And they make music, and some of them run away from the light while others enjoy it. Others howl like dogs and bite whomever approaches them, who in turn get afflicted also. Some people mentioned that they saw one or two men bitten and loose, and that Odimus and Hemson were affected by the disease and that one of them succumbed to the disease after being bitten and then expired; the other, however, was staying with a friend and manifested fear of water and ran. (Translation, courtesy of Mr. A. E. Najjar.)
The Natural History of Rabies
2nd Edition

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To Olga
THE EDITOR

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He received his doctorate in veterinary medicine from the New York State Veterinary College at Cornell University, Ithaca, New York, in 1959, and after a year of private equine practice in New York and California entered the School of Public Health, University of Michigan, Ann Arbor, where he received his masters degree in public health in 1961. That same year he entered the Epidemic Intelligence Service (EIS) at the Centers for Disease Control (CDC) in Atlanta, first assigned as a veterinary epidemiologist to the New York State Health Department in Albany, New York (research on psittacosis, brucellosis, and various aspects of rabies). In 1964 he was assigned to the Southwest Rabies Investigations Laboratory in Las Cruces, New Mexico (studies on bat rabies). From 1966 to 1969 he was consultant to the Pan American Health Organization in Mexico City (canine rabies vaccine production, surveillance of zoonotic diseases, and research on vampire bat rabies). He returned to the CDC in Atlanta in 1969, where he continued studies on wildlife immunization, including the demonstration in 1971 that an attenuated rabies vaccine would immunize foxes orally (in collaboration with Drs. Jack Debbie and M. Abelseth of the New York State Health Department). His research has continued with other wild animals, including raccoons, skunks, mongooses, and dogs.

He is the author of over 70 scientific publications and the editor of a two volume treatise on rabies. He is a member of the American Public Health Association, the New York Academy of Sciences, the American Veterinary Medical Association, and secretary of the International Society for Veterinary Epidemiology and Economics.
PREFACE TO THE FIRST EDITION

Rabies is a unique virus in that it manages to exit in the saliva when its host is stimulated to bite — a mean accomplishment. Most people are not aware that the dog is still by far the worst offending species for man and that rabid vampire bats cause hundreds of thousands of cattle deaths in the Americas annually. With few exceptions the disease is no less a worldwide problem than it was centuries ago.

This two-volume treatise should serve to underline those aspects of the virus for which control methods are known (and often not applied) and those requiring further investigation (many, indeed, in order to bring us out of the virological dark ages). This volume deals with the more fundamental aspects of the virus. Chapters in Part I emphasize virus characteristics: morphology, chemistry, physical makeup, and relationships to related viruses. Part II deals with virus growth. The chapters on in vivo pathogenesis begin with the entrance of the virus, then go on to its spread in the central nervous system and its subsequent exit. Also included is a chapter on latency, still a subject of much disparate opinion. Chapters in Part III cover current diagnostic methods, including those used for determination of virus presence and those used for antibody titration.

Each chapter emphasizes a special area of the disease, and there is a danger that such areas assume unwarranted importance compared to the whole. The thundering words Ortega y Gasset wrote in 1929 come to mind:

The 19th century begins its destinies under the direction of those that still live encyclopedically, although their training is already of a specialized character. But when, in 1890, a third generation takes the intellectual command of Europe, we find a type of scientist unique in history. He is a man who, of all that a discreet person should know, knows only a certain science, and even of that science really only knows that small portion in which he is an active investigator. He actually proclaims it a virtue not to know anything outside the narrow field in which he specializes, and accuses those having curiosity for general knowledge of “dilettantism.”

But this creates an extraordinarily strange class of men. The investigator who discovers something new in nature necessarily has a sense of dominion and self-confidence. With apparent justification he thinks of himself as “a man who knows.” And, in reality, there is within him a piece of something that, together with other absent pieces, really constitutes knowledge. The specialist “knows” his minimum corner of the universe very well, but ignores the very roots of all the rest.

I have said that he is thus a figure without counterpart in history. Because before now men could be divided, simply, into wise or ignorant, into more or less wise and more or less ignorant. But the specialist cannot be placed under either of these two categories. He is not wise, because he ignores all except his speciality; but neither is he ignorant, because he is a “man of science,” and knows very well his tiny piece of the universe. We would have to call him a wise ignoramus, an extremely serious situation, since he is thus an individual who will behave, in all those fields which he ignores, not as ignorant, but with all the petulance of one who is wise in his special area.

But specialization, which has made possible the progress of experimental science for a century, is approaching an era in which it cannot progress alone, unless it results in the next generation’s building new and stronger bonds. But if the specialist is not aware of the internal physiology of the science he cultivates, he especially ignores the historic conditions for his existence, that is, how society — and mens’ hearts — must be organized for there even to continue to be researchers.

Reproduced with permission from La Rebelión de las Masas, by Ortega y Gasset (1929), Revista de Occidente, Madrid.
(Translated by the editor.)

This book was conceived by Dr. Goeffrey Bourne, distinguished scientist and director of the Yerkes Regional Primate Center, Emory University, Atlanta, Georgia, and I thank him for this wonderful opportunity and also for his continued help. Many people have assisted me in preparing this treatise and revising it for final publication, too many to
acknowledge individually. Most special thanks for its publication are due Mrs. Barbara B. Andrew, my tireless secretary, who worked after hours on many evenings and weekends, typing draft after draft, to put it in final form.

George M. Baer
PREFACE TO SECOND EDITION

In 1975, when the first edition of this book was published, oral rabies vaccination of foxes was only a laboratory phenomenon, human diploid vaccine was not yet in widespread use, and neither monoclonal antibodies nor recombinant rabies vaccines had been prepared.

Remarkable changes have occurred since then. Oral rabies vaccination was given its first successful field test by Drs. Franz Steck and Alex Wandeler in Switzerland in 1978, when they distributed chicken heads containing small aluminum packets filled with attenuated vaccine for consumption by foxes, with the result that rabies has now been virtually eliminated from that country, and markedly reduced in other parts of Europe. Since the attenuated vaccine that immunizes foxes is not effective in other species, efforts are being made to immunize raccoons, skunks, mongooses, and dogs with recombinant vaccines, as well as testing a variety of baits for those species. The viruses in affected areas have been identified by monoclonal antibodies, a technique developed in the 1980s to differentiate virus variants.

The widespread use of human diploid vaccine and other potent cell culture vaccines has changed human treatment in the last decade. As a result, the regimen used for exposed persons has been both reduced and refined from the administration of equine antiserum plus 21 to 23 doses of vaccine to, now, human rabies immune globulin and five doses of purified cell vaccine.

Little of this has been applied to the developing countries of Asia, Africa, and Latin America, where rabies is still rampant in dogs, resulting in hundreds of people dying of rabies, almost none of whom have been received postexposure prophylaxis. I made the comment in 1975 that ‘‘with few exceptions the disease is no less a worldwide problem than it was centuries ago.’’ This is still true. It will require considerable ingenuity and continuity to control canine rabies in developing countries. Oral canine vaccination is one tool that holds promise for such a goal, with various candidate recombinant vaccines shown effective in laboratory studies.

Although notable progress has been made in various aspects of rabies, there is still a splintering of efforts in research and control and, as I commented in the first edition, a great need to bring these efforts together. The concerns that Ortega and Gasset expressed in the early part of this nineteenth century, already quoted in the first edition of this book, are still most relevant. The same doubts have been expressed by Edna St. Vincent Millay, who wrote that:

Upon this age, that never speaks its mind,
This furtive age, this age endowed with power
To wake the moon with footsteps, fit an oar
Into the rowlocks of the wind, and find
What swims before his prow, what swirls behind—
Upon this gifted age, in its dark hour,
Rains from the sky a meteoric shower
Of facts . . . they lie unquestioned, uncombined.
Wisdom enough to leech us of our ill
Is daily spun; but there exists no loom
To weave it into fabric; undefiled
Proceeds pure Science, and has her say; but still
Upon this world from the collective womb
Is spewed all day the red triumphant child.

Edna St. Vincent Millay—Sonnets (Collected Poems, 1949)

Let us hope that efforts to control and even eliminate rabies can be woven together in the future to radically reduce human rabies exposures and deaths.
I would like to thank all those people who have made publication of this book possible, too many to list individually. Special thanks go to the rabies section at the Centers for Disease Control, a group that has always been most supportive over these many years.

