Historical Perspectives

CHAPTER 1

KEY TAKEAWAYS

Seizures were likely one of the first recognized ailments observed by early humans to affect themselves and animals.

Throughout the ancient world, the care of domesticated animals developed at roughly the same time.

The development of human medicine and veterinary medicine started off on parallel tracts, diverged, and once again are closely tried together.

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Myelominutia: All domesticated cats today can trace their genealogical origin to *Felis silvestris lybica*, the African wildcat, originally native to the Middle East—still roaming around today—pretty much everywhere and looking like house cats.

PREHISTORIC AND ANCIENT OBSERVATION

The first ancient humans who witnessed an animal having a seizure were probably as "wide eyed," surprised, and scared as people are today. That first observed seizure likely corresponds to the beginning of the human/animal relationship. The very first human/animal relationship originated at a point in our history, where we as a species started to feed off the leftover scraps of organized packs of wild dogs. Thus began a relationship with canines, most likely around the time, we decided to supplement our diet with more than what Mother Nature would provide. We became hunter-gatherers rather than just gatherers. At some point in human history, we started to spend more time observing animals in their natural environment, learning *from* them (e.g., how they hunted, social interactions, etc.) as opposed to just killing them for food (Figure 1.1). Considering the fact dogs were the earliest purposeful cohabitants of humans, early domesticated dogs were perhaps the first animals (other than our own species) humans witnessed to have a seizure. Ancient humans were well on their way toward higher cognitive abilities, which allowed them to associate the characteristics of a convulsing wolf/dog as comparable to those of a human exhibiting similar signs. Considering the genetic predisposition to have seizures in both species, epileptic seizures secondary to brain injury may have been observed as commonly as spontaneous seizures.

Seizures in Dogs and Cats, Second Edition. Sean Sanders.

Companion website: www.wiley.com/go/sanders/seizures2e

FIGURE 1.1 Some of the first observations by humans of canines having seizures may have occurred while watching wild dogs hunt. While the incidence of epileptic seizures in dogs is similar to humans, seizures secondary to head trauma were most likely witnessed during these early observations. Heinrich Harder (1858–1935) / Wikimedia Commons / Public Domain.

Traumatic brain injury to either a human or a dog would probably account for some of the first observed occurrences of seizures. Seizures and epilepsy have undoubtedly been part of our species from the very bottom of the evolutionary tree. Historically, epileptic seizures are one of the oldest described afflictions of humans. As early man would recognize a cut on their finger as similar to a cut on an animal's digit, so too would they recognize the similarities in symptoms associated with a convulsion, fit, or seizure among humans, dogs, and cats.

It is estimated the natural occurrence of seizures in dogs is similar to that of humans (about 0.5 to ~1% of the population), whereas in cats, seizures may be less common or more common in the population compared to dogs depending on which reference you read (Berendt *et al*., 2004; Schriefl *et al*., 2008; Heske *et al*., 2014; O'Neill *et al*., 2020). Regardless of the percentage in the population, epileptic seizures are the most common neurological condition a veterinarian will encounter. Observation of the first cat having a seizure would most likely to have occurred following head trauma inflicted on a wild cat by another animal or man or with the domestication of cats, as opposed to natural observation, since they tend to have more reclusive lives. The earliest *recorded* history of animal observation dates to approximately 51,200 years ago, when the Neanderthals painted images of animals on cave walls in what is now modern-day Indonesia (Figure 1.2). The earliest recorded history of animal/human *cohabitation* dates back to Cro-Magnon humans (early *Homo sapiens*) at around 20,000–15,000 BP, when humans started to dabble in agriculture and the domestication of animals, which naturally came with it. It is suspected, however, that humans and animals coexisted together thousands of years prior to 15,000–20,000 BP. The discovery of a child's footprint along with that of a large dog in the Chauvet Cave of southern France suggests humans and dogs (wolf/dogs) coexisted as early as 26,000 BP (Garcia, 2005). Humans and dogs began hunting together around 12,000 BP. This time also coincides with the development of early civilizations, further strengthened by the domestication of livestock, namely, sheep and goats (Wilkinson, 1992).

