The impact of rabies and its treatment until the 19th Century: a lesson from the past

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Mentions of rabies are found in the early literature as far back as the 4th century BC. In the words of Aristotle, 'Dogs suffer from madness that puts them in a state of fury, and all animals which they bite when in this condition, become also attacked by madness'. This work is focused on the treatments used until the 19th century, analysing treatises that detail ancient treatments as well as more modern ones, but still based on the same ancient concepts. Current research and development are much more costly than in the past and therefore strategies for reducing the risk are sought. High-risk strategies, which explore new activity relationships, are less prevalent in the literature, reflecting a growing focus on established knowledge. We believe there is still room for investigations which start from the re-investigation of ancient recipes in the light of the latest technologies and equipment.

Introduction

Rabies is an infectious disease. The rabies virus is a species of the *Lyssavirus* genus, in the family *Rhabdoviridae*, order *Mononegavirales*. The word 'rabies' originates from the Latin *rabere* to rage or rave. Before Pasteur's discovery of a rabies vaccine, patients were shocked and afraid of a possible development of the disease leading to death. Alongside stories about werewolves and vampires, there was only one absolute certainty: survival was almost impossible. References to rabies are found in the early literature as far back as the 4th century BC. In the words of Aristotle, 'Dogs suffer from madness that puts them in a state of fury, and all animals which they bite when in this condition, become also attacked by madness'. References to the disease are found in the works of Virgil, Horace, Ovid and Plutarch. In humans, the disease was first recorded by Celsus in the 1st century AD, and he applied the name 'hydrophobia'. Galen, in the 2nd century AD, prescribed special remedies for rabies.

The transmission of the disease to humans by rabid wolves was recorded in 1591. An epizootic of rabies appeared in Paris in 1604, toward the end of the 17th century in Italy, and during the 18th century in France, Germany and England, and was first reported in the United States in 1768. Toward the end of the 18th century and during the 19th century, rabies had spread all over Europe. In Australia, it has been kept out by the enforcement of rigid quarantine laws. In the United States and throughout North America, the disease is widely distributed. Between the years 1876 and 1882, 44 people died of rabies in Massachusetts, then 45 deaths were recorded from 1888 to 1894,. From 1895 to 1908, according to Massachusetts Health Board statistics, 497 people were exposed to rabies and were given the Pasteur treatment.

Aim of the research and sources

This work is focused on the treatments used until the 19th century. In the first document,[1] *Discorsi di Dioscoride*, Pietro Andrea Mattioli reported and analysed the text of Dioscorides, resulting in an overview of ancient and contemporary (16th century) knowledge (Figure 1).

Figure 1. *De i segni del cane rabbioso*. I Discorsi di M. Pietro And. Matthioli sanese. In Venetia: Appresso Vincenzo Valgrisi MDLIX.[1]

Other 18th and 19th century rabies treatises[1-28] have been analysed. In the last considered essays, Luigi Toffoli, member of the *Accademia medico-chirurgica di Ferrara,* still linked rabies to ancient theories.[5-26] Our efforts in the field of the History of Medicine and Pharmacy are addressed not only to raising the profile of the History of Medicine and Pharmacy within the scientific community, but also to disclosing the field to the general population as a part of the traditional knowledge that needs to be preserved from globalisation. Furthermore, the History of Medicine and Pharmacy plays an important role in supporting modern pharmaceutical science and clinical practice today, as demonstrated by the link to current researches. Some examples of this will be reported throughout the present work.

Rabies treatments as reported by Pietro Andrea Mattioli in *Discorsi di Dioscoride*

He considered the human body consists of four cardinal humours: blood coming from the heart; phlegm from the brain and expanding to the whole body; yellow bile secreted by the liver; and black bile going from the spleen to the stomach. These four humours circulate in our body and, when combined in various ways, lead to health or disease. Sometimes they are too abundant, sometimes insufficient. They often decay, putrefy and are corrupted, and illness appears. Expelling these corrupted humours is the task of a drug, which will act differently in relation to its qualities and structure. Purgatives, emetics, diuretics and diaphoretics are among the favourite medications. Stress conditions, such as extreme cold or heat, lead to an imbalance of humours by causing a consequential illness.

