Crocus Metall: thus injected, the Dog immediately fell a Vomiting & so vomited till he died. It will be too long to tell you the Effects of Opium, Scammony† and other things that I have tried this way: I am now in further pursuit of the Experiment, which I take to be of great concernment, and what will give great light both to the Theory and Practice of Physic."

A further description of these activities and a confirmation of Wren's priority for iv injection is provided in the collected correspondence of Robert Boyle, another known observer of the earliest experiments.⁹

"The inventor (Wren) of it (injection) afterwise practised it in the presence of that most learned noble man, the Marquis of Dorchester, and found, that a moderate dose of the infusion 'crocus metallorum' did not much move the dog, to whom it was given: but once that he injected a large dose (about two ounces or more) it wrought so soon, and so violently upon a fresh one, that within a few hours after, he vomited up life and all, upon the straw, whereon they had laid him."

There exists yet another eyewitness account of such an experiment that seems to have been overlooked. Thomas Willis, renowned anatomist and physician, writing in 1674–1675, related that years previously he had witnessed iv administration of opium to a dog:¹⁰

"Many years ago I saw about three ounces of the tincture of opium, made very strong in Canary wine, and transfused into the jugular vein of a live dog. When his vein was closed, the dog ran about as he used to do, seeming to be little or not affected with it: but after a quarter of an hour, he began to be a little dozed to nod his head and at last to fall asleep: but we having no mind he should do when we had hindered him for some time of it by beating, threatening him, and trying to make him run, at last by that means his sleepy inclination was quite off of him, and he became very sound and lively."

Thomas Willis (1621–1675) was educated at Oxford University and was a member of the brilliant scientific circle at Oxford in the 1650s. Members of this group included Robert Boyle, Thomas Millington, Robert Hooke, Richard Lower, John Mayow, and others. The scientific association between Willis and Christopher Wren at Oxford was particularly close. Wren produced a magnificent series of drawings to illustrate the text of Willis's book "*Cerebri Anatome*" published in 1664. In this volume, which remained a definitive textbook of neuroanatomy over 2 centuries, the vascular anastomotic vessels

at the base of the brain were described and their function correctly explained. These structures still retain the name "Circle of Willis." Wren also assisted in some of the vascular injection experiments designed to clarify the structure of the cerebral circulation.¹¹

Willis was appointed Sedleian Professor of Natural Philosophy at Oxford University upon restoration of the monarchy following the English civil war in 1660. This was partly as a reward for his unswerving loyalty and service to the Royalist cause. In 1667 he moved to London where he established a thriving medical practice.

The above quoted account by Willis of an injection experiment at Oxford appeared in his last book, the "*Pharmaceutice Rationalis*", first published in 1674–1675. The particular experiment described may not have been the first such trial and neither the date on which the event occurred nor the identity of the investigator can be established from Willis's account. Nevertheless the quotation is eyewitness testimony by an individual who was a close professional associate of Wren and who was certainly at Oxford in 1656, further confirming that such activities did indeed occur. This account by Willis and the mental picture of the experiment elicited in the reader seem to convey some of the excitement and enthusiasm that must have been experienced daily by the Oxford group of natural philosophers working at the beginning of the modern scientific era.

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† Scammony—material obtained from the plant *Convolvulus scammonia*, usually the dried root, and used as a purgative in the 17th Century.