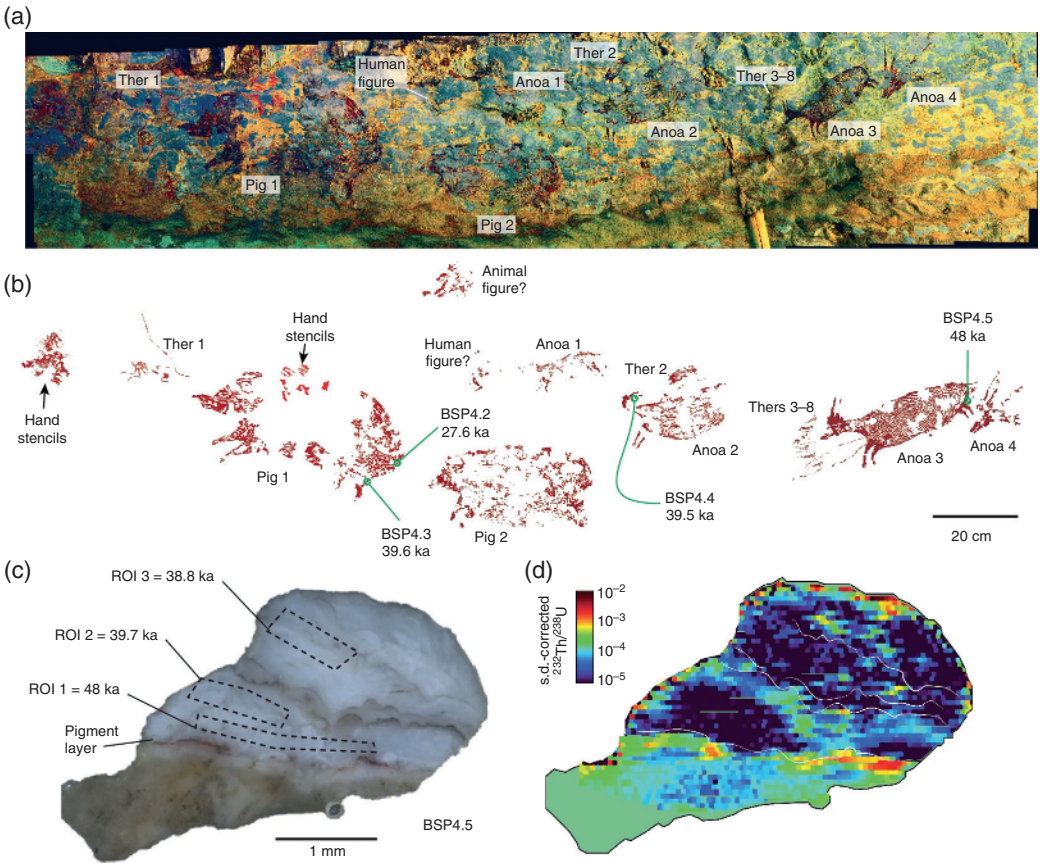


FIGURE 1.2 Cave painting at Leang Karampuang, Indonesia, is the current oldest known cave painting of animals. In the painting, three humans are shown interacting with a wild pig. Dated to 51,200 years ago. (a) Photo-stitched panorama of the rock art. (b) Tracing of the dated rock art panel showing the results of LA-U-series dating. (c) Transect view of the rock art sample BSP4.5 after removal from the artwork, highlighting the paint layer and the three integration zones (ROIs) and associated age calculations. (d) LA-MC-ICP-MS imaging of the BSP4.5 $^{232}Th/^{238}U$ isotopic activity ratio. From: Oktaviana, A.A., Joannes-Boyau, R., Hakim, B. et al. Narrative cave art in Indonesia by 51,200 years ago/Springer Nature/ CC BY 4.0 Adhi Agus Oktaviana et al., (2024) / Springer Nature / CC BY 4.0

The domestication of cats is thought to follow dogs by several thousand years. The contribution of cats to the survival of humans is a little more ... nuanced. They certainly benefit our emotional well-being, and one could argue they help to prevent the spread of infectious disease by annoying the rodents in our lives. The domestication of the cat was purely for companionship and maybe to keep early habitations pest free. Truth be told, cats pretty much *domesticated us*. And to add to that, they really do not need us to survive in the wild. The common house mouse moved in with humans once we figured out *shelter*, to feed off spilled grains and other food, and cats being obligate carnivores followed the mice. All domestic cats originate from a common ancestor, the European wildcat, *F. silvestris lybica*, native to the Middle East (look it up, these cats still look pretty much like house cats). Originally, it was thought the Egyptians were the first to live among cats; then, it was thought to be the ancient people of what is today modern-day China. Current evidence for the cohabitation of humans and cats points to the Middle East at a time of roughly 10,000 years

ago, based on a burial site on the island of Cyprus, where a human and a cat were buried together. Cats are not native to Cyprus, so it is hypothesized, they traveled to the island by boat (with people) from the Middle East (Driscoll *et al.*, 2009).

With the development of a relationship centered on cohabitation, humans were now applying their knowledge of "self" to other species. The earliest development of medicine would have little distinction between that practiced on other humans and that practiced on animals. The origins of comparative medicine likely began with animal sacrifice, as those doing the sacrificing were the earliest vivisectionists and often local healers. Humans would easily be able to make the connection between similar medical conditions, such as a vomiting dog being very comparable to a vomiting human. Unless a medical condition was the result of a known trauma, most afflictions were thought to be due to a combination of mystical or magical sources. Demonic possession by many cultures was the foundation of early medicine, although this was shadowed by the development of religious explanations for "disease." The application of medical knowledge between species was in parallel and often applied to each species by the same "medical" (often religious) practitioner. Our understanding of prehistoric medicine is deduced from the first *recorded* history on the planet.

EARLY CIVILIZATION

While we do not think of epilepsy today as a disease per se, historically, it was regarded as one of the earliest recognized afflictions of humans. It has been described in ancient Mesopotamian, Babylonian, Indian, Egyptian, and Chinese civilizations. The earliest description of epilepsy in humans dates back to about 6000 years ago (4000 BP) in a Babylonian text describing epileptic psychoses. The *magico-mystical* or *magico-religious* notion that seizures (and most diseases in general) occurred through possession of an individual by spirits or punishment of an individual by the gods for evil doing arose in ancient Mesopotamia. The earliest *documented* recorded history of human observation of animals dates roughly to 4500–3750 BP in ancient China. According to myth, Fuxi, the god who created humanity along with his wife, Nuwa, taught humans how to domesticate animals, so they would not have to spend so much time hunting them and then how to take care of them using acupuncture, medicinal herbs, various procedures, and incantations. Similar development of the care of animals would follow in Mesopotamia (modern-day Iraq) and the Asian subcontinent (modern-day India).

Further descriptions of seizures were made around 1000 BP within a Babylonian text on diagnostic medicine known as the *Sakikku* (meaning "all diseases") (Reynolds and Kinnier Wilson, 2008). The Mesopotamian word *antašubbû* is commonly referred to as "the falling disease" or "the hand of sin," which was brought about by the god of the moon and the notion that it was a manifestation of the possession by evil spirits (i.e., "lunatic" from *lūnāris*, Latin for "cresent-shaped") (Labat, 1951). The Ayurvedic medical texts describe the oldest known medical system, developed in ancient India between 4500 and 1500 BP, and within the *Charaka Samhita*, dated at around 450 BP, is a description of a condition labeled as "apasmara" (meaning "loss of consciousness") (Magiorkinis and Diamantis, 2011). In contrast to other civilizations, the ancient people of present-day India did not think of disease from a magico-religious stance; rather, they believed the cause of seizures was due to physiological and physiochemical disorders of the body. Rather than praying to the gods or visiting temples, they took a more practical and proto-scientific approach to treat the condition through altering etiological factors, diet changes, and lifestyle changes, which allowed those afflicted with the condition to have better management of their seizures (Manyam, 1992).