Dogs become 'melancholy', and rabid. Infected humans become melancholy as well. Symptoms of rabies were anxiety, confusion, agitation and hallucinations. Patients became dangerous to themselves and others. Dogs either became ill by eating animals that died from the bite of poisonous animals, or because of lightning, or also by drinking cloudy and putrid water. In Galen's opinion, dogs were not the only animals to become rabid. It was also possible for foxes, wolves, weasels, martens, baboons and many others. Aristotle in the *VIII libro della Historia degli animali* also included camels and horses, and Avicenna also included mules. The dilemma was: were these last cited animals rabid because of a bite?

Treatments for rabies were the usual remedies used for the bite of venomous animals and there were also specific remedies for the bite of a rabid dog. Freshwater crabs burned with shoots and crushed gentian roots were mixed with wine to obtain a paste which was administered by mouth. If late, the dose was tripled. Crab powder was known as a rabies remedy and gentian as an alexipharmic. Some physicians confused freshwater crab with crayfish (Fig. 2). Crabs were called *Molleche* in Venice.

Scratches were worse than wounds as they could not expel the poison by bleeding. Torn parts had to be cut out with a razor. The venom had to come out of the body. Suction cups were employed in this process, and the addition of incense could increase its efficacy. A plaster made of tar, strong vinegar and opoponax was employed. Opoponax is a gum resin said to be obtained from the *Pastinaca opoponax* tree by a trunk or root incision.

Incense was replaceable with turpentine. Alyssum in honeydew water could be administered and treatment continued for 40 days. Jewish bitumen (*Bitume giudai)*, recommended by Aetius and administered with water treated patients with the fear of water. Seahorse (*Hippocampi marini*), minced with black vinegar and honey, could be drunk or applied to the wound.

A decoction of *Rumex* sp. L. (*romice* or *lapazio acuto*), was used to wash wounds after grass was applied to them. It is interesting to note that in a recent paper the dimeric proanthocyanidin epicatechin-3-O-gallate-(4ß-8)-epicathechin-3'-O-gallate (procyanidin B2-di-gallate) was identified as the main active principle of *Rumex* and that an enriched extract protects cells from influenza virus infection (an RNA virus like rabies) by inhibiting viral entry into the host cell. *R. acetosa* and procyanidin B2-di-gallate appear to be a promising expansion of the currently available anti-influenza agents.[29] The powder was drunk to purge the urine. The same key ingredient was also found responsible for inhibition of HIV virus replication (another RNA virus).[30]

Avicenna suggested cantharides, with blood in the urine as a sign of healing. Galen recommended oral or applied theriac. Common remedies were pondweed (*Potamogeton* spp.) plastered with salt on the bite, bark of wild fig pounded and drunk with water), wormwood, garlic, centaury, aristolochia, artemisia, germander (*Teucrium, camedrio*), water germander (*Teucrium scordium,* an alexipharmic or antidote to poison), bryony roots, pennyroyal, and *Silphium* (*lasero,* taken orally or applied to the wound*)*. In a recent research project that aimed to investigate natural products in drug discovery, the *in vitro* cytotoxicity and antiviral activity of extracts from traditionally used Mediterranean plants were highlighted as effective inhibitors of the replication of several viruses. This is another confirmation that ancient recipes were weak remedies in their traditional use but were not devoid of rational observations.[31] As an example, the literature contains several reports of the antiviral activity of *Artemisia*.[32]

Roasted liver of rabid dog was a more imaginative remedy, but Dioscorides disagreed with this method and Galen was doubtful about it. Dioscorides said that a tusk of a rabid dog could be tied to the arm in a leather bag in order to free patients from the fear of the water.

It was necessary to release the blood with razors, suckers or leeches. Bloodletting was not recommended as it could draw the poison inside. Or you could rely on St Donino and St Bellino: certain priests performed exorcisms and administered the so-called Benedict bread, which they may have thought contained something like a medicine. A safe treatment was cautery: fire would defeat the poison for sure. The wound should be kept open with salty things, with chopped wild garlic, onions and Cyrenaic liquor (*Medico Parthico*).

Wheat seed (both whole and wheat chewed while fasting) was applied to the wound. This could permit healing by increasing its volume and by expanding the wound continuously. It should be open, cut and cauterised, then a poultice made of salts should be applied followed by crushed mustard. Poultice, adhesive plasters, pitch, turpentine, and gum were recommended. The wound had to remain open for 40 days.

Rabies treatments reported in treatises of the 18th and 19th century

Mercury was ubiquitous in medical practice, especially in the 19th century, and was also used in the treatment of


De i Granchi de i fiumi. Cap. X.