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Chapter 1

HISTORY OF RABIES AND GLOBAL ASPECTS

James H. Steele and Peter J. Fernandez

Rabies has a long and interesting history that is lost in antiquity. Plutarch asserts that, according to Athenodorus, it was first observed in mankind in the days of the Asclepiadæ, the descendants of the god of medicine, Asculapius. Acteon, the famous hunter of myth who was torn to pieces by his hounds when he surprised Diana and her attendants at the bath, was thought to have been destroyed by rabid dogs. In the Iliad, Homer is thought to refer to rabies when he mentions that Sirius, the dog star of the Orion, exerts a malignant influence upon the health of mankind. The dog, Sirius, was associated with mad dogs all through the eastern Mediterranean and Egypt, and later Rome. Homer further uses the term "raving dog" in the epithets that are thrown at Hector by Teucer. The Greeks had a special god in their mythology to counteract the effect of rabies, Arisaeus, son of Apollo. Artemis is represented as the healer of rabies.

The Greeks called rabies Lyssa or Lytta, which meant madness. The disease in man was described as hydrophobia in which the sick person is tormented at the same time with thirst and the fear of water. The Latin word "rabies" comes from an old Sanskrit word "rabhas" which translated means "to do violence." The German word "tollwut" originates with the Indogermanic "Dhvar", to damage, and "wut" from middle German "wuot" which is rage. The French word "rage" is derived from the noun "robe", to be mad.

Democritus is thought to have made the first recorded description of canine rabies some 500 years B.C. Aristotle, in the 4th century B.C., wrote in the Natural History of Animals, Book 8, Chapter 22, "that dogs suffer from the madness. This causes them to become very irritable and all animals they bite become diseased." Fleming states that Aristotle believed that mankind was exempt from its attacks. This is strange indeed, when hydrophobia was already known as a disease of men. Hippocrates is supposed to refer to rabies when he says that persons in a frenzy drink very little, are disturbed and frightened, tremble at the least noise, or are seized with convulsions. He is said to have recommended boxwood (Buxus) as a preventive. Plutarch also writes about the dangers of rabid dog bites, and that the illness can be spread by the bite of a rabid dog. Others who mention rabies in ancient times include Xenophon, in the Anabasis, Epimarcus, Virgil, Horace, and Ovid. Lukian, a Roman writer, was of the belief that not only was the disease spread by biting dogs but that persons who became rabid could spread the disease by biting other persons, and could affect a whole group of people.

The infectivity of the saliva of rabid dogs is described by Cardan, a Roman writer. The Roman writers described the infectious material as a poison for which the Latin was "virus". Another cause of rabies which is first mentioned by Pliny and Ovid is the so called dog tongue worm. To prevent rabies, in ancient medical times, the attachment of the tongue (the frenum linguae, a mucous membrane) was cut and a fold removed in which the worm was thought to be. This idea was to persist until the 19th century, when Pasteur demonstrated the cause of rabies.

* A near such episode occurred in southern California in the 1950s when a patient who was suffering from rabies escaped from a hospital in a restraining gown. In bringing him under control, he attempted to bite nurses, doctors, and policemen. Fortunately no one was bitten severely but many persons took antirabies vaccine because they were uncertain of their exposure.
Celsus, a physician and naturalist, made rabies his particular study in the 1st century. He was emphatic that the bites of all animals that contained virus were dangerous to man and beast. Indeed, Celsus and his contemporaries recognized that the saliva alone contained the poisonous agent. In his description of wounds he says, "I have spoken concerning those wounds which are mostly inflicted by weapons, so it follows that I may speak concerning those which are made by the bite, sometimes of a man, sometimes of an ape, often of a dog, and sometimes of wild animals or of serpents. But every bite has mostly some venom" (autem omnis morsus habet fere quoddam virus). Of the malady itself he writes "The Greeks call it hydrophobia, a most wretched disease, in which the sick person is tormented at the same time with thirst and the fear of water, and in which there is but little hope".  

He recommends the practice of resorting to caustics, burning, cupping, and also sucking the wounds of those bitten by rabid dogs. He points out that there is no danger in sucking wounds except if there should be an abrasion or sore on the lip or in the mouth. If the wound is serious the cupping instrument is to be applied; if slight, a plaster can be used. Afterward, if the wound does not involve a nerve or muscle, the wound is to be cauterized. If it cannot be burnt, bloodletting should be attempted. The wound should then be treated as a burn. But if it cannot be burnt then use those medicines which violently corrode, after which the ulcer will be healed in the usual way.

These sagacious precautions not only show the disease was well understood but that it was more or less prevalent and taxed the medical skills of the times. Hot and cold baths were other measures recommended by Celsus. He states that when the disease appears, "The only remedy is to throw the patient unexpectedly into a pond, and if he has not a knowledge of swimming to allow him to sink, in order that he may drink, and to raise and again depress him, so that though unwillingly, he may be satisfied with water; for thus at the same time both the thirst and dread of water is removed."* Celsus also mentions the danger of cold water, lest it destroy the enfeebled body. In those cases, the patient should be put into hot oil. In some cases, he says hot baths should be given immediately after the bite of a rabid dog, allowing the patient to sweat while he still has the strength. In doing this the wound is also opened and the virus distills out. Then, large quantities of pure wine should be taken which is antagonistic to all poisons. When this has been done for 3 days the person should be free from danger. Celsus also recommends salt as an application to wounds caused by the bites of dogs.

Virgil, in his Georgics, classes rabies among the diseases caused by a pestilential state of the air. Pliny, in his hearsay story of the dog tongue worm, states further, if the worm is removed and carried three times around a fire and is given to an exposed person, this will prevent him or her from becoming mad. Many other tales of the prevention and treatment of disease are found in Fleming.† These include eating a cock’s brain or a cock’s comb pounded and applied to the wound, and using goose grease and honey as a poultice. The flesh of a mad dog is sometimes salted and taken with food as a remedy. In addition, young puppies of the same sex as the dog that inflicted the wound are drowned, and the person bitten eats their liver raw. The urine of mad dogs was also considered poisonous by the ancients. If trod upon it was considered injurious, more so if a person had an ulcerous sore. In these cases, horse dung sprinkled with vinegar and warmed should be applied. Other treatments stretch the imagination. They include applying the ashes of a dog’s head to the wound, or ashes used in a potion; some even recommended eating the dog’s head. Others were the placing of a maggot, taken from the carcass of a dead dog, on the wound. The

* This formidable treatment was continued until the 19th century according to Fleming, who cites a cooper of Ghent being cured by submersion in the sea. He was dropped in the ocean from a ship and allowed to sink with the aid of irons. After a couple of submersions he was brought to the deck, revived, and lived.
hair or ashes of the hair of the tail of the dog that inflicted the wound were also inserted into the wound.*

Another story of antiquity — which has lived down to this day in some parts of the world — is related by Columella; shepherds believed that if, on the 40th day after the birth of a pup, the last bone of the tail is bitten off, the sinew will follow with it. After this the tail will not grow, which will prevent the dog from getting rabies.

Writers of the early Christian era had much to say about rabies, describing it both in dogs and man. This is true of all of the Roman empire but especially Greece and Crete, where the disease was widespread. Sicily must have had much disease, as noted by the frequent references. The administration of fluids is discussed by many writers. Some recommend snow, others the use of a straw in a dark room and, if no oral methods succeed, the use of enemas. Treatment of lower animals is described in the 3rd century by Vegetius Renatus, one of the early writers on veterinary medicine. He recommended as an antidote for cattle that have been bitten by a mad dog, to feed the boiled liver of the dog to the cattle to eat, or to make it into balls and force it down as medicine. In the 6th century there are further accounts of the disease. Aetius, a physician of Mesopotamia, has left an accurate description of the dog disease. The symptoms were manifested by the dogs becoming mute, then delirious and incapable of recognizing their masters and surroundings; they refuse food, are thirsty but do not drink, and usually pant; they breathe with difficulty, keep the mouth open with the tongue hanging out, and discharge an abundance of frothy saliva; their ears and tail hang down, they move slowly and are dull and sleepy; when they run it is faster than usual and in an irregular and uncommon manner.

A century later Paulus Aegineta, a Greek physician, offers a good account of hydrophobia. He follows previous authors in enumerating the symptoms and distinguishes between the disease due to the bite of dogs and that emediable, simple nervous hydrophobia arising from other causes. The inoculated hydrophobia was always fatal.