References to rabies in animals can be found as early as 2000 BP in the *Codex of Eshnunna*. These collections of laws inscribed on two cuneiform tablets are similar to the *Laws of Hammurabi*, which are also of the early Mesopotamian origin. The laws specifically refer to the penalties

one might face if a rabid dog they owned was to bite a person. Certainly, we can infer if rabies was being observed in dogs, then seizures were being observed in dogs.

With specific reference to animal disease, the earliest written description may come from the veterinary papyrus of Kahun. By this time, domestication of the dog, including selective breeding for various traits, was well underway (Figure 1.3). This document produced in ancient Egypt at around 1900 BP contains the oldest known veterinary writings outside the Ayurvedic texts. Within the Kahun papyrus is a specific passage, which *could be* (note: extreme emphasis on "could be") interpreted as the description of a dog having a seizure or collapse:

FIGURE 1.3 (a) Egyptian depictions of various domesticated dogs painted by Guiseppe Angelelli, Gaetano Rosellini, Salvador Cherubini, and Ippolito Rosellini and engraved by Carlo Lasinio; Pisa, Italy. From: The New York Public Library / https://digitalcollections.nypl.org/items/510d47d9-47cb-a3d9-e040-e00a18064a99 / Last accesed on May 26, 2025 . (b) The Veterinary Papyrus of Kahun was produced during the Middle Kingdom of Egypt ca. 1825 BP. Flinders Petrie discovered the fragments in 1889. With thanks to the Petrie Museum of Egyptian Archaeology, UCL. University College London UC32037/Wikipedia/CC BY SA 4.0.

> *. . . if when it courses (?) scenting (?) the ground, it falls down, it should be said "mysterious prostration as to it." When the incantations have been said, I should thrust my hand within its hemu, a henu of water at my side. When the hand of a man reaches to wash the bone of its back, the man should wash his hand in this henu of water each time that the hand becomes gummed (?) until thou hast drawn forth the heat-dried blood, or anything else or the hesa (?). Thou wilt know that he is cured on the coming of the hesa.*

Of course, much can be said about the *interpretation* of the passage (focusing on the phrase "it falls down"); however, similar behaviors observed in humans would have been applied to those observed in animals, especially, the domesticated animals, for which humans interacted with the most. There is no ancient Egyptian word for "veterinarian"; therefore, it is presumed ancient Egyptian physicians treated both humans and animals (Gordon and Schwabe, 2004).

Shalihotra (ca. 2350 BP), one of the earliest Ayurvedic *veterinary* practitioners, focused on the anatomy, physiology, surgery, and diseases of horses and elephants in the *Shalihotra Samhita* text (Singh and Chauhan, 2001). He is considered the "Father of Veterinary Medicine." An important distinction should be made. Even at this time in ancient India, similar to ancient Egypt, those who provided medical service to animals and humans were the same individuals. The division between the practice of veterinary medicine and human medicine is fairly vague, and its definition was dependent on where one lived and to which specific culture they belonged. For the most part up to the *Renaissance*, there was no division between the medical treatment of humans and animals. Because many afflictions were thought to be due to possession of the body by evil spirits or the punishment from angry gods, mystics, or members of the religious orders often performed the "treatments." Medicines (loosely speaking) used to treat humans and animals were often identical or very similar.

In the late 6th century BP, a switch started to occur from the traditional mythological and theological explanations of the world to one more grounded on pure reason. The birthplace of natural science and philosophy (in a Western sense) was the city of Miletus, which was a Greek city at the time and is now on the Aegean coast of modern-day Turkey. Here, what came to be known as the *Milesian philosophy* started as an attempt to explain the physical universe through observation, reason, and the beginning of the ancient scientific method. *Hippocrates* (ca. 400 BP) was the first to link epilepsy to the brain and the potential for a hereditary basis of the disease. He also noted that the prognosis associated with epileptic seizures was worse the earlier it was seen in life and that it could often be brought on by head injuries. Additionally, we can attribute the term *grand mal* to Hippocrates, who called epilepsy "the great sickness." *Dioscorides* (AD 40–90) was one of the first individuals documented to prescribe medications based on observed properties of certain herbal remedies to help with epileptic seizures. He used *mugwort* (*Artemisia vulgaris*) or ragweed to treat epileptic seizures (Chapter 9). The first classification scheme of the epilepsies is attributed to *Galen* (AD 131–201), who derived the system of idiopathic (primary disorder of the brain), secondary epilepsy due to abnormalities of cardiac flow to the brain, and a third type due to a disorder of another part of the body that is secondarily transmitted to the brain.

THE MIDDLE AGES

Just when it looked like that humans were starting to get a head start on science, the *Dark Ages* came with the fall of the Roman Empire, and the figurative *pause button* was pressed on science. In Medieval times (ca. AD 6th century to 13th century), mysticism, religious fanaticism, and dogmatism were the common themes in all aspects of life, including science. Humans went from treating epilepsy with empirical results derived from herbs to exorcism and trephination to *rid the body of demonic possession*. How animals who experienced seizures in these times were treated remains unknown; however, because it was thought animals could be possessed by demons, we

would assume the same "sorcerer, magician, priest, or alchemist" would be called upon to cure the animal of seizures (if the animal was considered valuable enough). Diseases such as rabies and the plague were present in many civilizations, and to a significant degree, the *value* of animals was more related to their ability to provide food, fiber, and work as opposed to companionship. People were having a hard time taking care of themselves, let alone their animals. Farriers, around the time of the beginning of the Middle Ages, were the first professionals to focus their attention on the health of animals. Toward the end of the Middle Ages and the beginning of the Renaissance, farriers in London were organized with the goal of providing better care to horses. This organization is thought to be the beginning of modern veterinary medicine.

