Definition of Comparative Medicine: History and New Identity

1

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Contents

Abstract

Most of today's knowledge on molecular mechanisms in mental and physical health and disease is significantly supported by animal studies. Innumerous nutritional and medical products such as vaccines were developed based on animal and human experiments, including heroic self-experiments, and on constant comparison of effects in different species during the history of medicine. The achieved medical standard changed our life expectations significantly by combatting or even eradicating many of previously deathly diseases. Directives for drug development for medical (Directive 2001/83/EC of the European Parliament 2001) and veterinary medicine (Directive 2001/82/EC of the European Parliament 2001) today comprise obligatory proof of concept and toxicity studies using different species of laboratory animals, followed by clinical studies in human or veterinary patients, where in fact the procedures do not differ substantially (Lombard 2007). However, comparative medicine

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today aims to foster the constant exchange of know-how between human and veterinary medical disciplines and encompasses the treatment of animal patients in clinical studies as a modern means of drug development simultaneously following the 3R rule.

1.1 Introduction

Since the introduction of the 3R rule and its legislative implementation in 2010 (Directive of the European Parliament 2010), all researchers are forced even more to plan studies carefully according to replacement, reduction, and refinement of animal experiments (Editorial in Nature Immunol 2010) (see Chap. 14). This indicates an increased sensitivity in our society for ethical aspects and responsibility in animal and human experimentation. In vitro alternatives for animal studies allowing efficacy and nontoxicity testing at the same time, and reflecting all possible effects in a complex organism, are thus urgently searched for and supported (FRAME 2005). Several improvements have been achieved and include methods like cryo-conservation of embryos of transgenic animals or the development of in vitro 3D tissue models as an approximation to the real-life situation (Table 1.1).

We believe that the constantly improving electronic accessibility of scientific literature from the beginnings of “modern medicine” will strongly contribute to the 3Rs by preventing duplication of experiments.

There is, however, an agreement in the scientific community that it will not be possible to entirely replace animal models in the near future (Festing and Wilkinson 2007). The matter is emotionally discussed on both sides (Cressey 2011; Stephens 2011) and needs ethical reflection (see Chap. 15). Nevertheless, the overwhelming knowledge on molecular disease mechanisms and therapies has been gathered by previous, even historic, animal studies.

We are today convinced that comparative medicine can contribute to the 3Rs simultaneously by following its overall aim to improve the health of humans and animals.

Comparative medicine is a discipline with a broad knowledge on anatomy, physiology, and molecular pathophysiology for promoting health (Monath et al. 2010) and for the generation of novel therapies for humans as well as for animal patients (Schwabe 1968). According to the intriguing concept by the Comparative Oncology Trial Consortium of the National Cancer Institute, veterinary patients should be included early into clinical developments (Gordon et al. 2009). Thereby, animal numbers needed in preclinical studies would be reduced and simultaneously the animal patients provided with cutting-edge research. This strategy requires consequent “comparative” thinking and a constant interdisciplinary dialogue.

In the course of the formation of a new identity and redefinition of Comparative Medicine, it was obligatory to search the roots of this discipline in history. A single

Table 1.1 Alternative methods for animal experiments identified by the ECVAM (European Centre for the Validation of Alternative Methods) in 1999 (FRAME 2005)

1. Models, mannequins, and mechanical simulators
2. Films and interactive videos
3. Computer simulations and virtual reality systems
4. Self-experimentation and human studies
5. Plant experiments
6. Observational and field studies
7. In vitro studies on cell lines
8. Clinical practice

book could be identified specifically targeting the topic "History of Comparative medicine" by Lise Wilkinson which the author found concise and informative (Wilkenson 1992) and which will serve as "the red line" through this chapter. What was found is an amazing coevolution and cross-fertilization of medical, veterinary and later experimental medicine during the centuries. The developments were mostly driven by curiosity, by plagues of the time, and by the need of surrogate models for the human body. Animal cadavers were studied in order to get insights into anatomy and, later, physiology and pathophysiology of humans and other organisms (Adler 2004). Only few doctors were trained in medicine *and* veterinary medicine, and only in 1862 that the first professorship and chair dedicated to comparative medicine was established in France (Isensee 1845).