LA CENERE de i Granchi de i fiumi bruſciati, data tre'dì à bere alla quantità di due cucchiari insieme con un cucchiaro di radice di gentiana,gioua efficacemente al morſo del cane rabbioſo. Impaſtata con mele cotto,mitiga le fiſſure del ſedere, & de i piedi,le bugance,& i cancari. Triti,& beuuti crudi con latte di aſina,giouano al morſo de i ſerpenti,de i ragni,che chiamano phalangi, & alle punture de gli ſcorpioni. Cotti, & mangiati con la loro decottione,giouano,à i phtiſici,& à chi ha ueſſe beuuto il lepre marino. Meſsi triti cõ baſilico ſopra à gli ſcorpioni,gli ammazzano. Tutto queſto fanno anchora i marini,ma con aſſai minore ſucceſſo.

SONO in manifeſſo errare coloro,che ſi penſano,che i Granchi ſcritti da Dioſcoride,& da Galeno,ſieno quelli che uolgarmente per tutta Italia ſi dimandano Gambari. Imperoche carcinos in Greco(come ſcriue Dioſcoride nel ſecondo capitolo)ui ſignifica il medeſimo animale,che chiamano i Greci aſtacos,ma quello di rit ôda figura,et senza coda

Nel ſecondo lib. di Dioſcoride. 195

che noi chiamiamo propriamente in Toſcana Granchio: & à Vinegia, doue ne uiene de marini una infinità, quando hanno mutato il guſcio ſi chiamano Molleche, della cui ſpetie ſono anchora quelli che chiamano Macinette, ſe

Figure 2. *De I Granchi de I fiumi.* I Discorsi di M. Pietro And. Matthioli sanese. In Venetia: Appresso Vincenzo Valgrisi MDLIX.[1]

rabies. Ravelly was the first to propose the use of mercurial preparations against rabies in *Traité de la maladie de la rage* in 1696.[2] The use was internal, as morsels. Later, mercurial frictions were also proposed. The aim was to cause salivation.

(a) Non immediatamente, ma più preſto. Anzi ſonvi non poche oſſervazioni di ferite anche gravi alla faccia, le quali non furono ſeguite da *idrofobia*. Vedaſene una notabiliſſima nel RAVELLY (*Traité de la maladie de la rage. Metz 1696.* 12.). Queſto Medico è ſtato peravventura il primo a proporre contro la *rabbia* l'uſo interno delle *preparazioni mercuriali*: ecco le ſue ricette:

℞. *Antimon. diaphoretic. g. xx,*
cinnabar. antimon. g. x,
ſal. volatil. e cornu cervi g. xii,
camphor. g. v; m. f. b.

Oppure

℞. *Mercur. dulc. g. xii, vel xv,*
pulver. oculor. cancror. præparat. g. xij;
ſal. volatil. e ſuccin g. v;
cum conſerv. roſar. ſ. q. miſ., f. b.

L'uno, o l'altro di queſti bocconi ſi dee prendere ogni mattina a digiuno, purgando il malato ogni

Figure 3. Ravelly preparations against rabies.[3]

In the third edition (1787) of an anatomical-surgical treatise of 1759,[3] mentioning Ravelly, all treatments of the time were traced: use of caustics; mercurials for internal and external use, turbit, powdered oyster shell alone or with herbs, meadowsweet, *Polypodium* fern (from near oaks), centaury; wormwood, St John's Wort, plantain, rue; betony, artemisia, lemon balm, savin, vervain, mint (powder of *Palmario*), leaves of rue, garlic, filings of tin, wine (Remedy of *Mayerne*), powder of terrestrial lichen, cinnabar (mercury sulphide) and mosses, opioids and antispasmodics, immersion and submersion, strong purgatives and hellebore (Dioscorides), and cantharides (Rhazes). The use of drastic purgatives and overly abundant bloodletting was not approved. Other remedies, like the most innocent powder of *Palmario* or the powder of oysters, were provided to please the patient, while continuing with other more effective remedies. Further remedies, such as pimpernel, *angolam* (a Malabar tree), scarabs and belladonna, are cited.