THE RENAISSANCE

The Renaissance marked the beginning of the end of the notion that epileptic seizures were brought on by demonic possession, evil spirits, or bad luck. Advances in anatomy, physiology, and pathophysiology led to the connection between symptomology correlated with pathophysiology and anatomy. Additionally, a distinction began to arise between the medical treatment of humans and animals. *Gaston de Foix* wrote about the sickness and care of dogs in *Livre de la Chasse* (translated to *Book of the Hunt*) between AD 1387 and AD 1390. He described many common maladies of dogs and how to treat them, including mange, broken bones, neovascularization of the cornea, and the various forms of rabies (Figure 1.4). His description of disease and its treatment in dogs is rational and based chiefly on observation utilizing common remedies at the time, such as valerian and other herbs (Chapter 9). Of special note is the lack of superstition or any reference to a magico-religious cause for disease. It is also apparent ole' Gaston cared deeply for the dogs he wrote about. The original book was copied many times over by other authors claiming the work to be their own or referring to it heavily. *Edward of Norwich*, the second Duke of York, translated the book and added some of his own comments in *The Master of Game* between 1406 and 1413 (Baillie-Grohman and Baillie-Grohman, 2005). In his descriptions of the various forms of rabies, he refers to a form that does not result in the death of the dog nor does the dog run about biting "man and other beast." In this form of *madness*, referred to as "running madness," the dog will show many of the same signs as a dog with rabies with the exception of biting other animals or humans and eventual death. The dog will run about howling and crying in a form of madness, ". . . go up or down without any form of abiding." This phrase means there are no lasting or enduring features of the condition as one would *expect* with transient epileptic seizures.

Charles Drélincourt (1633–1694) was the first recorded experimenter to induce seizures in a dog by placing a needle into the dog's fourth ventricle (Temkin, 1971). Experimentation on animals was extremely common during the transition from the Renaissance to the Enlightenment and was one of the driving forces toward the age of reason and the beginning of the modern biological sciences.

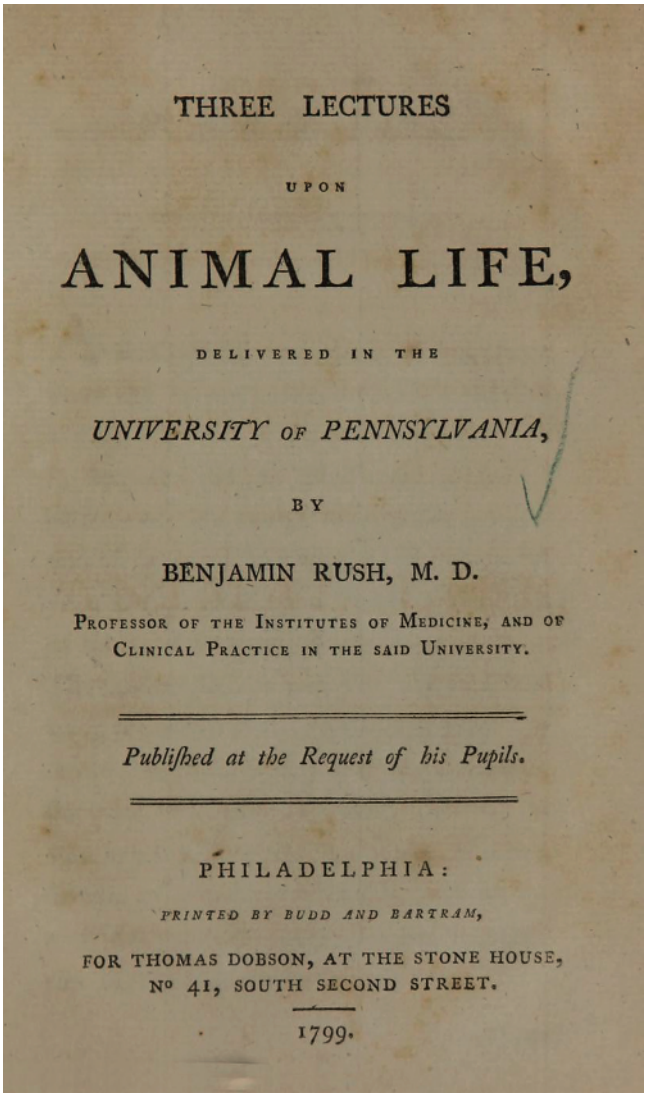
THE ENLIGHTENMENT

Claude Bourgelat (1712–1779) founded the first veterinary college in 1761 at Lyon, France, in response to a rinderpest outbreak in cattle. Undoubtedly, convulsions in animals, still referred to as *falling sickness*, were addressed similar to the means of his predecessors. However, scientists such as *Felice Fontana* (1730–1803) were beginning to conduct electrical experiments on tissues such as nerves, muscles, and the brains of animals. Fontana demonstrated convulsions could be generated through direct pressure and electrical stimulation on the brain of frogs in 1757 (Marchand and Hoff, 1955). The Veterinary College of London was founded in 1791 as a way for farriers to gain better knowledge regarding the care of horses. For the most part, the science revolving around convulsions was attempting to distinguish epilepsy as a true medical condition as opposed to that which afflicted the insane and in many instances was still considered contagious.