1.2 Medical Remedies Based on Comparative Observations Before Modern Medicine

In history the relation between humans and animals changed significantly several times depending on the culture (McClellan and Dorn 2006). In 20000–15000 BC, the animal-human relation between **Paleolithic men** and animals was that between the hunter and the hunted. The first interest in the health of herds may have risen, when humans followed wild sheep, cattle, and horses, in a hauling alliance with the canine packs from 12000 BC on. The interest of humans in the health condition of the herds raised when animals were domesticated, first around 9,000 BC in nomadic form, especially with sheep and goat, and when from 3700 to 3100 BC more solid associations between men and cattle or horses were built up. From this time point on, healthy herds represented food, survival, and wealth for man. It remains open whether primitive herbal remedies already were developed for both human and animal patients then.

Around 2000 BC, medicine and pharmacology had reached a high specialization level (Schwabe 1978) in ancient Egypt (Riviere and Papich 2009). With respect to animals, the major focus was given on bulls and cows, which were worshipped and treated by remedies as documented in the famous Kahun papyrus of the Lahun papyrus collection in the University College London (http://www.digitalegypt.ucl.ac.uk/lahun/papyri.html, Kahon papyrus: University College London). Even though it was a tradition to embalm human and animal bodies, Egyptian physicians had in fact restricted knowledge about the human anatomy.

In parallel, in **India** animal healing got highly developed due to the Hindu belief of reincarnation and awareness of all animals (Somvanshi 2006). As a consequence, Indian physicians were trained in animal care and treatment, with major focus on cattle, horses, and elephants. The *Charaka samhita* represents the oldest teaching book of Ayurveda medicine (Indian healing medicine, "Knowledge of life"), containing the *Haya-Ayurveda* for horses and the *Hasti Ayurveda* for elephants, from 300 to 500 AD.

The most important sources from **China** documenting herbal medicine for horses date back to 1122 BC. Horses were of impact for work and military defense and a symbol for aristocracy, and requiring specific prescriptions for equine diseases (Buell et al. 2010) (Fig. 1.1). For instance, isotherapy, was developed, i.e., transfer of diluted sweat of a domestic animal to diseased human.

The great Greek philosopher **Plato** (ca. 428–347 BC) taught the superiority and immortality of the human soul. In his opinion animal observations or even dissections were taboo, although the Greek god of medicine and healing, **Asklepios**, was believed to be treating man and animals (Wickkiser 2008). This is also the reason why the rod of Asklepios is used as a symbol of human medicine and pharmacy as well as veterinary medicine. Accordingly, **Hippocrates** (460–370 BC) found comparative pathology useful. In his opus *Airs*, *Waters*, *Places* he described case histories relevant for herds and the human population (Adams 1849). Hippocrates suggested that an approach to diagnosis and treatment should always be based on experience, observation, and logical reasoning. Later **Aristotle** (384–322 BC) described animal species and diseases and philosophized about mechanisms of interspecies transmission (Aristotle, translated by Farquharson 2004). He inspired **Erasistratus of Chios** (404–320 BC) and **Herophilus of Chalcedon** (ca. 330–255 BC) (Bay and Bay 2010) to open schools for comparative anatomy and physiology in Alexandria, where also cruel vivisection methods on prisoners have been practiced. Unfortunately, the burning of Alexandria's library has destroyed most of their opus.

The Roman erudite **Marcus Terentius Varro** (around 100 BC) attempted to create a universal encyclopedia on the most important disciplines, among them medicine (Disciplinarum libri IX, *or* Nine Books about the Disciplines) where he propagated the separation of human lepra groups based on his concept that *tiny invisible animals carried with the air* cause disease which enter the body through the mouth and the nostrils (Wilkenson 1992).

Aulus Cornelius Celsus (25 BC–50 AD) reported in his opus "De Medicina Libri Octo" experimental physiology based on his experience in dissecting and vivisecting many species. He also reported specific interventions, for instance, cupping, as a method to "*...drew out the poison from dog bites, especially if the dog was mad*" (Fooks et al. 2009).

The dissection of the human body remained no longer acceptable in Rome in **Claudius Galen**'s era (129–200 AD) (Lyons and Petrucelli 1978; Aufderheide

Fig. 1.1 Armée de terracotta à Xi'an—China. © [Delphimages]—Fotolia.com

2003). By his work and teachings, Galen's influence remained after several 100 years until the middle ages. He used vivisection as a method of dissections on living animals; the term "Galenic formulation" is today still used and indicated the composition of medical remedies. To circumvent the prohibition of human dissection, he dissected animal cadavers. He analyzed multiple species, ranging from pigs, sheep, cattle, cats, dogs, to weasels, bears, mice, and also a single elephant. The animals mostly used for anatomy studies, however, were Barbary macaques from which he concluded to human anatomy. This strategy had caused several persistent errors in the understanding of human anatomy in medical history.