Native Syrian doctors believed at the beginning of the ninth century that the disease was incurable. They attempted to give water in a globule of honey which was to be put in the mouth.

Rhaazes, a celebrated Arab physician, mentions hydrophobia and says that a certain sick man barked like a dog by night and died.** He also described a patient who, when he beheld water, was seized with trembling and rigors, but the symptoms ceased when the water was removed.

The Arab physician Avicenna, of the 11th century, speaks of rabies. He directs that the wound be kept open for 40 days and that ordinary blisters be placed on it. He alludes that persons with hydrophobia bark like dogs, and have a desire to bite people; patients who attempt to drink suffocate, and the illness terminates in apoplexy. Altogether his observations mark a step forward in understanding the disease. He describes a dull redness of the skin, or erythema, which had been designated as rabic roseola. There have been other cutaneous symptoms in man which received the names of rabic pleiads and rabic bubo.¹

The 12th century Talmudic scholar and physician, Moses Maimonides also addressed the treatment of rabies. In his treatise on Poisons and Their Antidotes, written in 1198 at the request of Sultan Al Afdal, Maimonides enumerates various “remedies against the bite of mad dogs”.³

The earliest mention of the disease in Great Britain is in the laws of Howel the Good, of Wales, in 1026, in which an outbreak is alluded to as a most noteworthy event, and the assertion that there was a madness among the dogs during that year.⁴

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* This form of therapy brings to mind the recommendation of bacchanals of centuries past and present to seek relief by resorting to the potion which hung them over.

** Karl Habel (National Institutes of Health) describes such a patient near Washington, D.C. in the 1940s who made barking sounds and died of rabies.
From this period the literature of rabies gradually expands, and with the progress of medicine the remarks become more valuable and comprehensive, though, so far as the successful prevention or attempts at curing the malady are concerned, little progress appears to have been made.

The Sorbonne condemned all superstitious practices for the treatment of rabies in a declaration June 10, 1671. Earlier in the 15th century the celebrated theologian, Gerson, had already pronounced against them. There was great faith in the miracles of St. Hubert, practiced as late as the 19th century, even though many who went to the shrine near Liége, Belgium, died of madness. A critical history of superstitious customs published in 1709, by Father LeBrun, states that those cured have either not been bitten by mad dogs or have had other ailments distinct from hydrophobia; or, it has been the strength of their constitutions or the physical remedies which have cured them, and not the miracle suggested by the most skilled theologians and some medical people. He treats the practice of the miracle as eminently superstitious and refutes the system.

The clergy of St. Hubert of course replied to the attack, but by arguments which failed to meet the objections raised, and the question appears to have rested where all such questions remain — the world of common sense denies the miracle, the superstitious affirm it.

In many Rhine villages the so called Keys of St. Hubert consisted of an iron, heated red hot and applied to the animals bitten by mad dogs. It never appears to have been in the form of a key. In St. Hubert itself, the amulet was an iron ring inserted in the wall of one of the houses in the principal street. It no longer exists, but in the 19th century the belief in the potency of St. Hubert among the peasantry was as strong as ever. In other towns such as Liége there was also an iron ring, while in Utrecht there was an iron cross.

Up until the Middle Ages rabies epizootics appear to have been rare. Most cases were single bites of rabid dogs, and occasionally of wolves, badgers, foxes and even bears. Fleming\(^5\) tells of the invasion of Lyon by a rabid bear (about the year 900) which bit some 20 people who attempted to kill it. Six people developed madness and were smothered to death in the next 27 days.

The first large rabies outbreak is that described in Franconia in 1271 when rabid wolves invaded towns and villages attacking herds and flocks, and that no fewer than 30 persons died following bites inflicted on them. In 1500, Spain was said to be ravaged by canine rabies. By 1586 there were epizootics of rabbits among dogs in Flanders, Austria, Hungary and Turkey. In 1604, canine rabies was widespread in Paris and caused great alarm. In the 1700s rabies appeared in many parts of Europe. From 1719 until 1721 rabies was uncommonly frequent, especially in France and Silesia. It continued to be a problem in central Europe, where it erupted among the wolves and foxes. In England the disease appeared in 1734 to 1735, many mad dogs being seen in the late summer.

Rabies was reported by a priest in Mexico to his superiors in 1703. Malaga Alba\(^6\) goes on to state the the priest was admonished by superiors in Spain that rabies was not a problem he should be concerned with. This report of 1703 is the earliest in the Americas.

Fleming\(^1\) states that in 1741 many dogs went mad in Barbados, where even cattle were affected. A correspondent writing from Charles Town, November 10, 1750, says that since the first of the year a kind of madness has appeared in the dogs, first in the country and later in the city. No mad dogs had previously been reported in the colony. He reports no persons bitten but says that the disease spread rapidly among the dogs. If the dogs were not killed they died in 2 or 3 days. He also states that some hogs were affected in the same way.

In 1752 rabies appeared about St. James in London, and orders were issued to shoot all dogs on sight; such orders were also issued in country towns. The years 1759 to 1760 saw a serious outbreak of disease in and around London, and the city officials issued orders for all dogs to be confined for a month and ordered the destruction of all dogs on the streets.
with a reward of two shillings for each dog killed. Great cruelty resulted from this bribe to slay unfortunate dogs, and the most barbarous scenes were enacted by the brutal rabble which received a premium for their savage behavior. The London outbreak lasted until 1762. By 1774 the disease was general in England and people were discouraged from keeping dogs. Paupers were not allowed to keep dogs. Up to five shillings were paid for every mad dog killed. In 1763 rabies was reported in France, Italy, and Spain. The authorities slaughtered dogs by the hundreds. In Madrid 900 dogs were killed in 1 day.

In 1768 rabies was already alarmingly frequent in Boston and other towns in North America. The archives of the State of Virginia contain references to rabies in dogs as early as 1753, and those of North Carolina as of 1762. The first major epizootic in North America was reported in 1768, continuing until 1771 when foxes and dogs carried the disease to swine and domestic animals. The malady was so unusual that it was reported as a new disease.¹

From 1776 to 1778 the French West Indies was affected for the first time, and in epizootic form. In Guadaloupe the dogs were attacked with dumb madness. Many dogs died of dumb rabies but others became mad and bit everything that came in their way. Many cattle (as well as humans) were bitten and died.

In 1779 rabies was very common in Philadelphia and Maryland. It first appeared in Jamaica and Hispaniola (Haiti and the Dominican Republic) in 1783, and continued until 1784. Domestic animals including horses, swine, and goats perished from the disease, and many persons were bitten and died. The disease was so extensive in Kingston that all dogs were ordered killed. Likewise, thousands of dogs were killed in Port-au-Prince.

Canine madness was raging all over the colonial states of North America in 1785 and continued until 1789. That year a man died of hydrophobia in New York after skinning a cow that died of rabies. In 1797 the disease appeared in Rhode Island as an epizootic among dogs and domestic animals. The disease reappeared in the eastern United States in 1810, and in Ohio was epizootic in dogs, foxes and wolves.¹

In the 19th century rabies appears to have become more widespread in Europe, especially France, Germany, and England. An extensive fox outbreak occurred in the Jura Alps in eastern France beginning in 1803.² This was reported as the largest outbreak ever seen. Hundreds of dead foxes were seen in the country foothills of the Jura Alps. Many people, dogs, pigs, and other animals were bitten. The epizootic continued unabated until 1835, and in the interval spread all over Switzerland. In 1804 the disease appeared in the West German states. In 1819 the disease spread into the upper Danube and Bavaria, and by 1825 had entered the Black Forest. In 1821 to 1822 it was widespread in the forests of Thuringia. In the Voralberg, northwest Austria, 17 cows and goats died from fox inflicted rabies in the summer of 1821. As late as 1836 a man and a girl were bitten by a rabid fox in the district of Rottenburg. The girl died of rabies. In 1837 mad foxes were killed at Ulm. The fox rabies did not spread to north Germany, unlike the experience in the late 20th century. In some places all the foxes died, causing panic among the villagers.

At Crema, Italy, in 1804, a mad wolf descended from the mountains and bit 13 persons, nine of whom died of hydrophobia. In 1806 rabies was very common in England, especially in the vicinity of London. It continued as an epizootic for 2 years, becoming less prevalent but never disappearing. In the winter of 1807 it was a serious problem in Dover, where many human cases occurred. Until 1823 it was more or less prevalent in London and suburbs every year.