FIGURE 1.4 Veterinary medicine in the Renaissance. An illumination from *Livre de la Chasse* (*Book of the Hunt*) ca. 1390 by Gaston III Phoebus, Count de Foix. with permission of he Pierpont Morgan Library, New York.

Dr. Benjamin Rush (1746–1836), a Philadelphia physician and one of the signers of the Declaration of Independence, addressed a class of medical students at the University of Pennsylvania in 1799. In his speech entitled "On the Duty and Advantages of Studying the Diseases of Domestic Animals," Rush encouraged the young soon-to-be physicians to "embrace his studies and labors the means of lessening the miseries of domestic animals" (Figure 1.5). Rush was inspired by a study abroad at Edinburgh University on the advances of veterinary medicine in Europe, especially when compared to the abysmal practice he witnessed in the fledgling democracy. Rush was instrumental in creating one of the first veterinary colleges in the USA.

The vast majority of investigations looking for a physiological cause for seizures continued to be propagated through animal experimentation, primarily in dogs and cats. Numerous investigators observed convulsions induced through *bloodletting*, although even at the time of Hippocrates, it was


THREE LECTURES

UPON

ANIMAL LIFE,

DELIVERED IN THE

UNIVERSITY OF PENNSYLVANIA,

BY

BENJAMIN RUSH, M. D.

PROFESSOR OF THE INSTITUTES OF MEDICINE, AND OF CLINICAL PRACTICE IN THE SAID UNIVERSITY.

Publiſhed at the Request of his Pupils.

PHILADELPHIA:

PRINTED BY BUDD AND BARTRAM,

FOR THOMAS DOBSON, AT THE STONE HOUSE, Nº 41, SOUTH SECOND STREET.

1799.

FIGURE 1.5 In 1799, physician Benjamin Rush addressed a group of young medical students, imploring them to use their talents to "lessen the miseries of domestic animals." Rush was instrumental in developing one of the first Veterinary Teaching Colleges in the USA. *Source:* Budd and Bartram, 1799 / Public Domains.

noticed animals would *convulse* when slaughtered (Eadie, 2009). Much like the ancient Egyptians, who noted convulsions with head trauma and paralysis with spinal trauma in animals, early observers of symptomology had no physiological basis to connect the clinical signs to a pathophysiological mechanism for the behavior. The experimentation, which fostered the connection between symptomology and pathophysiological mechanisms, is a hallmark of the Enlightenment. *Charles-Édouard Brown-Séquard* (1817–1894) observed convulsive-like behavior when the spinal cord was transected in animals (Brown-Séquard, 1857). While he was the first to describe the anatomy and function of the spinal cord, he advocated trephination and cauterization of the *larynx* with silver nitrate for the treatment of epilepsy (that sounds ... horrific). Much of his work focused on the *reflex* epilepsies, which could be induced in animals following hemi-transection of the spinal cord. He noted that if the face or neck were scratched, the nonparalyzed side of the animal would involuntarily convulse. He suspected there was a degree of dyscognition; however, it was later speculated that he was inducing an exaggerated scratch reflex. His contemporaries were of the general agreement that a lack of unconsciousness during the convulsions did not fit with standard epilepsy experiments, and therefore, it was

not a good model for the study of convulsions in animals. To this day, there is no good explanation for Brown-Séquard's observation of "spinal epilepsy" (Eadie, 2009).

In 1857, *Edward Sieveking* introduced the use of potassium bromide for the treatment of epileptic seizures, which was further supported by *Charles Locock* (Locock, 1857). However, it was not until 1861 when *Samuel Wilks* provided solid evidence as to the efficacy of potassium bromide, catapulting it into popularity for the treatment of epileptic seizures (Wilks, 1861). This instance was the beginning of modern pharmacology for the treatment of epilepsy. Potassium bromide is still, to this day, widely used to treat epileptic seizures in dogs. *Pietro Albertoni* (1848–1933) performed some of the earliest experiments in the late 1800s, investigating the effects of various drugs and medications on their ability to prevent experimentally induced seizures in animals (Albertoni, 1882). Albertoni demonstrated that single doses or continued high doses of potassium bromide reduced the excitability of the cerebral cortex and prevented convulsions with electrical stimulation of the cortex in dogs. Expanding on this finding, he showed that ethyl ether or chloral hydrate, when administered in doses that left dogs awake, effectively prevented electrically induced seizures. Up to this point, epileptic seizure remedies may have been classified as spiritual (e.g., amulets, prayer, and exorcism), botanical-based (e.g., skullcap, valerian, and mistletoe), chemical (i.e., sulfur, silver nitrate, and mercury), alterations to the physical form (e.g., bleeding, trephination, cauterization, castration, and induced vomiting), and therapies derived from fauna (e.g., seal genitals, tortoise blood, and crocodile feces). Undoubtedly, a lack of perceived benefits led to an early philosophy of therapeutic *nihilism*, in which the intrinsic lack of benefit of anything led to the practice of "doing no harm," as many concoctions had undesirable side effects. Interestingly, we still use this common philosophical practice today.