In spite of his many different talents, **Publius Flavius Vegetius Magnus** (500 AD) has been long interpreted as a key person specifically for veterinary medicine due to his publication of "*Digestorum Artis Mulomedicinae libri,*" which was even much later, in the sixteenth century, published in Latin and German (Vegetius and Gargilius 1871).

1.3 From Middle Ages to Humanism and Renaissance, ca. 500–1600

In the Arabic world the famous Persian physician **Muhammad ibn Zakariyā Rāzī, in** short called **Rhazes** (865–925), wrote the first book on the contagiosity of measles and smallpox, al-Judari wa al-Hasbah (Modanlo 2008). As no dissection of humans was allowed for Muslim physicians, dissection of animals and comparative anatomy was pursued as a surrogate strategy.

However, at least in Europe, the antique period was followed by an era without significant progress in terms of science and medicine, and also dissections were prohibited (Aufderheide 2003). This was also due to the change from polytheistic belief as a basis of free philosophy and open scientific discussion to the monotheistic Christian belief.

In Europe, the Catholic Church was much empowered leading to aggressive expansion strategies, termed crusades, with tens of thousands of participants.

Traveling over several years, crusades were not only using horses but also accompanied by whole cattle trains for supply. Crusades prompted the transmission and outbreak of zoonotic diseases, anthrax and cattle plague across their routes. In parallel, natural catastrophes weakened the human population and typhus, influenza, smallpox, and bubonic plague were epidemic (Boccaccio, translated by Aldington 1930). The crusades enabled the import of the Oriental rat flea carrying the plague bacterium Yersinia pestis (Haensch et al. 2010). Although this all resulted in a demographic disaster, the contagious principle was recognized only vaguely and counterregulations like quarantine were hardly known (Mazzeo 1955).

As a result of these massive and deleterious plagues, however, the way of inoculation and transmission was thoroughly considered. **Albertus Magnus** (1206–1280) started studies on the anatomy and physiology of animals after joining the Dominican monastic order. In his work *Liber de animalibus*, he discussed human and animal plagues and even brought down the mechanism of inoculation to three possible reasons: (1) bites or injuries, (2) actual contact with diseased animals, or (3) respiration of air from the sick. His sphere of influence ranged between Paris and Cologne (Lindner 1962). He also specifically addressed dogs' health in *Practica canum* (Giese 2007).

Jordanus Rufus (around 1250) was supported by Frederic II, king of Sicily, and did profound research with special impact on the favorite species of his mentor, horses and falconry birds. He left detailed sketches on manipulation on diseased horses including the necessary mechanical apparatuses (Prévot 1991).

Knowledge and know-how on, for instance, quarantine measures gathered in the antique, had been lost at that time. However, the capacity of knowledge dissemination was largely improved by the invention of movable printing machines by **Johannes Gutenberg** around 1439 (Febvre and Martin 2010). From that time point on, official guidelines could be distributed much more effectively as broadsheets to the public, for instance, recommendations for common diseases of horses and cattle.

The Renaissance physician and philosopher **Girolamo Fracastoro** (1476–1553) from Verona made the significant observation that "germs" can transfer diseases and are species specific in animals or even plants (http://ocp.hul.harvard.edu/contagion/contributors.html 2013). **Andreas Vesalius** (1514–1564) practiced human dissections (Prioreschi 2001), whereas otherwise students still had to learn from animal dissections. Medical understanding was additionally facilitated by inventions, such as magnifying lenses by **Zacharias and Hans Janssen** around 1590, being improved to a focusing device in 1609 by **Galileo Galilei** (1564–1642), and finally to the first microscope by **Antonie van Leeuwenhoek** (1632–1723) (Nature 2009). He microscopically observed spermatozoa, bacteria, and sporozoa which he altogether termed *Animalcules*. Thus from today's point of view, he was an ultimate trigger of parasitology, microbiology, and bacteriology.

Within a short time, the microscope was applied for medicinal studies. **Athanasius Kircher** (1602–1680) reported in his book *Scrutinium Pestis* that in the blood of plague-infected patients *tiny worms* in tissues could be seen below the microscope, which affirmed his opinion that living organisms might transfer disease (Winkle 2005).