In 1803 rabies appeared for the first time in Peru, spreading as an epizootic from north to south. Forty-two persons are said to have died in Ica, 12 to 90 days after being bitten. These patients were violently ill and threatened to attack the attendants looking after them. None survived more than 5 days after the onset of their frenzy. The slaughter of dogs in Lima saved the city from the epizootic — this practice continued for a number of years.
The disease remained active for many years, reaching Arequipa in 1807. All kinds of animals were affected including horses, donkeys, cattle, swine, goats and even fowl (sic) as well as dogs and cats. By 1808 the epizootic subsided but the disease remained enzootic.

Rabies invaded Chile in 1835 where it became prevalent, and men were bitten and died of the disease.

Fleming\(^1\) states that rabies was introduced into La Plata, Argentina, in 1806 by sporting dogs belonging to English officers. The disease has been brought under control in almost all of Argentina in the 1980s.

Rabies was common in the Ukraine in 1813. Fourteen persons are stated to have had the disease. As with all diseases, rabies follows wars, and the disruption caused by the Napoleonic war most probably contributed to its spread in Europe. In 1815 rabies was much more frequent than usual in Austria, and particularly Vienna. There had previously been only four or five sporadic cases of rabies in dogs in Vienna and its suburbs between 1808 and 1814, but the disease assumed epizootic proportions in October 1814, increasing to 15 by December; in 1815 there were 46 dog cases. There was also an epizootic in Copenhagen in 1815.

In 1819 the Duke of Richmond, then Governor General of Canada was bitten by a pet fox near Ottawa and died of hydrophobia shortly thereafter. In 1822 rabies was common in Holland and in 1824 was epizootic in Sweden, affecting foxes, wolves, dogs, cats, and reindeer. It was likewise widespread in Norway and Russia, as well as England. From 1823 to 1828 there were more cases than usual in Berlin. In 1828 the English Registrar-General Report lists 28 persons dying from hydrophobia.

During the 1830s the disease was frequent in Saxony, and again in Vienna and England. In 1831 to 1832 Posen was affected. Pomerania also suffered from the disease. In 1834 the Canton of Thurgau ordered the destruction of all foxes, since rabies continued among these animals. In Zurich animals were attacked. In Lausanne sheep were attacked.

Vienna was again invaded by an epizootic in 1838, which lasted until 1843. In 1838 there were 17 cases; in 1839, 63 cases; in 1840 only 42, but in 1841 no fewer than 141 cases were reported — an unprecedented number which caused much alarm. The following year, 1842, there were 42 cases and in 1843 only two dog cases.\(^4\)

The 1840s saw the disease still rampant in Germany. In Wurttemburg there was an epizootic from September 1839 to the end of 1842, believed to have begun with foxes. From the first of January 1840 until the end of February 1842 rabies was observed in 251 dogs.

From 1839 to 1840 the Veterinary School of Lyons reported few rabies cases — but during 1840 to 1841 rabies was seen in great numbers. Out of 64 suspect cases 33 developed symptoms and died. Professor Rey states that they were able to transmit the disease through several animals by the inoculation of saliva.\(^1\) In 1804 Zinke\(^9\) had first demonstrated that rabies could be transmitted by saliva. His experiments were crude, however, and not entirely convincing.

Zinke’s experiment was quite simple. He took saliva from a mad dog as soon as it had been killed and, by means of a little paint brush, painted the saliva into incisions he had made on the foreleg of a 1-year-old dachshund. He painted as much saliva on the wounds as the paint brush would hold. The dog, according to his report, remained lively and ate and drank until the seventh day. On the eighth day the dog ignored his food, did not drink, was sad and crawled into the corner of his cage. By the tenth day the dog had overt rabies. Zinke wrote quite extensively on rabies as to its source, pathogenesis, and treatment. One author he quotes is Hayworth, who advised extensive irrigation of the wound with warm water for several hours, whereas other authorities urged the use of the hot iron or blistering agents. Some even advocated quicksilver and other metals. Zinke closes his booklet with the admonition that one should take care not to be contaminated with saliva, and not to touch anything with bare hands that had been in the mouth of the patient. Everything in
contact with the patient should be burned or buried deep in the ground. The book is a curious mixture of ancient superstition and sound modern ideas, especially the extensive irrigation of the wound.

Another experimenter, Hugo Alt Graf zu Salm-Reifferscheid, was able to transmit rabies among dogs by saliva from an inoculated animal which sickened,\textsuperscript{10} and also claimed that food smeared with contaminated saliva caused rabies. He was convinced that the saliva contained the infectious agent.

In 1826, Krugelstein\textsuperscript{11} wrote an extensive book (640 pages) on every phase of rabies. He likewise thought that the causal agent was in the saliva, but believed that the agent appeared \textit{de novo} under various conditions. Neither he nor Zinke had any idea of a living agent. On the other hand he says that rabies is a disease of the nervous system. He further states that if any nerve ending is infected by the saliva poison, it sickens locally and sends the poison along the sympathetic nerves until it reaches the coeliac plexus, where the poison affects the entire nervous system. From there it spreads by the way of the spinal cord and the disease reaches its acme. This is an interesting thought for the period in which it was written. He sought diligently for changes in the nerve system, but could only find congestion. As to treatment, he lists 60 medicaments in addition to bloodletting, drinking blood, galvanism, magnetism, and applying pressure on the carotids. We can be thankful that suffocation was no longer listed.

The Swedish epizootic of 1824 led to an interesting paper by Ekstrom.\textsuperscript{12} In his paper he recommends that treatment should consist of making deep incisions of the wounds which were then to be washed diligently for several minutes, either with water, or diluted muriatic acid, or solution of muriate of lime. After the wound was clean and dried a hot iron or strong muriatic acid was to be applied. This is the first instance of the use of acid. Later, in 1899, Cabot\textsuperscript{13} reported on the use of nitric acid following its experimental use in guinea pigs. Webster,\textsuperscript{14} in 1942, asked what nitric acid did to rabies virus when applied to a dog bite wound. Today we recognize soap and water as the best method of dealing with superficial wounds from rabid animals and antiserum or quaternary ammonium compounds for deep wounds.\textsuperscript{15}

Bouchardat was another reporter of the 19th century who put to rest many therapeutic claims in his extensive reports of 1852\textsuperscript{16} and 1854.\textsuperscript{17} He was also among the first to think about inoculations against rabies, and had an early influence on Pasteur. He attempted many experiments at the Lyon Veterinary Faculty.

During 1841 to 1842 rabies was epizootic in Lyon. The veterinary school reported that they had never seen so many rabid animals. Of 104 dogs that died in the hospital from various causes, 62 perished from rabies. Eight persons died from the bites of rabid dogs. The Lyon Veterinary School had records of rabies going back to 1800 — during that period 779 dogs had died of rabies in the hospital. In 1943 only 14 cases were seen at the School.\textsuperscript{1}

An unusual outbreak of cattle rabies occurred in the district of Heyden, Rhineland, in 1843 to 1844. The affected animals were vicious and attacked each other with their horns. They kept up a continuous bellowing and foamed at the mouth. The hind parts were weak and the weakness increased so rapidly that on the third day the animals were on the ground and could not rise. The muscles of the face, shoulders, and thighs were contracted at intervals by spasms. There was no unusual thirst and the ability of swallowing remained unimpaired. Any fluids poured into the mouth were sucked down, although some animals had choking motions and a twitching of the muscles of the face. The disease was usually fatal about the fourth day. The officials in charge believed the disease to be spontaneous rabies, since they found no evidence of dog bites among the cattle.

In 1847 rabies appeared at Roscommon, Ireland, where many dogs were affected. The disease also appeared in Malta that year, supposedly for the first time.

Canine rabies raged as an epizootic in northern Germany in the 1850s. In Hamburg 267
cases were seen among dogs in 1851, after an absence of 23 years. Active measures included the restraint of all dogs and the killing of all stray dogs. The total number killed exceeded 1400; in addition, some 300 or 400 were killed by their owners. The epizootic continued until 1856. By that time nearly 600 rabid dogs had been reported.

