Animal testing in the history of anesthesia: Now and then, some stories, some facts

Arthur Guedel called him "Airway"
Dr. Hasnain calls her "Morphine"
I call mine "Magic"

The dog is man's best friend. There are many interesting anecdotes, serendipitous stories and mesmerizing details about how dogs have been loved, named and tested by many anesthesiologists, in the past and present. However, the contribution of experiments on animals such as rabbit, monkey, mice, guinea pigs etc., also played a significant role in the evolution of both general and regional anesthesia. Some facts and intriguing stories from the history of anesthesia have been put together though not chronologically, in this report to make an interesting subject of reading.

Arthur Guedel first successfully demonstrated the safety of a cuffed tracheal tube in 1926 on his dog that he affectionately called "airway."[1] In his famous "dunked dog" demonstration at a medical convention, Guedel submerged his dog in an aquarium after anesthetizing him with an ethylene-oxygen mixture via a cuffed tracheal tube. A to-and-fro circuit with soda lime absorption system was used to provide positive pressure ventilation underwater by his fellow anesthesiologist and friend, Ralph Waters. Guedel wanted to show that if his cuffed tube could prevent the dog from drowning in water, it could also effectively protect the trachea from aspiration of water. The dog was crowned "airway" and since then, airway and anesthesia are almost synonymous.

Andreas Vesalius used bellows to resuscitate an asphyxiated dog in the 16th century. Robert Hook also performed the demonstration of artificial respiration in 1678 on a dog that had an open chest, but was kept alive by attaching rhythmically contracting bellows to its trachea. By exposing fresh air with oxygen to the circulating blood, he proved that the chest movements are not the fundamentals of respiration.[2]

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In 1884, Carl Koller applied a suspension of cocaine crystals to the eyes of a dog in his laboratory and noticed that it made the corneas totally numb, even to pin prick. Koller was so convinced that he tried the same on his own eyes and finally used the local anesthetic properties of the drug for superficial ophthalmic surgery.[3]

In 1885, Corning injected cocaine to a dog and noticed that he fell down because of the weakness of his hind legs.[4] He was actually experimenting on some neurological problem when he accidently punctured the dog's dura mater. He witnessed a motor block in the hind legs and noticed that it reversed in some time on its own. Theodore Tuffier in 1900 and later in 1915, Smith and Porter demonstrated sympatholysis associated with spinal anesthesia on dogs and cats.[5]

During World War II, it is said that the Jews mysteriously sneaked out of Germany in boats after duping the Nazi dogs.[6] The captains dipped handkerchiefs in rabbit's blood and sprinkled cocaine on them. The ferocious search dogs came for the smell of blood and sniffed the cocaine. This numbed their strong sense of smell and gave them a high so that they lost their focus for some time.

An interesting anecdote is related to the introduction of halothane into clinical practice. In 1955, Bull, an eminent anesthesiologist, who was then working in the Nuffield Department of Anesthetics at the University of Oxford, received a sample of a secret new anesthetic agent for trial in dogs.[7] The agent had not been named then even by its inventor, Raventos, and the "nondescript little bottle" was labeled nonexplosive agent (NEA). A number of nylon bags were filled with 1-5% concentrations of this NEA and several dogs were anesthetized using a low resistance one-way valve. Dr. Bull noted that NEA had superb handling characteristics and provided both a smooth induction and a steady maintenance in dogs. These trials of NEA on dogs significantly led to the clinical use of the most popular inhaled anesthetic in the history of anesthesia-halothane. As Professor Bull mentions "compared with the elaborate protocols that surround the acceptance of any new drug today, the introduction of what was for years the most popular inhalational anesthetic was unbelievably simple."