1.4 The Establishment of Colleges, Societies, and Congresses

Clearly, progress could be achieved faster with regular exchange of knowledge in a structured form, also allowing quality control of data instead of spontaneous, individual observations and opinions. In 1662 the basis for such was shaped with the foundation of the Royal Society in London. For the spreading of the scientific news, the classical journal *Philosophical Transactions* was established, which still exists today. **Robert Boyle** (1626–1691) published several key experiments there, among them the blood transfusion experiments from one animal to another, including from sheep into men, thus using human test subjects (Boyle 1666; Knight and Hunter 2007). Only rarely veterinarians achieved to publish their work in this journal. However, also other contemporary scientists were unlucky to do so.

The onset of the eighteenth century brought a new wave of plagues to Europe, among them bubonic plague (Haensch et al. 2010), smallpox, and cattle plague. Faster communication and access to knowledge fostered comparative approaches, especially with respect to the transfer and contagion of infections. The technology of transference, i.e., transfer of infections from human patients to animals and vice versa, was developed and may be regarded as experimental in vivo approaches. It had already been settled earlier in China (Temple and Needham 1986) and probably also in India (Dharampal 2000) that pox crusts might be used for therapy of the pocks and smallpox infections. There was even a market for buying smallpox crusts which were sniffed or eaten, possibly as the first prophylactic vaccine (Moore 1815). It is difficult to say whether this practice was developed de novo in the eighteenth century or whether it was overtaken from published work. However, **Emanuel Timone** (1665–1741) was the first to publish inoculation, also called grafting (Woodward 1714). This technique was widely practiced throughout the eighteenth century in Europe.

At this time, animal medicine was actually more or less nonexistent in Europe. This was changed with the cattle plagues in 1711 and in 1745–1757 (Cáceres 2011). **Bernardino Ramazzini** (1633–1714), from the faculty of Padua, and **Giovanni Maria Lancisi** (1654–1720), the pope’s physician, were the first to acclaim the danger for the population from the plagues (Wilkinson 1984; Klaassen et al. 2011). But, any interest was in the beginning rejected by the arrogance of physicians who found it below their dignity to discuss cattle (Wilkenson 1992; Talbott 1970). However, **Mortimer Cromwell** (1693–1752), secretary of the Royal Society, raised the topic of plagues to an issue of national concern. The general strategies were quarantine, isolation of the diseased animals, fumigation of stables, and slaughter (Spinage 2003).

Erasmus Darwin (1731–1802) also was impacted by the tragedy of the plagues. He published thoughts on contagion in *Zoonomia* where he discusses infectious diseases in both humans and animals (Darwin 1796).

Possibly, these events together paved the way for the foundation of the first veterinary college in Lyon, France, in 1761, by **Claude Bourgelat** (1712–1779) (Isensee 1845; Grognier 1805). Bourgelat was a lawyer and an expert in horses and concerned about the devastating cattle plagues. Thus, like many personalities in the beginnings of veterinary medicine, he was a generalist. In fact, he invented "comparative pathobiology" before the veterinary profession (Mammerickx 1971). His major interest in horses biased the veterinary teaching and activities in Lyon during several years, but numerous colleagues from all over Europe visited Lyon at that time. When **Vicq d'Azyr** (1748–1794) (Isensee 1845) was appointed as the chair of comparative medicine in Lyon in 1782, he reoriented the institute's outlook more scientifically and towards comparative medicine, because he strongly believed in the unity of human and veterinary medicine. Equally important, he proposed '*...to carry out valuable experiments* (*in animals*) *which would be criminal if attempted in the treatment of human disease*'. According to Lise Wilkinson, these significant words actually introduced the use of animal models in medicinal research (Wilkenson 1992).

The foundation of other veterinary colleges followed, among them in Maison-Alfort, near Paris, which for the first time also comprised a farm.

Only 4 years after Lyon's foundation, the first veterinary school of Austria was initiated in Vienna by Empress Maria Theresa in 1765 (Mösle's Widow 1839). **Anton Hayne** (1786–1853) took first human surgical education but became later professor for animal medicine with focus on infectious diseases in Vienna (Hayne 1836, 1844). When Ignaz Semmelweis claimed his detection of puerperal fever and possible prevention by aseptic technique and hygiene, Hayne claimed priority for the discovery (Carter 1981).