THE MODERN ERA

The modern era in the history of epilepsy begins in the late 19th century with the discovery of potassium bromide, more refined animal experimentation, and a distinct correlation between seizure semiology and pathology. One of the most influential neurologists ever was *John Hughlings Jackson* (1835–1911). The discovery that organic disease (brain tumors, pus, or head trauma) was often present in humans and animals on necropsy further solidified the notion that seizures were not a disease but rather a *sign of brain dysfunction*. Granted, even the ancients were able to make the association between head trauma and seizures. While their ability to recognize symptomology was impressive, they did not have the underlying knowledge of pathophysiology needed to link the two. Jackson, through observation, was able to draw many conclusions, including the notion that epileptic seizures originated from the cerebral cortex gray matter (Jackson, 1873). *Eduard Hitzig* (1838–1907) and *Gustav Fritsch* (1838–1927) performed some of the earliest experiments in dogs when they applied electrical current to portions of the dog's cerebral cortex in order to elicit muscular contractions. Following the cessation of cerebral stimulation, Hitzig and Fritsch noted the convulsions spread to affect both sides of the dog's body with extensor rigidity and dilated pupils (Eadie, 2009). John Hughlings Jackson was able to bring together both symptomology and physiology in a more complete *pathophysiological* model of epilepsy (Jackson, 1869, 1873). Jackson came to the conclusion that epilepsy was not one disease but many different etiologies, which brought about epileptic convulsions based on the area of gray matter which was discharged (Engel, 2013). Jackson was aided greatly by the experiments of his friend and colleague *Sir David Ferrier* (1843–1928), who used electricity to stimulate areas of the brain of dogs, cats, and rabbits to provide an early understanding of the somatotopic organization of the brain (Ferrier, 1873) (Figure 1.6). His experiments on animals validated the semiology of what Jackson observed in humans with epileptic seizures and, in Jackson's words, were the "starting point for a comparative physiology of the convulsions" (Jackson, 1873). *Luigi Luciani* (1842–1991) performed cerebral resections in dogs and demonstrated that removing portions of the cerebrum could result in

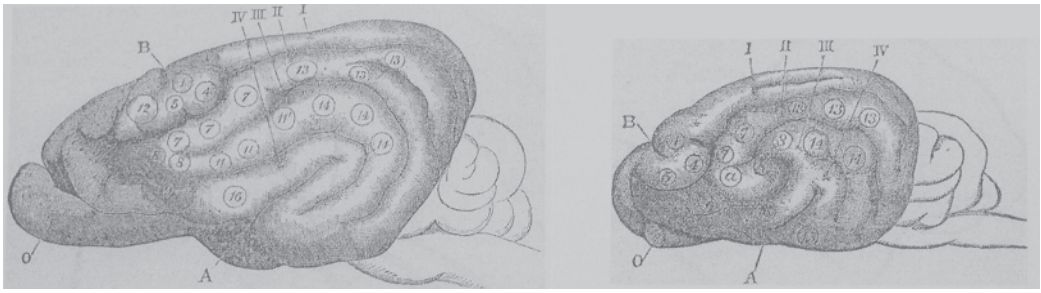


FIGURE 1.6 Experimental electrical stimulation points and associated movements in the dog and cat brain as described by Sir David Farrier in 1890. From Ferrier, D. 1890. The Croonian Lectures on Cerebral Localisation. *The British Medical Journal*. 1(1537). 1349–1355. *Source:* Public Domain.

convulsions. Surprisingly, some dogs *survived* his surgeries and would go on to continue to have convulsions. Luciani's work further validated the cortical origin of epileptic seizures (Manni and Petrosini, 1997). *Charles Horsley*, a neurosurgeon—guided by the observations of Jackson, a neurologist, and Ferrier, an electrophysiologist—applied his colleagues' observations in an attempt to cure epilepsy by removing brain tissue suspected to be epileptogenic in a man who suffered from focal motor seizures secondary to a depressed skull fracture. The surgery performed in 1886 was successful, resulting in a seizure-free patient (Horsley, 1886).

At about the same time, Jackson and Ferrier were formulating the beginning of our modern understanding of the functional brain (thank you, by the way, dogs, cats, frogs, and rabbits), veterinary medicine in the USA was getting its formal start. *Dr. James Law* (1838–1921), of Cornell University, published *The Farmer's Veterinary Adviser* in 1876. In this document, epilepsy was also referred to as "falling sickness." It was associated with distemper, teething in the young animal, and parasitic infection (two out of three isn't bad). A reference was made to *reflex* seizures elicited in guinea pigs by Brown-Séquard by tickling the neck and how a similar condition may be observed in humans. A description of the symptoms was followed by treatment recommendations consisting of removal of possible inciting causes, such as verminous infestations, restriction of diet, and more exercise for "excitable animals" (at least Dr. Law was consistent) (Law, 1876). Epileptic seizures were treated with injections of chloral hydrate or inhalation of chloroform or ether. "Convulsions and fits" of young dogs and cats were considered separately from epilepsy but still under the category and chapter concerning disease of the nervous system. Interestingly, treatment did not include potassium bromide but rather the removal of the offending cause (worms or "other irritating matters"), good feeding, air, exercise, lodging, and tonics made of bitters and iron. In the ninth edition (1889), salts of bromide were advised as treatments for excitability of the nervous system, along with the aforementioned tonics of bitters, chloral hydrate, chloroform, and ether.

THE 20TH CENTURY

Advances in the anatomy, physiology, and pathophysiology of the nervous system continued into the early 20th century. Thousands of years of experimental research on dogs, cats, and other animals built a foundation for our understanding of the brain and epilepsy. The development of the electroencephalograph (EEG) in the same year as phenobarbital (1912) provided a noninvasive way both to continue to study the electrical activity of the brain and to treat seizures with the first effective drug since the introduction of potassium bromide over 50 years prior. The first EEG recording of a mammal (a dog) and published photograph of an EEG were made by *Vladimir Pravdich-Neminsky* in 1912, at that time referred to as the "electrocerebrogram" (Niedermeyer *et al*., 2011). It would be another 12 years before the first human EEG was recorded by *Hans Berger* in 1924, who is credited with inventing the *electroencephalograph* (sorry, Vladimir).