Rabies and its treatments were the subject of study both for physicians and for veterinarians. Scarlet pimpernel (*Anagallis arvensis*) was investigated in one single study and found active; the action was due to inhibition of virus-host cell attachment. In particular, the main component, a saponin, interfered with both early and late stages of herpes virus replication.[33]

A passage in a veterinary treatise edited by Hurtrel D'Arboval is very interesting.[4] Beside the usual prescriptions, bloodletting, emetics, purgatives, and, of course, antispasmodics, unexpected and prolonged diving in the sea or in fresh water were recommended. Other remedies included: oyster shell powder, mercury, artemisia, wormwood, white hellebore, cantharides, onion, root of plantain, opium and chlorine. Drinks or mucilaginous mash, infusions with orange leaves, arsenic, *scordio* (*Teucrium scordium*), sabine, clove, liverwort, wild valerian, *Scutellaria laterifolia*, copper filings, and tin filings mixed with theriac or Mithridate were suggested as remedies. The use of tin filings against the bites of rabid dogs was very well known. Cantharides beetles, *Lytta vescicatoria*, are well known for their vesicant properties due to an irritant component, cantharidin, a terpenoid comprising up to 5% in the insect. It is interesting to note that cantharidin has proved inhibitory activity against HBV virus in comparison with lamivudine and ribavirin.[34,35] Most of the activity of *Scutellaria laterifolia* is certainly due to its high flavonoids content (baicalin and its aglycone baicalein). The related plant *S. baicalensis,*[36] in view of the content of baicalin, has been shown to inhibit a number of viruses including Epstein-Barr[37] and influenza[38]. The flavonoids have demonstrated strong inhibition of reverse transcriptase and *in-vitro* inhibition of HIV infection[39].

As mentioned in the literature, pimpernel (alone or with ammonium carbonate), terrestrial lichen *cerognolo* (*Lichene cerognolo terrestre*) and *Meloe proscarabaeus* beetle were suggested as remedies against the bites of rabid dogs. *Anagallis* (pimpernel) is a plant of *Ranunculaceae.* Some species are still used in medicine. The decoction of this plant was used for plagues and bites of vipers and rabid dogs, while the juice was used for the treatment of scurvy. The use of the powder and extracts was reported in the Campana's *Farmacopea ferrarese* against hydrophobia.[40] *Lichene cerognolo terrestre* is an organism resulting from the symbiotic association of a fungus and an alga. Its use as a remedy against the bite of rabid dogs was just a popular belief as its effectiveness had never been demonstrated. *Meloe proscarabaeus* is reported in Campana: *Meloe majalis Lin. Meloe proscarabeus Lin Insetto intiero.* These insects were the ingredients of the electuary against rabies that was published in Berlin a few years before. Their supposed therapeutic activity is nowadays ascribed to the content of cantharidin (in particular in *majalis*) for its vesicant and diuretic properties.[41]

Tobacco, *Asclepias*, root of *Corydalis ussuriensis* (*aparina*), ash bark, and camphor (known as an antidote for the stings and bites of poisonous animals) were also reported as remedies. Tobacco is a herbaceous plant of *Solanaceae*. The juice was used for stings and bites of poisonous animals. To support the traditional use, a recent study has described the antimicrobial activity of cembranoids from tobacco leaves.[42]

Asclepias, milkweed, is a shrub of the Gentianaceae. The powdered root was considered a good antidote for bites of poisonous animals. Juice of *aparina* that was purified, mixed and drunk with warm white wine was used against the bites of poisonous animals. Ash is a tree of Oleaceae; Dioscorides advised applying the juice from its leaves to the wounds caused by snakebites. Camphor also acts as an antidote against bites of snakes.

Pimpinella, garlic, sage, pepper and vinegar remedies were known as alexipharmics (antidotes), as reported in this veterinary treatise. *Pimpinella* (also known as anise) is a herbaceous plant of the Umbelliferae. Boiled garlic root was used against intestinal worms and, if boiled in milk, it was a very powerful alexipharmic. Beside this, a

very recent publication has confirmed the use of this herb in infective diseases.[43]

Salvia (Labiatae) as a decoction was effective in spasmodic contractions, such as epilepsy. It was also considered an alexipharmic. The water produced by the distillation of the flowers was prescribed to prevent the poisons. *Pepe lungo*, pepper and vinegar were known as alexipharmics.