Veterinary schools were founded and curricula developed not only in Austria but also in Sweden, Denmark, France, the Netherlands, and in Germany. When the Royal Veterinary College was founded in 1790 (http://www.rvc.ac.uk/About/Museums/Milestones.cfm, The Royal Veterinary College, University of London), some of the Lyon students decided to move to London. Among them **John Hunter** (1728–1793) moved back to London. He was originally trained in human anatomy and surgery, but had a great interest in comparative anatomy and animal physiology. He established a collection of more than 10,000 human and animal preparations and wax teaching models including exotic animals from the menagerie of the London Tower. The "Hunterian Collection" can still today be visited at the Royal College of Surgeons in London. His teaching on infectious diseases significantly encouraged next generations, including his student Edward Jenner, to tackle this topic.

Edward Jenner (1749–1823), who later should be coined the inventor of the smallpox vaccine (Jenner 1798; Riedel 2005), dissected many different species and had a general interest in diseases (Jenner, foreword Drewitt 1931). He should be recognized as a key person in comparative medicine, too (Fig. 1.2). Jenner turned first to rabies as an increasing problem in and outside London. He noted that previously infected dogs developed protection. He further introduced and developed animal models for rabies and proved that a healthy dog could be inoculated

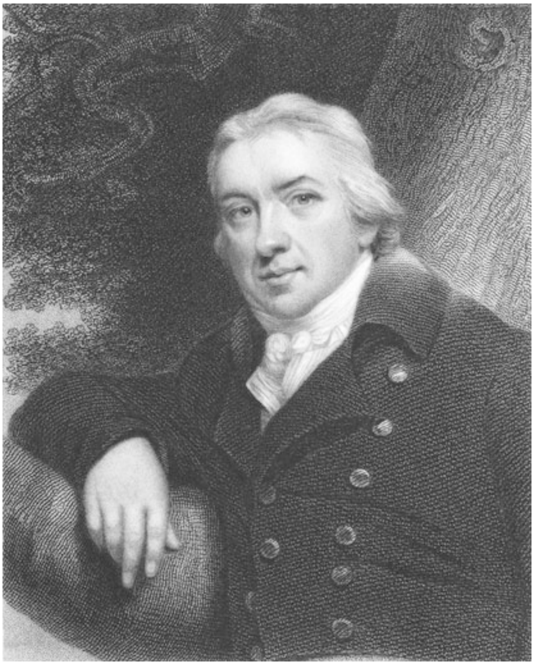

Fig. 1.2 Edward Jenner. © [Georgios Kollidas]—Fotolia.com

with rabies using the saliva of a rabid dog. Transmission experiments were in general a tool at that time to understand the pathophysiology of infections. Jenner had also observed that people (milkers) who had been in contact with cowpox-infected cows did not develop vaccinia (smallpox, variola minor). Instead, they developed milder cowpox only (Jenner 1798). In 1796 Jenner made a historic experiment: He infected a healthy 8-year-old boy James Phipps first with lymph derived from a cowpox lesion of a milker's hand, followed by a challenge (variolation) with the smallpox virus. The boy developed a mild disease upon the cowpox infection, but was protected against the smallpox challenge. This indicated that cowpox could induce protective immunity against the severe smallpox infection and was a breakthrough in vaccinology and an important stimulator of immunology.

As a consequence of Jenner's inoculation experiments and many others, in animals and humans, the time became mature for the introduction of specific inoculation programs for the population. A commission on vaccinations of the Royal Academy of Medicine in France was established, being directed by **Jean-Baptiste Edouard Bousquet** (1794–1872), which elaborated guidelines on the advisability and frequency of vaccination and revaccination (Bazin 2011).

In Germany, **Robert Koch** (1843–1910), a country practitioner who had studied in Berlin and Göttingen, experimented with infections and become a truly notable personality in the history of epidemic diseases (http://ocp.hul.harvard.edu/contagion/contributors.html 2013; http://www.nobelprize.org/nobelprizes/medicine/

laureates/1905/. The Nobel Prize in Physiology or Medicine 1905; Robert Koch. Nobelprizeorg 1905). He discovered the anthrax bacillus, tuberculosis bacillus, and tuberculin, as well as Vibrio cholerae. Among experiments in many other species, he made infection experiments with young cattle that were not susceptible for the human strain of tuberculosis and proposed that a transmission of tuberculosis via cows' milk to humans and vice versa can be excluded (Koch 1903). This assumption, however, had to be corrected later (Raw 1906).

An important stimulator in the history of comparative medicine was the first veterinarians' conference in Hamburg organized by **John Gamgee** (1831–1894) in 1863, from which "The World Veterinary Association" evolved (Asch 2013). After the first conference in animal vaccination in London in 1880, **George Fleming** (1831–1901) proposed in *The Lancet* that chairs for comparative pathology should be established in all medical schools (Fleming 1871).