In France a rabid wolf caused much damage in 1851, in the vicinity of Hue-Au-Gal, where during a single day 46 persons and 82 head of cattle were bitten. The consequences were that many persons died; all of the cattle were purposely destroyed.5

Another wolf episode occurred in the Turkish territories in the town of Adalia, where the people were defenseless because of the governor’s seizure of all weapons. The wolf bit several people in the town and then fled to a garden where several hundred individuals were camping during the silkworm harvest. There, 128 persons were severely wounded. From the garden the wolf attacked a flock of sheep, killing 85. It was not until the following day that the wolf was killed with weapons returned to the people. Fleming (in his Rabies and Hydrophobia) does not state how many people died, although several of those bitten died raving mad.1

Rabies was prevalent among dogs in England in 1856. The disease appeared among a herd of deer after a mad dog had been in the community, with nearly 100 deer dying of the disease. The symptoms included foaming at the mouth, biting one another, tearing off the hair and flesh, and biting at whatever they came in contact with. Several dogs also died at the same place, exhibiting symptoms of rabies. The disease was not suspected of being rabies until a child was bitten and an investigation was made by the local board of health; they concluded that the disease was rabies and people should take precautions.

Another outbreak was reported in Berkshire, England, where a flock of sheep was attacked by a mad dog. About 20 sheep were wounded and 4 killed. Nearly all of the 20 sheep died after several weeks, during which many lambed. The lambs were not affected. The diseased ewes trotted backward and forward, and repeatedly bit at the fence, foamed at the mouth, and tore mouthfuls of wool out of one another. A similar outbreak occurred in 1966 in Germany, where 17 of 22 sheep bitten on the head — by foxes — died of rabies, with signs including pica, pruritus, and sexual excitement; both paralytic and furious rabies were observed.18

Rabies appeared in Hong Kong for the first time in 1857.* An English bloodhound suddenly became rabid and bit several people; one man died of hydrophobia. This appears to be the only case reported for many years. Rabies was reported in China in 1860, when a man died of hydrophobia near Canton. In 1861 Fleming1 reports that the disease was present at Tientsin near Peking, and that the natives died of hydrophobia caused by the bites of rabid dogs. The disease appeared in Shanghai in 1867 in English dogs. Several persons were bitten. Two Europeans bitten by their own dogs died of hydrophobia. Rabies became very common among dogs of European residents, and several people were bitten and treated. In the winter of 1869 a Scotch terrier became rabid at Chinkiang and bit a buffalo which subsequently died.

Hydrophobia appears to be well known to Chinese physicians and there was a formidable list of cures. Among these was one said to be infallible, musk and cinnabar combined and suspended in rice spirits. Calm sleep and copious perspiration were supposed to follow, otherwise a second dose of the material is given, and a sure cure was to follow.

In 1858 the disease was so extensive in Algeria that the Governor General issued a circular relative to preventive measures.

By 1860 rabies had spread all across America and was attributed to the large number of idle dogs everywhere which were free to prowl around.19 Skunks were such a problem in the plains of Kansas and Colorado that Hovey, in 1874, proposed the name of Rabies

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* An epizootic was reported in Hong Kong in 1981 which affected dozens of dogs. Dog control and vaccination stopped the epizootic, but the disease continued in the neighboring provinces of China.114
mephitica for skunk-transmitted rabies; he reported 41 human cases from skunk bites, more than from dogs.20

In the 1860s rabies was epizootic in many parts of Europe. Vienna appeared to be the center of the epizootic. Both furious and dumb rabies were seen at the Imperial Veterinary Institute. A boy bitten by a dog diagnosed as rabid died 4 weeks after the exposure. Three other persons bitten by the same dog had their wounds cauterized and escaped the disease. The boy’s wounds were not cauterized because they were so extensive.

The disease reappeared in Saxony after 10 years. The city of Dresden had not seen a case from 1853 to 1863. In 1863 it began to spread gradually and soon the whole country of Saxony was affected; 10 cases were reported. In the following year there were 33 cases; in 1865, 227; in 1866, 287.

About 1862, Sir Samuel Baker, exploring the Nile tributaries of Abyssinia (Ethiopia), reported that rabies was epizootic in the country. To prevent the disease, a grass hut was filled with straw and fired, after which each dog was brought by its owner and thrown into the flames. The dogs were able to escape although they would be badly frightened and scorched.

In 1864, there were 12 hydrophobia deaths in England. There was an extensive outbreak in Lancashire. In Liverpool, 1000 dogs were destroyed. There were seven human deaths in Ireland, but none in Scotland.

In the middle of 1865, rabies was epizootic in and around London. Many persons were bitten and three deaths occurred from hydrophobia. The total human deaths in 1865 was 19 for England. In 1866, rabies was widespread in England, especially in Lancashire. The Register-General reported no fewer than 36 deaths, of which 11 were in London, 13 in Lancashire, 3 in Northumberland, and others scattered. In 1867 the Metropolitan Streets Act was passed, enabling the police to seize all vagrant dogs. In June 1868, the Act was put in force and rabies was greatly decreased in England.

Rabies appeared in Belgium in 1868, where the disease had been rare. It began in several provinces in January. Up to May, 32 dogs, a horse, and a cat were diagnosed as being rabid at the Curehem Veterinary School near Brussels. Two human cases were seen.

In 1869 rabies was noted in Paris, with the disease transmitted to a human by a cat. A few years earlier, 1865, Trousseau21 had published his masterful clinical description of rabies. He was of the opinion that a specific virus was the cause of the disease, which was transmitted only by the bite of a rabid animal. With the methods then available he found no special anatomic lesions. As to treatment, he advised cauterization with a hot iron. He raised the question of the value of curare to relax the patient. He also describes the old Chinese formula, which was supposed to be infallible, of musk and cinnabar.

Early in 1869, a rabies epizootic began to spread from Lancashire to Yorkshire and to the borders of Scotland. Two human deaths occurred in March 1869, where six rabid animals were destroyed in Preston. In September, several cases occurred at Yorkshire and a 3-year-old boy died of hydrophobia. At Newburgh in the same month, a mad dog bit a man and several animals; the man died. Animals and human beings continued to be bitten during this epizootic, with the loss of life; dogs, cats, pigs, sheep, cows and horses died of the disease. In 1870, many men and children died of hydrophobia in England, and one case occurred in Dundee, Scotland. Officials recommended that all animals exposed to a rabid animal be destroyed. Hundreds of dogs were killed during the 1870s when rabies was so rampant in England. The alternative was to confine an exposed dog for 10 months.2

Rabies was also an epizootic problem on the continent, in France, Germany, and Austria. In 1871, rabies reappeared in Barbados, West Indies. The custodian of the library there was severely bitten while separating two fighting dogs. He later died of rabies. In addition, three children in one family died of the disease. In another family two children died of rabies. Gibraltar had an outbreak of rabies in 1870. Of 13 people exposed, 11 died. Algeria had
many cases of rabies in man and animals in the 1860s and 1870s. The French were of the opinion that the disease was indigenous there before their occupation.

Russia had an increase of rabies in the 1860s and 1870s. In 1863 only eight, with seven suspected, dogs were rabid but three people died in St. Petersburg. From that year up to 1874 there was a varying increase. In 1874, 49 persons were bitten by rabid dogs and eight people died. Altogether in 12 years, 2724 people were bitten; of 1895 dogs, 1066 were healthy, 198 rabid, 103 suspected, and 528 dogs were affected with various other diseases. In St. Petersburg during that period, 47 people died from rabies. The rabies problem was extensive in Russia.1

In 1874 the Registrar-General reported 74 deaths in Great Britain, and 47 in 1875 in England. The Lancet remarks “It is an undoubted fact that hydrophobia has been increasingly fatal in England in recent years. The annual death rate from this disease to one million living, which according to the Registrar-General’s report, did not exceed 0.3 in the five years 1860 to 1865 rose successively to 0.9 and 1.8 in the two succeeding five years and further increased to 2 per million in 1875. In London, six deaths from hydrophobia were reported in both 1875 and 1876, and in the first 29 weeks of 1877, ending July 21, nine cases have already been recorded.” The British rabies problem was serious.4