Belladonna, asafoetida, meadowsweet and mint, which were commonly used as antispasmodics, were suggested for the treatment of rabies. Belladonna is a herbaceous perennial plant of the *Solanaceae* from which atropine was extracted and used medicinally as both an analgesic and an antispasmodic. Asafoetida gum resin derives from the root of a native Persian plant, and was used as an antispasmodic. Meadowsweet (Rosaceae, *ulmaria*)) is used as both an antispasmodic and antiepileptic. Mint (Labiatae) was used as a balsamic oil for the treatment of convulsions. Some of these plants, in view of their traditional uses, have been re-investigated in recent years.[44,45]

Sleep apple (bedeguare) is an outgrowth that forms on branches and fruits of *Rosa canina,* and from which tannin was extracted. The outgrowth appears at the point where the gall wasp *Cynips* attacked the plant.

In Campana's *Farmacopea ferrarese*,[40] the decoction of broom *Spartium scoparium, ginestra*) was proposed as a treatment for hydrophobia as a gargle, in addition to the remedies mentioned above.

Existing blisters under the tongue, near the frenulum, were freed from the poisoned hydrophobic matter first. After that, they were cauterised and the patient had to gargle. The same decoction had to be to drunk for six weeks after the operation described.

All these remedies were confirmed by Ederle:[27] prophylactic measures, local applications to the wound (with a view of preventing the absorption of the hydrophobic virus), amputation, cautery, cupping-glasses and *Belladonna*, *Anagallis arvensis*, *Lichen cinereus* (principal ingredient in *pulvis antilyssus* of Dampiere), water plantain (*Alisma plantago*), *Scutellaria lateriflora*, strong vinegar, cantharides, *meloe majalis*, and opium. No remedy could be considered better than mercury to prevent hydrophobia.

Luigi Toffoli

Luigi Toffoli (1796-1867) was a chemist-pharmacist who published a myriad of treatises on rabies. Among many societies, he was a member of the *Società Medico-Chirurgica* of Ferrara. Many of his volumes are present in the library of this academy,[6-25] while only one can be found in the University library[26]. In three of his works – two[17,18] in 1859 and one[25] in 1864 – his theories are clearly expressed: *Rabbia primitive* (primitive rabies) is developed in the dog, and then transmitted to other animals and humans. A health plan for animals was useful to prevent rabies through the segregation of dogs. Conflicts with rivals and sexual frustrations could be avoided for possible development of the primitive rabies in the dog. In the treatise *Sulla rabbia ed altri argomenti: lettera al dott. Luigi Bosi* [On Rabies and other arguments: letter to Dr Luigi Bosi],[24] which was published in 1863, we can find a clear link to the *Accademia di Ferrara* (the letter is addressed to Bosi, ex-President of the same). In some works, acclaim from eminent colleagues emerges. These baseless theories apart, what is reported in *Osservazioni di Luigi Toffoli sopra il rimedio contro l'idrofobia pubblicato d'ordine superiore in Parigi* [Observations of Luigi Toffoli on the remedy against hydrophobia published by the higher order in Paris] (1836) are very useful for our research to continue describing the remedies of the 18th century.[5] Toffoli did not approve of washing the wound with a rough diaper and squeezing the blood to irritate the skin. Even the use of cupping was judged not very reliable. In contrast, he approved: showers; making wounds more extensive (as stated by Aetius) to release as much blood as possible; washing with chlorine solution; and cauterising deeply and widely with caustic, with application of plaster vesicant in order to maintain an abundant suppuration. He agreed with Celsus, Aetius and Dioscorides regarding the use of surgical instruments. He suggested either the amputation of 'part-biting' (in the case of fingers, hands and feet) as a safe remedy, or the cauterisation (*ambustione*) with a red-hot iron when the wound is wide but not deep. Cauterisation with *butirro di antimonio*, the use of oil of vitriol and silver nitrate powder methods are abandoned. The preparation *Butiro di antimonio* (antimony chloride) is reported in the *Farmacopea ferrarese* of Campana.[40] The caustic product had an oleaginous consistency, which is why it was called *butirro* (butter*)*.

Francesco Jachetti, professor of the School of Pharmacy in Ferrara, was also a member of the *Accademia* and wrote on hydrophobia.[28] Remedies were: cauterisation (chlorine or fire), *Parenti* powder (made of cantharides and pepper), enemas (made of antispasmodics or of *Nicotiana*), epigastrics, morphine acetate pills, opium, calomel, and finally, blessing with the keys of St Donino. Symptoms of rabies were vesicles under the tongue, as described by Marocchetti.