Rabies, sepsis, or putrid intoxication were further eminent burdens of that time. In 1803 the French physiologist **Francois Magendie** (1783–1855) inoculated a dog with saliva from a human rabies case and could by this animal experiment for the first time prove the interspecies transmission of rabies (Stahnisch 2003). Magendie was also interested in sepsis and experimented with putrid fish that was injected in animals. He observed that symptoms were elicited similar to yellow fever or typhus. Magendie introduced animal experiments with dogs and other species as a common physiological practice, notably in a time before anesthetics were invented 1846 (von den Driesch 2003). This prompted the foundation of the world's first anti-vivisection organization in the UK in 1875 (Pedersen 2002). **Pierre Victor Galtier** (1846–1908) in Lyons (Goret 1969), in 1879, used rabid saliva for inoculation of a sheep via the jugular vein resulting in *acquired immunity* (Galtier 1879, 1881). Comparative medicine was interpreted as experimental medicine at that time.

During this time a high knowledge of experimentation was gathered and many names of the experimental forerunners are still remembered: **Bernard Gaspard** (1788–1871) inoculated dogs, fox, pig, and lambs, thus carnivores and herbivores with lymph, blood, bile, and human urine, to test the prophylactic value of these treatments (Magendie 1822). **Rudolf Virchow** (1821–1902), the initiator of modern pathology, distinguished between pyemia and septicemia and thrombosis and embolism by dog studies. Thus he made key observations leading to precise medications based on animal experiments. In his *Address on the value of pathological experiments*, he fierily advocated the value of these experiments, comparing work on isolated tissues, animal studies, and vivisection, in the light of the formation of vegetarian and anti-vivisection movements (Virchow 1881).

The Danish physiologist **Peter Ludvig Panum** (1820–1885) described in dogs dose-dependent effects using putrid blood, flesh, brain, or human feces for experimentations (Kolmos 2006). **Friedrich August Johannes Löffler**, German bacteriologist and student of Koch, identified bacteria as a cause of diphteria, virus as cause of foot-and-mouth disease, Pseudomonas mallei causing glanders, and bacteria as the causes of swine erysipelas and plague (Biographie 1987). Thus scientists were regularly active in human and veterinary topics.

Also, anthrax infections were common, e.g., due to gunshot wounds providing anaerobic milieu (Swiderski 2004). **Pierre Rayer** in 1850 inoculated sheep with anthrax, whose blood was agglutinated. When he with his assistant **Casimir Davaine** (1812–1882) investigated the blood microscopically, he could see that it also contained small rod-shaped, nonmoving bodies, approximately twice the length of an erythrocyte. Typically, researchers did not only sacrifice animals for their studies but also human (poor) patients or criminals. Davaine, who also brought down animal experiments to a smaller laboratory scale (rabbits, rats, guinea pigs), inoculated a pregnant woman with anthrax blood who consequently died only 2 days later (Swiderski 2004). When she was dissected, her placenta was full of anthrax bacteria, whereas the fetus was completely clean. By this cruel experiment, Davaine detected the biological filter mechanism of the placental barrier. A series of filtration and precipitation experiments followed in order to be able to separate the infectious agent from the blood cells. **Robert Koch** followed the idea of a *contagium vivum*, a living organism that transfers disease. He focused on culturing techniques for which he became famous. He was the first to approve anthrax in culture in 1877 and demonstrated its spore formation and its transferability to animals (von den Driesch 2003). The Robert Koch Institute (RKI), founded in 1891, is today still a research and reference institution for monitoring infectious diseases in Germany. **Louis Pasteur** (1822–1895), among others, developed attenuation: Upon heating to 42–43 °C, no spore production took place, reducing the danger of infections during vaccination (Pasteur and Chamberland 2002). Others like **Pierre Paul Èmile Roux** (1853–1933) improved attenuation by potassium dichromate treatment of the vaccines. These developments were also very useful for other vaccines, like anthrax. The first anthrax vaccine for humans was introduced in 1954 only.

Inoculation experiments were also performed by researchers in comparative medicine: **Jean-Baptiste Auguste Chauveau** (1827–1917), a professor from the Lyon Veterinary School (Bazin 2011) did not only himself experiment on sepsis (Sanderson 1872) but also chaired a commission which evaluated comparative experiments in cattle, showing that the co-inoculation with smallpox and cowpox induced cowpox only, thereby proving species specificity of the infection. In contrast to Jenner's concept of cross-protection by cowpox inoculation against smallpox, Chauveau anticipated that smallpox itself could be attenuated by passage through these animals (Swiderski 2004). The commission, in 1864, hence decided for a human experiment in seven children from an orphanage. They were all inoculated with smallpox six times, passaged through cattle. Unfortunately, two developed confluent smallpox and the other five the more discrete form (Cookshank 1889).