Hill22 reports that rabies was made a notifiable disease under the Contagious Diseases (animals) Act in 1886 and in 1887 the Rabies Order gave local authorities power to muzzle, control, seize and detain, and dispose of stray dogs. The local authorities were lax in enforcing this legislation and in 1890 the Rabies Order (muzzling of dogs) brought the disease under central control. The muzzling orders reduced the number of cases of rabies in dogs from 129 in 1890 to 38 in 1892. There was considerable opposition from the public to the muzzling orders, and they were withdrawn and control was handed back to the local authorities. The situation became acute again and in 1895 there were 727 cases of rabies recorded, and in 1896, 463. A new Rabies Order and the control of the Importation of Dogs Order came into operation in 1897. These measures succeeded in eliminating the disease by 1902. Fortunately, Great Britain did not have sylvatic rabies, but even so, the elimination of dog rabies was a great achievement. The country remained free until 1918, when rabies reappeared at Plymouth in a dog illegally brought back from the continent, and the epizootic spread to Devon and Dorset, where 129 cases were reported; another 190 cases occurred in other parts of the country. It could not be determined whether all these were attributable to the Plymouth case, or to other dogs brought home by returning soldiers. The disease was eliminated by 1922. Since 1922 nearly 100,000 dogs and cats have been imported and been quarantined; 27 cases have been confirmed in quarantine; 25 dogs, one cat, and one leopard cub. Nearly all were observed within 1 month of landing, but two cases occurred between 6 and 7 months, and one at almost 8 months. Fortunately none of these latter animals had been released after 6 months quarantine. In addition, a case of rabies occurred in a rhesus monkey imported for medical research in November 1965. In 1969 a case occurred in a dog imported from West Germany, which had been in quarantine for 6 months. It died 2 weeks after being released, but before it died, it bit a cat and its owner. A further case was confirmed at Newmarket, almost 9 months after landing and 3 months after release from quarantine. These cases will be discussed in detail under quarantine control measures (see Chapter 28). In the 1980s there were two cases among dogs in quarantine or just released from quarantine.

Smithcrons23 reports that rabies was widespread in most of the U.S. following the Civil War. Mad dogs were reported in many urban and rural areas. Sylvatic rabies had been recognized in the eastern states in the 18th century, and in the 19th century was seen in foxes in the eastern part of the country. Rabies appears to have gone west with the pioneers. Skunk rabies was reported by the mountain men on the Great Plains in the 1830s, and was first reported in California in the 1850s. The United States Army reported that skunk rabies was so common on the Great Plains that the early settlers referred to skunks as hydrophobia
cats, or phobey cats (see Chapter 15). At the turn of the 20th century rabies was a dreaded disease throughout the U.S. Control measures were not effective since the public would not accept dog control and muzzling. It was not until the 1940s, when dogs could be successfully vaccinated by a single inoculation, that the fear of rabies was alleviated. The sylvatic problem remains, with thousands of rabid skunks reported each year, although a possible solution is now visible (see Chapter 27).

Fox rabies was recognized as a source of disease in eastern North America in the colonial period, but did not take on the epizootic importance until the 1940s when it was studied as a principal source of rural rabies from Canada to Florida and west to Texas. 24 At about the same time a disease in northern Canada, Arctic fox disease, was described. 25 Subsequently this was identified as rabies and was the beginning of an epizootic that moved south and east in the 1950s to 1970s and continues to be enzootic in Canada.

Skunks were known to transmit rabies in the mid 19th century and epizootics were reported by the U.S. Army frontier doctors in the 1870s. But they did not become a major source of disease until the late 1940s and 1950s, when the Great Plains epizootic erupted in 1950 to 1951. The University of Minnesota had a skunk rabies conference in the spring of 1952. Stories were told of tens of thousands of skunks coming out of winter hibernation and dying. Wildlife officers said they piled up frozen dead skunks in cords — a measurement of wood piles. There was no method to control them.

The recognition of raccoon rabies in south central Florida was made in the 1950s by Held. 26 Raccoon rabies first became a problem in the southeast, then a national problem as the disease was transferred to the mid-Atlantic states by raccoon hunters in 1977. Today it is an urban problem as far north as Pennsylvania and New York (see Chapter 16). There have been no reported human deaths due to raccoon exposure.

Madstones (or moonstones) have long been used as a means of warding off rabies. The original amulets — apparently “hair balls” from the stomach of white deer (or their gallstones), gallstones of white cows, or any smooth white stones — were used by the American frontiersmen and early settlers. The origin of the special effects of amulets is lost in antiquity. Gallstones in sheep and cattle are rare, and were therefore thought to have special attributes, including preventing rabies after attacks by a rabid animal. Some people boiled the stone in milk to “prepare” it for a particular application. If the milk turned to a color other than white, the boiling was continued to free it of impurities from previous applications, but if the milk stayed white the stone was ready for use. 27 The longer the stone “stuck” on the wound the better. In some cases where rabies appeared in humans, the madstone was used to treat the person by placing it on the patient or on the wound.

Fleming 28 used the example of rabies in Algeria and Peru to support the theory of the spontaneous origin of rabies in many cases of the world. Fleming was a strong proponent of spontaneous disease, citing glanders, farcy, and strangles in the horse, anthrax in cattle, typhus in pigs, and distemper in dogs as examples of the spontaneous disease. He did accept the inoculation of a virus by a bite as the cause of disease, but he falls back on spontaneous generation in considering the origin of the virus — not unlike our concepts of certain chronic diseases in the late 20th century.

Galtier 29 studied rabies in 1879, and was able to transmit rabies to rabbits by serial passage from rabbit to rabbit, but he does not state the specific method of transmission. The symptoms were paralysis and convulsions, and the average incubation period 18 days. This appears to be the first report on the transmission to rabbits, but unfortunately without much needed detail. The work of Pasteur was, on the other hand, definitive. A little later, Maurice Raynaud 30 reported that he took saliva from a rabid patient and injected it subcutaneously into a rabbit’s ear. Four days later the rabbit was stricken with a sort of paralysis and died during the night. Fragments of submaxillary salivary gland inoculated into other rabbits subcutaneously are said to have reproduced the disease, as they died on the fifth and sixth
day. An autopsy showed only congestion of the lungs. These observations are not convincing, but are mentioned as leading up to Pasteur's great work.

Pasteur published his first report on rabies during 1881, a period when many scientists were attempting to transmit rabies from man to animals, and animals to animals. Pasteur's first experiments with saliva from a child dead of rabies produced a pneumococcus/streptococcus septicemia in the rabbit. This was recognized by Pasteur, while other investigations thought they had produced rabies even though the rabbits died in 48 h. Pasteur, with his extraordinary acumen and experimental ability, resolved the question in his report. Both the symptoms and histologic changes led him to the conclusion that "the central nervous system and especially the bulb which joins the spinal cord to the brain are particularly concerned and active in the development of the disease". He then reported success in producing rabies by the injection of central nervous system material and spinal fluid, thus demonstrating that the source of the virus is not solely in the saliva. Pasteur was bothered by the experimental difficulties of the long incubation period. He soon found that by injecting brain material from rabid animals directly into the brains of dogs the incubation was shortened to 1 or 2 weeks, or at the most 3 weeks. This was an important advance in experimental rabies studies.

Pasteur reported further on his fundamental studies. He pointed out that saliva was not a satisfactory source of virus for experimental work, since its effects were uncertain and the incubation period might be very long. He again referred to the certainty and rapidity with which rabies could be produced by direct intracerebral injections of central nervous system material from rabid animals. He pointed out that virus was not only found in the low centers of the brain but in the spinal cord as well. He differentiated dumb rabies, characterized by paralysis, and furious rabies in which the animal attacked everything. He found that inoculation into the bloodstream first affected the spinal cord and was likely to produce the dumb type rather than the furious. He also found that an animal which recovered after early symptoms of rabies was immune to later inoculations, and that some dogs seemed to have a natural resistance. Finally, he produced rabies by the intracerebral injection of all parts of the brain of a cow dead of rabies.

In 1884, a year of much rabies in France, Pasteur made a more definitive report. Intravenous injections, as previously reported, usually produced a paralytic type of rabies, and dogs sacrificed at the first symptom of paralysis revealed the spinal cord containing virus when there was no evidence of any virus in the bulb. Pasteur also demonstrated virus in pneumogastric and sciatric nerves, and in the salivary glands, with the conclusion that the entire nervous system is susceptible. Virus preserved its virulence in spinal cords kept at 0 to 12°C. Pasteur was unable to cultivate any bacteria from the nervous system, but he stated that "one is tempted to believe that a microbe of infinite smallness, having the form neither of a bacillus nor a micrococcus is the cause." How right he was when the electron microscope studies of Matsumoto, Davies et al., and Atanasu et al., some 79 years later revealed the virus as being bullet shaped. Pasteur reported that the clinical signs produced depended somewhat upon the dose of infective material, and that injections of small amounts of virus did not produce immunity. He discussed the hypothesis of the passage of virus from the periphery to the central nervous system via the nerves as against the distribution of virus by the bloodstream and, whether or not the former was correct, he regarded the latter as proved. Finally, and most important, he discussed the theoretical basis of immunizing injections and made a general statement that he had already achieved some success.