At the end of the 19th century, the research of Pasteur led to the discovery of the agent responsible for the disease. It had a neurotropic character and it was demonstrated that the virus was present not only in saliva, but also in the nervous system. In 1884, Pasteur produced the attenuated virus, which allowed him to develop a vaccine in 1885. In that year, the vaccine was used for the first time to treat a child in an emergency situation. This child, Joseph Meister, remained at the Pasteur Institute as a collaborator.

Louis Pasteur

On Monday 6th July 1885, Joseph Meister, aged nine, was brought by his mother to Pasteur from Alsace in the hope of preventing the disease (Figure 4). He had been bitten by a rabid dog on 4th July Several factors made Pasteur's potential involvement in the boy's care controversial.

Pasteur had never before successfully used the vaccine on a human. Pasteur's notebooks indicated that two previous attempts had been made. One involved a 60-year-old man who left the hospital after only one injection and did not return. The other was a 10-year-old girl, treated with one injection, who died before the second could be given.

The concept of attenuation of viruses and bacteria was at an embryonic stage at this time. Injecting a human with a disease agent, even a weakened one, was a new and controversial action. Pasteur was not a medical doctor and might have faced serious consequences had Meister not survived the injections. Louis Pasteur felt certain that the boy would die from rabies infection if he did nothing. With some reluctance, the scientist was persuaded by Drs Vulpian and Grancher of the Académie de Médecine to give Dr Grancher the emulsion from the cord of a rabbit that had died of rabies on 21st June, and had been kept in dry air for 15 days.[46-48] The child was given 13 further inoculations over 10 days with portions of the rabbit spinal cord that were progressively dissected so as to enable the attenuation of the virus in order to become avirulent. The vaccine was thus produced. After three months and three days he announced that the child's life was now out of danger and his health appeared excellent. Meister never developed rabies, and the incident was regarded as a success. Later in life, Meister became the protégé of the chemist, who made him guardian of his Institute and then, after the scientist's death, he became the guardian of Pasteur's tomb at the Institut Pasteur in Paris.[49] On 20th October of the same year, Pasteur successfully treated another patient infected by a mad dog six days earlier. By 1886, he had treated 350 patients from all over Europe, Russia and America.[50-51]

The death of Joseph Meister

From at least 1950 a mythical version of his death circulated widely. It was said that inn 1940, during the German occupation of France, Joseph Meister, the first man in the world that Pasteur had vaccinated and saved from rabies, now aged 64 and caretaker of the Pasteur Institute in Paris, refused to allow Wehrmacht officers who asked to visit the crypt of Louis Pasteur to enter the tomb in which the scientist and his wife since had rested for 45 years. Unable to prevent the soldiers from entering, Meister was said to have returned home to 25 rue du Docteur Roux, where the famous Institute is located, and committed suicide with his service revolver, which he had held since the First World War. The history of the dispute with the German soldiers was not however supported by additional elements or definitive evidence. But there is also another hypothesis that would seem the most accepted suggesting that Joseph Meister did not shoot himself with his revolver from the 1914-18 war, but committed suicide with gas.[52] On June 13, while the Germans were approaching Paris, Joseph Meister had forced his wife and two daughters to leave Paris against their will. About ten days after the capitulation of France, Meister, having no news of them, was persuaded of their death. Judging himself guilty, he wanted to end his days by committing suicide in his house with a gas stove, on June 24, 1940. That same evening, however, Mrs Meister and her daughters returned to the Pasteur Institute and learned of his death. Eugene Wollman wrote in his diary:

> If Meister had resisted for 24 hours to his trouble and depression for his family, everything would be back to normal.[53]

Contemporary sources and family narration from his grand-daughter, Marie-José Demouron did not mention an incident with the Wehrmacht. At the time of his suicide, representatives of the German army came several times to the Pasteur Institute, which became the centre of medical reference for venereal diseases for the occupying troops.