Nearly 500 years ago in South America, an arrow poison, later called curare was used to kill the game by progressive paralysis of the motor nerves from periphery to the center. However, in 1814, Brodie and Waterton injected curare to a donkey and demonstrated that it could only be kept alive if artificial respiration was given along with (the lungs

were inflated with a pair of bellows). The drug was called woorara and the donkey, Wouralia. He nurtured the donkey for 25 years on his estate and used the drug to treat tetanus and rabies.[4]

January 1976, Farber's investigation published in "The Times" about the suspicious deaths of 40 patients at River dell Hospital in Oradell Bergen County, New Jersey by an unidentified surgeon "Dr. X" created a media stir in the country.[8] Eighteen empty vials of curare were found in the locker of Dr. X, each of which had the potency to kill a man if not supported with artificial respiration. Dr. X was Mario Enrique Jascalevich, the chief surgeon at that hospital who in his statement declared that he used curare for experiments on dying dogs. Though there was no evidence of any dogs been supplied to him for this purpose, jurors acquitted Dr. X in 1978.

Pal discovered the drug to reverse the effects of curare in Vienna in 1900, decades before it came into clinical practice as a muscle relaxant during surgical anesthesia in 1942. While studying the physiology of the gut, Pal injected physostigmine to a dog that was already paralyzed with curare. To his surprise, the dog started breathing spontaneously, and the idea of reversal of the effects of neuromuscular drugs was conceived.[9]

Liver is not only the most important organ for drug metabolism (pharmacokinetics) but also gets affected by various drugs or their metabolites. Thus, the prediction of the human pharmacokinetics is an important tool when new drugs are developed so that their adverse reactions and toxicity may be known and/or avoided. Animal data have suggested certain significant paths in this direction, but its extrapolation may not be accurate and, therefore, chimeric mice with humanized liver have been used to predict human drug metabolism and drug-drug interaction.[10]

Several researchers studied anesthesia induced neuronal cell death or apoptosis on neonatal rodents and nonhuman primates. Following convincing evidence in animals, multi-centric human studies are now underway to test long-term neurocognitive outcomes in children after exposure to anesthesia.[11,12] Animal contribution is boundless, but the scope of this article is too small to acknowledge them all.

Some considered it as a contribution to scientific discoveries while the others accused it as cruelty to animals. Animal experiments have contributed immensely towards scientific progression, but it cannot be denied that they have not been totally either judicious or legal every time. Overzealous and irrational animal testing was not unknown until 1822, when the first law for animal protection was passed in the British Parliament, followed by the 1876 Cruelty to Animals Act. American Society for the Prevention of Cruelty to Animals (PCA) was formed in 1860s, and the boundaries between acceptable and illegal animal experiments began to be examined. A lot of arguments were exchanged between the pro (vivisectionists) and anti-animal testing (antivivisectionists) lobbies for many years. However, the fast development of medical science as well as the pharmaceutical industry did not stop on the grounds of misinterpreted and exaggerated accusations of animal exploitation. Claude Bernard, the prince of vivisectors and the father of physiology, finally established animal experimentation as part of the standard scientific methods.[13]

In 1966, the Laboratory Animal Welfare Act finally had a more focused approach towards animal protection and judicious use of animals for medical testing. At present, the Office of Laboratory Animal Welfare enforces the standards of the "Guide for the Care and Use of Laboratory Animals" in USA. Since 2010, the European Union follows the "directive 2010/63/EU" on the protection of animals.[14,15]

In India, the PCA Act, 1960 (amended in 1982), was made to prevent the infliction of unnecessary pain or suffering on animals. A Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) was formed by the Central Government to ensure the same. Every individual/institution is required to seek prior permission from CPCSEA for carrying out every animal experiment according to a notification published in Extraordinary Gazette of India (September 8, 1998). The government has further made "Breeding of and Experiments on Animals (Control and Supervision) rules, 1998" (amended during 2001 and 2006) to regulate the experimentation on animals. These rules prevent the indiscriminate use of animals for teaching, acquiring the surgical skills or for repeating a known fact.[16,17]

Modern scientific research sans animal testing would probably be incomplete and unthinkable. However, it is pertinent not to forget that all efforts should always be thoughtful, well-judged and lawful. The immeasurable contribution of animal research to the science of anesthesiology must be truly acknowledged.

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Rakhee Goyal

Department of Anesthesia and Critical Care,
Armed Forces Medical College and Command Hospital (SC),
Pune, Maharashtra, India

Address for correspondence: Dr. Rakhee Goyal,
NP-5 MH, CTC, Pune - 410 040, Maharashtra, India.
E-mail: rakheegoyalkumar@icloud.com

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