Later in the year, Pasteur, made another report to the Academy of Science dealing primarily with the problem of attenuation of virus. If one passed rabies virus from dog to monkey and then from monkey to monkey, the virulence of the virus fell off at each passage. If the virus was then returned to dog, rabbit, or guinea pig it remained attenuated. It did not immediately resume the virulence of street virus in the dog. Even intracerebral inoculation might not produce the disease, although it nonetheless established a state refractory to rabies.
But if the virus was passed back to the dog, it was much more virulent than street virus and, if inoculated into the bloodstream, it always caused fatal rabies. By using a series of injections of attenuated virus, he made dogs immune, or at least refractory. He alluded in a general way to some favorable observations on immunization of man, taking advantage of the long incubation period.

Although Pasteur had alluded to his method of prophylaxis of rabies in earlier papers, he gave his first detailed report in 1885 to the Academy of Science. The first step was the intracerebral inoculation of street virus into a rabbit and the passage through successive rabbits. The incubation period gradually became shorter, until it reached a fixed time of 7 days. The cords of these rabbits contained virus throughout their length, which gradually diminished in virulence as the cords were suspended in dry air.* The actual immunization was carried out by injecting a dog subcutaneously with a syringe of broth to which was added a tiny bit of rabbit cord, beginning with one dried long enough to be avirulent and successively using more virulent material until a virulent cord is finally reached. The dog was then refractory to rabies, as demonstrated in 50 dogs (see also Chapter 2). At about this time there arrived from Alsace a boy of 9 years, Joseph Meister, who had been bitten 14 times by a rabid dog. The boy was examined by Doctors Vulpian and Grancher who thought the child had received a fatal inoculation of rabies virus. Pasteur goes on to say "The death of this child seemed inevitable, and I decided, not without lively and cruel doubts, as one can believe, to try in Joseph Meister, the method which has been successful in dogs. Consequently, on July 6 at 8:00 in the evening, 60 hours after the bites, in the presence of Doctors Vulpian and Grancher, we injected under a skin fold in the right hypochondrium of the little Meister a half syringe of the cord of a rabid rabbit preserved in a flask of dry air for 15 days." Thirteen successive inoculations were made with cords of increasing virulence. The little boy never developed rabies.**

Pasteur, with his characteristic penetrating curiosity, was not satisfied with practical results, but wished to understand the mechanism of his method. He concluded that the dried cords contained fewer and fewer live virus particles which were not, however, attenuated in individual virulence. Thus, the method in essence consisted of injecting larger and larger quantities of virus each day.

An interesting discussion followed the paper at the Academy of Science. Vulpian said "Rabies, that terrible malady against which all therapeutic attempts have so far failed, has finally found its remedy." Others expressed equal enthusiasm, and Pasteur closed the meeting with gracious acknowledgment of what had been said.

A year later in 1886 Pasteur reported the results of treatment in 350 cases. Only one person developed rabies, a child bitten on October 3 that was not brought for treatment until November 9. According to contemporary statistics one half of those bitten should have developed disease. In no case did the injections produce local inflammation, abscess, and other untoward effects. Pasteur concluded "The prophylaxis of rabies is established. It is time to create a center for vaccination against rabies." A commission was appointed by the Academy of Science to implement Pasteur’s proposal. The commission proposed that an establishment, to be called the Pasteur Institute (Institut Pasteur), be founded for the treatment of both the French people and foreigners. Within a decade there were Pasteur Institutes throughout the world. These institutes were to become the center of scientific investigation in many countries.

Pasteur made further progress reports. By late 1886 over 2000 people had now been treated, including 38 Russians bitten by rabid wolves. Three of this group died, and Pasteur

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* Earlier, Pasteur had observed that the organisms of fowl cholera Pasteurella multocida, were modified or attenuated when they remained at room temperature for some days, and could be used to immunize fowl.

** Joseph Meister spent all his working life as a guard at the Pasteur Institute, Paris (1871 to 1940).
points out the great virulence of wolf bite compared with that of the dog. Pasteur recognized that the treatment was not always successful, especially in face bites. He noted that most of the fatal cases were in children bitten about the face. He was not sure that the treatment was adequate for this type of case. He decided to modify the procedure to make it more rapid and more effective by giving more injections daily and continuing the treatment longer. The standard treatment at this time was 10 daily injections, beginning with material dried for 14 days and concluding with the 5-day cord.

Detailed reports that appeared each year from Pasteur Institute cited some failures. In 1898, for example, Pottevin reported 20,166 persons treated with 96 deaths or a mortality of 0.46%.*

Roux, in a later report, 1887, found that glycerin was an excellent preservative for rabies virus. He found that fresh brain material would yield virus after 4 weeks. This was an important observation in a period when the specimens from rabid animals were frequently putrid. Calmette, following his suggestion in Indochina, kept a supply of desiccated cord preserved in glycerin on hand at the Saigon Pasteur Institute at all times so as to be prepared to give antirabies treatment. Various other methods of attenuating virus including phenol, formalin, and ether were to be used in the next century (see Chapter 31).

The first observations on the pathogenesis of rabies were made by Morgagni in his work from 1769 entitled The Seats and Causes of Diseases Investigated by Anatomy. In it he states that the "virus does not seem to be carried through the veins, but by the nerves." 7

In the 1880s there was considerable discussion as to the route whereby rabies virus reaches the nervous system: (1) by the bloodstream and (2) by the nerves. Pasteur had shown that inoculation by bloodstream and intracerebral inoculation were effective. DiVestea and Zagari in 1889 brought forward clinical and experimental evidence that rabies virus was spread from the bite to the central nervous system by passage along the nerves. They had shown, for example, that inoculation of fixed virus into the sciatic nerve of a rabbit and a dog caused death with the same symptoms as those of intracerebral inoculation. Furthermore, death could be prevented by cutting and cauteterization of the nerve after injection. Finally, the type of clinical phenomenon produced seemed to depend on the location of the inoculation nerve and where it entered the central nervous system. Roux agreed with these observations but had certain reservations. For example, he stated "One sees then that inoculation into the nerves does not always produce rabies with the certainty of trepanation." Meanwhile Nocard and Roux showed that large intravenous injections of rabid spinal cord could be given with impunity to sheep and goats, although immunity was conferred. Helman, another worker at the Pasteur Institute, concluded that rabies virus produced infection on inoculation only if introduced directly into the nerve cells; if introduced into subcutaneous tissue it could give immunity. All this shows how exceedingly complex and confused the subject was. Webster found, in 1937, that virus injected subcutaneously in Swiss mice is first detected 5 or 6 days later in the central nervous system, at the site in direct connection with the inoculated areas. This finding, like others, is consistent with the view that the virus does travel by way of the nerves.

Negri, who discovered the bodies which bear his name in 1903, thought he had uncovered a microorganism which should be included among the protozoa. This would be natural, since Negri was working in Golgi's laboratory in Pavia, where studies of malaria were being intensively pursued. These alleged parasites that Negri observed were seen especially in the dog, but Negri also observed them in one human case. The site of predilection was in the horn of Ammon. In this region, especially in the larger nerve cells, the bodies are present in large numbers. They exhibit the form of small, sharply outlined structures. They were also found in the spinal ganglia and in the spinal cord of dogs in which rabies occurred.

* Present day treatment with human globulin and cell culture vaccines has reduced mortality to virtually zero.
naturally or experimentally, and in rabbits experimentally inoculated. The bodies are of various size, from 1 μm up to 10 or 15 μm or even as large as 27 by 5 μm. They were stained best with eosin methylene blue. Four to six bodies may be found in one cell. Negri thought he saw evidence of the multiplication of these bodies. In another paper Negri\(^9\) used the presence of Negri bodies as a practical diagnostic test for rabid animals and laid the ground for the long-used test.