In 1912, a sleep-deprived resident psychiatrist, *Alfred Haupmann*, gave phenobarbital (then marketed as a hypnotic) to the epileptic patients within the ward he presided over so that he might get some high-quality "Z's." Not only did the patients (and Al) sleep throughout the night, but he also discovered they had fewer seizures during the day (I'd call that a *win-win*). Haupmann published his serendipitous finding, and phenobarbital went on to become the most widely used anticonvulsant to this day (Brodie, 2010). A cat model of experimentally induced seizures was used to screen a group of potential anticonvulsant drugs with presumably less sedative effects compared to phenobarbital. *Putnam* and *Merritt* reported a detailed description of the *cat electrocution apparatus* (yikes) in a 1937 *Science* article (Putnam and Merritt, 1937). In the report, the authors stated, "The method appears to involve no undue cruelty and indeed is similar to that used for executing stray animals by some animal protective societies" (Figure 1.7). One year later, Merritt and Putnam (1938) published the results describing the anticonvulsive effects of phenytoin. Prior to the discovery of the anticonvulsive effects of phenytoin, potassium bromide and phenobarbital were the most advanced pharmacological agents used to treat epileptic seizures. The ketogenic diet developed by *Dr. Russell Wilder* of the Mayo Clinic in 1921 was also used to a lesser degree (see Chapter 9) (Wheless, 2008). Cerebral cortical resection was performed in a limited number of cases to treat (and often *cure*) epilepsy. Following the discovery of phenytoin, the ketogenic diet fell out of favor, and a strong push was made to actively pursue other pharmacological-based therapies.

In the *People's Home Stock Book* by veterinarian W.C. Fair, published in 1919, there is little mention of the contemporary anticonvulsants used by humans to treat animals (Figure 1.8). There is no mention of epilepsy in dogs, other than convulsions associated with distemper. Cats, on the other hand, have a treatment section on "Fits–Convulsions" and "Epilepsy." It was noted that epilepsy in cats differed from fits and convulsions in that there was no *delirium* associated with convulsions (possibly similar to focal motor seizures of cats we identify today). Cats were treated with a cathartic of either buckthorn syrup or castor oil and wrapped in a hot

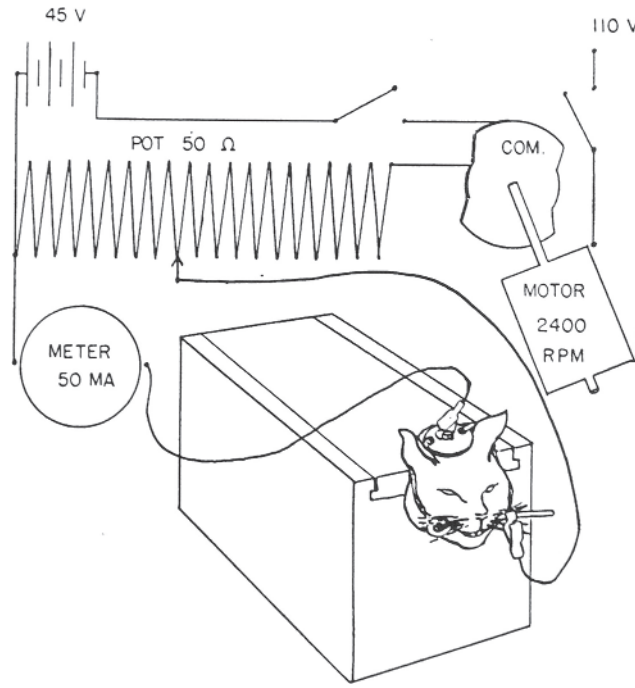


FIGURE 1.7 The *cat electrocution apparatus* utilized by Putnam and Merritt to test potential antiseizure drugs. Thousands of years of experimentation on animals helped greatly to expand human understanding and treatment of epilepsy. Putnam, T.J. and Merritt, H.H. 1937/ with permission of Elsevier.

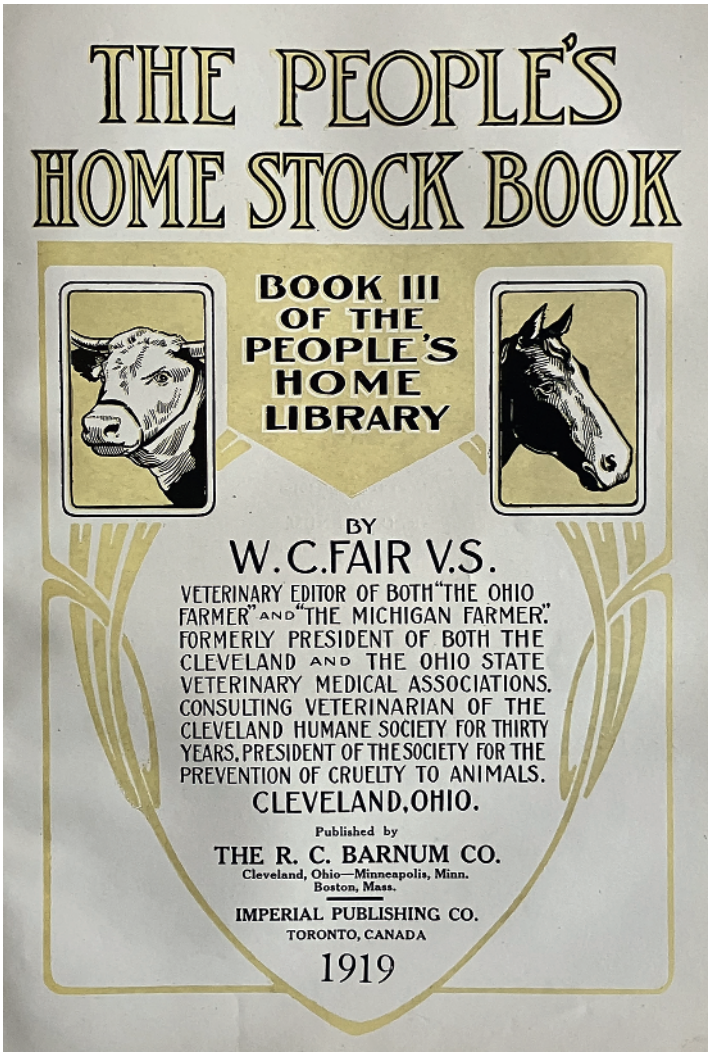


FIGURE 1.8 Even in the early 20th century, contemporary treatment of seizures in dogs and cats did not rely on the most "advanced" drugs at the time, such as potassium bromide and phenobarbital. Rather, emphasis was placed on numerous different treatments, including herbal remedies, good diet, and exercise. The R.C. Barnum Company, 1919 / Public Domain.