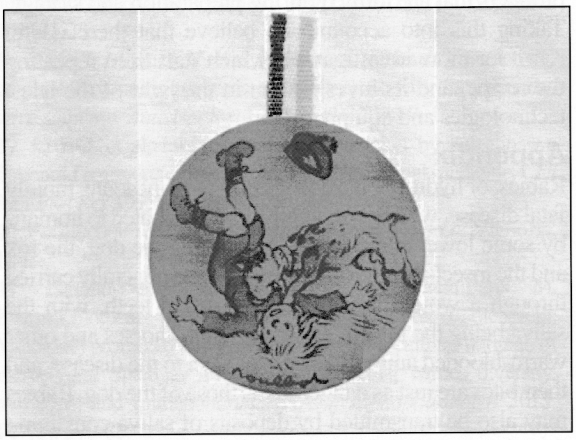

Figure 4. A 1923 commemorative tag represents the attack on Joseph Meister, the first person on whom Pasteur successfully used rabies vaccine. *The Historical Medical Library of The College of Physicians of Philadelphia.*

Conclusions

The four cardinal humours theory, which identifies the disease as an imbalance in the temperaments, defines the rabid melancholy. The theory that rabies could arise spontaneously in animals in stress conditions persisted until the 19th century (Toffoli). Transmission through the dog bite and saliva was known. The reliable solution, amongst many proposals, was either the use of a red-hot iron or amputation. The use of the razor to remove open parts that may have come in contact with the saliva and keeping the wound open for at least 40 days in various ways could not guarantee a cure. Scratches are more dangerous because they do not bleed. The wound should be washed and left to bleed as much as possible. Cupping glasses can be used. Bloodletting must be avoided as it would attract the evil in the body. The main remedies are classic alexipharmic treatments. Mercurial compounds are also used for internal use and as frictions. In the late 19th century, thanks to Pasteur, the vaccine finally arrived.

Current research and development are much costlier than in the past and therefore strategies for reducing the risk are sought. High-risk strategies, which explore new activity relationships, are less prevalent in the literature, reflecting a growing focus on established knowledge at the expense of new opportunities.[54]

In this context, an approach that takes into consideration past experience, such as those deriving from tradition, can be less expensive in terms of costs and time, thus reducing overall investment. Descriptions of traditional remedies are very useful in this contest,

because traditional uses still represent the largest 'clinical' study ever conducted by human beings.

One of the most complex aspects in reviewing ancient preparations is, however, related to the Galenic, i.e. preparative methodologies, which are not easily understandable and do not make clear what part of the activity is linked to original molecules or their by-products that are formed during preparation and storage. Taking this into account, we believe that there is still room for more investigations which start from repeating the recipe, and its investigation in the light of the latest technologies and equipment.

Appendix

Rabies, or hydrophobia, is a specific, highly acute, rapidly fatal disease, which is generally communicated to humans by some lower animal, most commonly the dog, the fox and the insect-eating bat. The infection is generally carried through a wound made by the animal's teeth, with the saliva being the infective medium. Cats, horses and other warm-blooded animals are also subject to the disease, and their bites are just as dangerous as those of the dog. Rabies may also be transmitted by deposits of saliva containing the virus on abraded surfaces, such as by licking, or through wounds received while performing autopsies on infected subjects. The saliva of the dog has been shown to be virulent 24 to 48 hours before the animal exhibits any symptoms of illness.

The disease in the dog appears in two forms: the dumb variety, which is by far the most common, and the furious type, which because of its wild, migratory character is more dangerous to the community. The dumb variety is characterised by progressive paralysis of the lower jaw and marked nervousness, and death usually results within three to six days. The animal may appear very affectionate, but may bite without warning. In the furious type, the dog will bite anything which comes its way.

The incubation period varies with the severity and location of the bite, the virulence of the virus, and the species of the animal that is biting and is being bitten. In humans, the incubation is roughly from 14 to 90 days or longer; in dogs, 14 to 60 days, but it may be as short as 6 days; in rabbits, 9 to 90 days; in guinea pigs 8 to 60 days. After the central nervous system infection is established, the virus spreads by autonomic and sensory nerves to multiple organs, including the salivary glands of rabies vectors including dogs and secreted in saliva.

The Pasteur treatment has reduced the mortality from rabies from about 16% in the untreated, to 1% or less, in the treated. Its effectiveness depends upon the incubation period being sufficiently long for an immunity to be established before the onset of the symptoms. Failure may be due to the virulence of the infection, proximity of the wound to the nerve centres, or a delay in the administration of the treatment.

The treatment is described as 'an emulsion of the cords of rabbits that have died as a result of the subdural injection of fixed rabies virus'. The fixed virus is obtained by passage of the rabies virus through a long series of rabbits until the animals die after a uniform period of incubation; this period may vary according to the strain of virus. The cords are removed from the rabbits and, as a rule, dried over potassium hydroxide for a period of from two to fifteen days. Antirabies vaccine is used for the preventive treatment of rabies.

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