A follower of Chauveau, **Jean Joseph Henri Toussaint** (1847–1890) cultivated fowl cholera bacteria in vitro and supplied it to Pasteur who finally developed the vaccine for this veterinary disease (Wilkenson 1992).

However, from the above it is clear that **Louis Pasteur** contributed significantly to vaccine development by numerous experiments (Fig. 1.3). He inoculated rabies to several species like rabbits, dogs, sheep, goats, and guinea pigs and found that

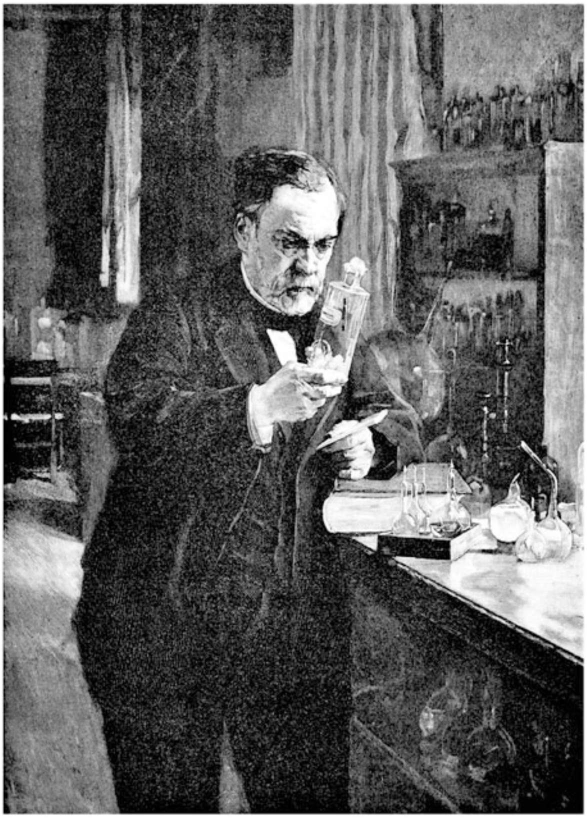

Fig. 1.3 Louis Pasteur, nineteenth-century scientist. © [Erica Guilane-Nachez]—Fotolia.com

especially brain tissue was highly infectious (Pasteur, interviewed by Illo 1996). At the International Congress of Medicine in Copenhagen, Pasteur announced that he had solved the rabies vaccine in rabbits. Much later, when his personally retained laboratory notebooks were finally archived in the Bibliothèque Nationale in Paris, they revealed that less of the reported animal experiments were actually documented than Pasteur had claimed (Geison 1995; Warner 1996). For instance, the famous and successful healing experiment in a 9-year-old patient, Joseph Meister, who had been bitten and infected by a rabid dog, was done with a specific rabies vaccine that had not been tested in dogs before. Anyway, the healing experiment contributed to the great international popularity of Pasteur. One should also remember that **Pierre Paul Émile Roux** (1853–1933) (Pasteur and Chamberland 2002) and others had contributed significantly to this development, however, without merit.

1.5 Expansion of Comparative Medicine from Europe to the USA

Hence, comparative medicine has paved the way to modern medicine. Especially in the fields of infectiology, immunology, and vaccination in the eighteenth–nineteenth century, great scientists and clinicians were quite used to "comparative thinking." However, overall coexistence or cooperation between medicine and veterinary medicine differed from country to country (Wilkenson 1992): In France there was coexistence and cooperation; in Britain old prejudices against veterinarians resulted in minimal cooperation between the disciplines; Italy sent veterinary students to the prestigious centers in France; in Germany the veterinary schools were characterized by an administrative uniformity; students from overseas went back from Europe to spread their knowledge to the USA.

Importantly, it was recognized during this period that clinical and experimental research must go hand in hand and that experimentally oriented institutions are urgently needed to accomplish what we would term translational research today. In Vienna the great patho-anatomist **Carl von Rokitansky** (1804–1878) triggered **Salomon Stricker** (1834–1898) to found the *Institute of Experimental Pathology* in 1873, which was from the beginning predominantly dedicated to laboratory research (Wyklicky 1985). In an attempt to adapt it to modern nomenclature, the institute was in 2000 renamed to Institute of Pathophysiolgy, and in 2010 during the leadership of the editor of this book renamed Institute of Pathophysiology and Allergy Research, indicating a still tight association to immunologic topics today.