blanket or dropped in warm water (all but the head). It was also recommended to give "two grains of bromide of potash four times a day" (Fair, 1919). For epilepsy, cats were given laudanum (tincture of opium) or chloral hydrate, syrup of buckthorn (to move the bowels), and it was recommended to feed a highly digestible diet and exercise the animal (exercise a cat?). In the human medicine section of the same book (*The People's Home Library*, Book One), epilepsy was under the category "Falling Fits" and treated with "bromide of potassium." Oxide of zinc and stramonium ointment (herbal remedy derived from Jimson weed) were also recommended as a treatment for the falling sickness.

Advances in the treatment of epilepsy for dogs and cats primarily, and to this day, rely on pharmacology similar to humans. Although there is a significant difference between the species, there are limitations with regard to the use of various antiseizure medications in dogs and cats. In the 1960s, carbamazepine and the benzodiazepines were introduced. Benzodiazepines found significant use in veterinary medicine, especially for controlling status epilepticus. Several dozen pharmaceutical options have been available in the last seven decades for the treatment of epileptic seizures in humans. Disposition limitations and toxic effects of certain human drugs prevent the

current use of many of these medications in dogs and cats; however, despite this, the pharmacological success in treating seizures of dogs and cats is similar (if not slightly better) to humans. Phenobarbital and potassium bromide continue to be the most commonly prescribed antiseizure medications in dogs, and for cats, phenobarbital is by far the most widely used antiseizure drug.

A more direct focus on the advancement of diagnosis and treatment of disease of the nervous system of dogs and cats was developed following World War II. Veterinarians such as *J.T. McGrath*, *A.C. Palmer*, *B.F. Hoerlein*, *John Lorenz*, and *Alexander de Lahunta* gave special attention to the nervous system of dogs and cats. Their research, textbooks, and education of thousands of veterinarians significantly advanced the field of veterinary neurology and opened the door for many others to follow in their footsteps.

Advances in experimental techniques and a general pejorative view on animal experimentation shifted the bulk of animal research to rodent models in the late 1970s. The discovery of the patch clamp technique for the study of electrophysiology by *Erwin Neher* and *Bert Sakmann* opened a whole new era of science for not only studying the underlying pathophysiology of epileptic seizures but also the underlying mechanisms of how many drugs worked to suppress seizure activity. In the early 1970s, *Dr. Terrell Holliday* contributed significantly to the understanding of the canine EEG associated with paroxysmal central nervous system disorders. The contributions of *Dr. Wolfgang Löscher* and *Dr. Dawn Boothe* continue to advance our understanding of canine and feline anticonvulsants and have prevented an incalculable number of toxic reactions of dogs and cats to common drugs used to treat seizures in humans. *Dr. Michael Podell* continues to advance our understanding of the clinical application of new antiseizure medications, and *Dr. Fiona James* is paving the way for new applications of the EEG. An entirely new syndromic classification of feline epilepsy has been uncovered by *Dr. Akos Pakozdy*. Advanced imaging techniques combined with various forms of EEG, the identification of new syndromes of epilepsy, and, most importantly, a desire to not only advance the field but also help animals, are driving the application of surgery for epilepsy, thanks to some of the pioneering work of *Dr. Daisuke Hasegawa* and his associates.

One of the most significant advances in the diagnosis of the causes of epilepsy was in the form of advanced imaging of the brain. *J.M. Cobb* described the technique of pneumoencephalography in the dog in 1960. While performed decades earlier in humans, this radiographic technique allowed for the first time the *visualization* of structures of the brain in a minimally invasive way (compared to vivisection) (Cobb, 1960). The 1980s brought computed tomography (CT) into clinical use for imaging the canine and feline brain. In the 1990s, magnetic resonance imaging (MRI) of companion animal brains was introduced, which "opened the door to the brain." MRI quickly became the gold standard of imaging the brain and today is used clinically in almost all veterinary schools and veterinary private practices by specialist veterinary neurologists.

SIX THOUSAND YEARS LATER

A quarter way into the 21st century, we find that the diagnostic tests and treatment modalities for seizures in dogs and cats are in step with those employed for humans just as they were 6000 years ago. Certain limitations continue. While there is no lack of sophistication or desire to investigate the causes of seizures in dogs and cats, those limitations, discussed in further chapters, are slowly being overcome. Epilepsy is one of the oldest afflictions documented in human history, and it is interesting that references to dogs and cats having seizures are, for the most part, absent. Comparative medicine receives little mention in the historical perspectives of human epilepsy other than the use of animals in experiments to further the advancement of our understanding of epilepsy, as it affects humans. Perhaps this is due to the notion that our predecessors found little difference between species and therefore have no need to *compare* them. While dogs and cats certainly have never suffered from the psychosocial stigma of epilepsy (as far as we can tell), they have undoubtedly

suffered in other ways, particularly through a lack of understanding of epileptic seizures as it applies to their species. We are lucky to be surrounded by investigators who continue to make important advances in the study of veterinary and human epilepsy. The *applied knowledge* of these researchers in a clinical setting is the duty and obligation of the practicing veterinarian.

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