William H. **Welch** (1850–1934) (Dhom 2001) had his training in Europe and strongly emphasized the European idea of medical research institutes directly linked to clinics. Being the first dean of the John Hopkins School of Medicine, Baltimore, Welch was also instrumental in formulating the policy for the foundation of the *Rockefeller Institute of Medical Research* in 1901 (Ackerknecht 2001), which was the first American equivalent to the Pasteur and Robert Koch Institutes in Europe and where he served as founding president. **Theobald Smith** (1859–1934) who had previously been appointed for comparative pathology at the veterinary school of Harvard became by Welch appointed professor and director for the Institute of Animal pathology at the Rockefeller Institute. The *Journal for Experimental Medicine* (*JEM*), printed by the Rockefeller University Press, is tightly connected with the Rockefeller Institute and still today belongs to the most prestigious scientific journals globally. The journal's webpage alludes to the alliance with comparative medicine by stating '. . .*The journal prioritizes studies on intact organisms and has made a commitment to publishing studies on human subjects*'.

Smith also was in personal contact with the Swiss **Karl Friedrich Meyer** (1884–1974), who was an exceptional scientist, eminent teacher, and "*walking encyclopedia*", active in the Berkeley University of California and at the Hooper Foundation for Medical Research. He followed ". . .*the tradition of Koch and Pasteur" and addressed medical problems in the fields of human and animal*

Table 1.2 Mission statements of international Departments of Comparative Medicine

Comparative Medicine at Stanford University
. . . advancing human and animal health through outstanding research, veterinary care and training naturally occurring and experimental animal models of human disease; biology and prevention of diseases of laboratory animals; research applications of animals
National Center for Research Resources: NCRR's "Division of Comparative Medicine helps meet the needs of biomedical researchers for high-quality, disease-free animals and specialized animal research facilities"
Comparative Medicine at Yale School of Medicine
. . .Research in the department is focused on modeling human diseases in laboratory animal models and diagnosing and treating disruptive diseases in laboratory animals
Comparative Medicine at UC Davis
. . . concept of "One Medicine" through interdisciplinary comparative medical research, teaching, and model development. The mission is to investigate the pathogenesis of human disease, using experimental animal models and naturally occurring animal diseases. . ..
Comparative Medicine at National Cancer Institute (*NCI*): *The Comparative Oncology Trials Consortium* (*COTC*)
. . .to improve the assessment of novel treatments for humans by treating pet animals-primarily cats and dogs -with naturally occurring cancer, giving these animals the benefit of cutting-edge research and therapeutics. . ..
Comparative Medicine at Messerli Research Institute, *Vienna*
. . .The chances of improving the fulfillment of the 3Rs (Replacement, Reduction, and Refinement) in medical research are realistic with the use of systematic comparative studies between humans and animals and the increasing encouragement of clinical studies in the veterinary field as an important alternative and supplement to studies using laboratory animals. . ..

diseases' (Sabin 1980). The following conveyed statement from Meyer indicates that the definition of comparative pathology and experimental medicine was indeed overlapping: '*You know*, *one must always get these infections either human or animal*, *into small laboratory animals*. *Then we can study them*, *because it*'*s too expensive to study them in larger animals*'. Meyer being called the Pasteur of the twentieth century shall be the last personality in this search for the roots of comparative medicine (Elberg et al. 1976).

Nevertheless, the (hi)story of comparative medicine goes on at the experimental medical institutes, where it is used as a basic principle for evaluating pathophysiological mechanisms and fostering drug development. Even though comparative medicine has been long regarded as a branch of experimental medicine or as a branch of veterinary medicine, it has developed its own identity. At least most of the prestigious universities have established institutes for comparative medicine. The interpretation of the topic, however, is diverse as can be seen from their mission statements (Table 1.2). The Comparative Medicine chair at the Vienna Messerli Research Institute is a joint venture between the Medical University, Vienna, and the University of Veterinary Medicine, Vienna. Its mission specifically encompasses the 3Rs by including animals as patients into scientific studies (Russell and Burch 1959), a strategy acknowledged by the European Centre for the Validation of Alternative Methods (Table 1.1) (FRAME 2005). Thereby, drug development will be simultaneously speeded-up for progress in human and animal medicine.

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