It would not be until 1958 and with the use of another diagnostic test, fluorescent antibody (FA), introduced by Goldwasser and Kissling,\(^5\) that the Negri body would be shown to be intimately associated with the rabies virion. The work of Miyamoto and Matsumoto\(^5\) correlated the Negri body to the viral matrix of moderate electron density seen by the electron microscope. Hummeler and his co-workers\(^5\) in 1968 using ferritin-labeled antirabies antisera, showed the matrix to be composed of randomly oriented viral ribonucleoprotein strands.

The study of events leading to the discovery of the causal agent of rabies is exciting. Pasteur himself had speculated that the agent was a tiny one, unlike ordinary bacteria. Babes reviewed various claims of a bacterial agent in 1887,\(^4\) and himself isolated several organisms from the nervous system of rabid animals, which he claimed could reproduce rabies, but interestingly enough he thought the causal agent was a minute body perhaps carried in the bacteria. In 1906 Babes confirmed\(^5\) the Negri bodies in rabies, but concluded that they represent a reaction to infection and were not parasites, although they might contain them. The causal agent, Babes concluded, must be more widespread in the nervous system (as the FA test has now revealed). In 1909 Negri\(^6\) redescribed his bodies, still insisting they were parasites, and pointing out that Calkins had named them Neurocytes hydrophobia. Calkins, it should be recalled, worked on the Guarnieri bodies of smallpox, and concluded that they, too, were living parasites. Meanwhile Remlinger, in 1903\(^7\) claimed to have produced rabies in rabbits with Berkefeld V filtrates of central nervous system material from rabid dogs and rabbits. Finally, Koch and Rissling\(^8\) described small coccus-like bodies in the gray matter of the central nervous systems of rabid dogs which they thought might be of etiological significance. Like Babes, they did not accept the Negri bodies as parasites. Later confirmation of the filtrability of rabies virus of course rules out the bodies of Negri and of Koch as causal agents, whatever diagnostic value they may have. The nodules described by Babes, which seem to be leukocytic accumulations related to blood vessels, are now thought to be common to neurotropic virus infections. Indeed the Negri body is perhaps the only specific anatomic change. Many stains have been developed for Negri bodies, including a commonly used one, by Sellers\(^9\) (see Chapter 23).

Remlinger was the first to give a comprehensive review of the paralyses occurring with antirabies therapy.\(^6\) He gave abstracts of 26 cases between 1888 and 1905. He attempted to analyze the whole problem and discussed various explanations, including the introduction of nonviral toxic substances. He leaned toward a "rabic toxin" as the explanation. Years later in 1935\(^6\) he discussed paralytic accidents as a Landry-like ascending paralysis. It was assumed that the accidents were true rabies, of a different type than laboratory-proven rabies. Remlinger discussed whether these accidents of therapy are actually rabies, especially the mild nonfatal ones. No final answer was reached although he concluded that with the exception of certain paralyses following dead vaccine, the accidents of antirabic therapy are largely due to fixed virus, a view not accepted today.

Stuart and Krikorian\(^6\) concluded in 1928 that there is a component in the basic nerve substance of all rabies vaccines capable of producing neuroparalytic disorders. They actually showed that paralytic accidents can be produced experimentally by the repeated inoculation of nerve substance, normal or rabid, homologous or heterologous. Later Rivers et al.\(^6\) at the Rockefeller Institute showed that repeated intramuscular injections of brain extracts and emulsions into monkeys might be followed by an inflammatory reaction, with demyelini-
zation. In 1949 Bell et al.\textsuperscript{64} described a rabies vaccine freed of the factors causing allergic encephalitis. Today, many vaccines, especially tissue culture products, are being prepared without extraneous materials that cause allergic reactions. These are discussed in Chapter 31.

Fermi, in a review of a large number of experiments,\textsuperscript{65} pointed out the difficulty of demonstrating rabies virus in the saliva. Bartarelli\textsuperscript{66} showed that virus reached the salivary gland of rabid dogs by peripheral nerves. He severed the nerves of one parotid gland, after which the animal was inoculated with rabies virus. The glands with severed nerves contained almost no rabies virus, but those glands in which the nervous connections were left intact produced rabies in another animals. Meanwhile Roux and Nocard\textsuperscript{67} showed that rabies virus could be found in the saliva of rabid dogs 2 or 3 days before the least clinical symptom. Nicola\textsuperscript{68} found saliva virulent as long as 6 days before the animal showed any clinical signs of rabies.

Fermi, in another report in 1908,\textsuperscript{69} points out various defects in Pasteur’s vaccination regime. He introduced a new method in which the vaccine was treated with carbolic acid. One hundred percent of the test animals were saved whereas 100% of untreated controls died. He mentions as advantageous the uniformity of the vaccine and simplicity of preparation instead of the complicated and useless Pasteur method of attenuation. This vaccine can be preserved and sent anywhere, so is always available. Later Semple,\textsuperscript{70} in a masterful article on the practical aspects of rabies in 1919, described a method for preparing a dead carbolized vaccine, and reported the treatment of 2009 Europeans in India, with only 0.19% failure. If immunization is complete before the virus traveling along peripheral nerves reaches the central nervous system, patients survive, otherwise they die. Hence, slight bites at the periphery with a long incubation period are more favorable for immunization than severe bites on the face, with a short incubation.

L. T. Webster in a 1939 critical review gives an elaborate review of all the reported laboratory experiences in rabies vaccination.\textsuperscript{71} He concludes, “All workers save Fermi have failed to demonstrate a significant protective effect of vaccination following experimental exposure to rabies virus by any route.” On the other hand, vaccine, given before exposure has been found effective under limited conditions. These rather gloomy conclusions were drawn before the addition of rabies antiserum to rabies prophylaxis. The advances in the prevention of rabies since 1940 are discussed in Chapters 30 and 31.

A big advance in the diagnosis of rabies was the mouse inoculation (MI) test by Webster and Dawson in 1935.\textsuperscript{72} They found that mice were quite susceptible to neurotropic viruses. They found that rabies was readily produced by intracerebral inoculation of mice with dog brain material containing Negri bodies. Rabies could occur within 7 days, but in some cases prolonged incubations up to 28 days were reported, Leach\textsuperscript{73} confirmed the practical value of Webster’s mouse test, and indeed found it positive in 12% of brains reported negative for Negri bodies, whereas only three specimens of 338 with Negri bodies gave a negative mouse test.

The mouse test showed that only 85 to 95% of rabies-positive cases were found by Negri body examination alone. The mouse test was to become the standard test for all Negri body negative tests, and is used to this day on negative diagnoses in laboratories which do not use the (FA) test. The advent of the FA test and its application to rabies by Kissling\textsuperscript{74} and later by McQueen\textsuperscript{75} in Florida opened a new chapter in the accuracy of rabies diagnosis. But even today the mouse inoculation test or isolation in mouse neuroblastoma cells are adjunct procedures when the FA test is not clear cut. A mouse protection test was also developed for the measurement of antibodies against rabies. The final outcome to these investigations was a mouse test for measuring the immunizing potency of antirabies vaccines in 1939.\textsuperscript{71} Webster, using the mouse test, was able to measure the potency of vaccines, showing that vaccine injected intraperitoneally as a vaccine immunized mice within 10 days
for a period of at least 9 months. Demonstrable neutralizing antibodies accompanied this immunity. Virus given subcutaneously failed to immunize as effectively. He found that commercial vaccines with virulent virus gave results similar to those obtained with laboratory virus, but commercial vaccines inactivated with phenol generally failed to immunize mice. The great variation in the potency of vaccines led to the development of the Habel test, which provided a standard for all vaccines in 1948. Similar results were obtained with commercial phenolized vaccines in dogs. This situation was likewise corrected by the Habel test.

An unusual event of the 20th century was the discovery of bat rabies in Brazil and later Trinidad. The earlier phases of this interesting study were told by Hurst and Pawan in 1931 following an outbreak of rabies in Trinidad without history of bites and with symptoms of acute ascending myelitis. In 1936 Pawan first showed that human beings bitten by vampire bats developed sensory symptoms at the bitten site, followed by paralysis and death. The unusual epidemic involving almost 100 persons has never recurred in Trinidad but lesser cases have in other countries. The bats biting the people were shown to be rabies infected, and died — but strangely some survived — and Pawan reported that some might become carriers capable of spreading infection by their bites for prolonged periods. Earlier, Quiroz-Lima showed that, in fact, rabies infected bats could apparently transmit the virus for several months while manifesting no symptoms.

Rabies in insectivorous bats were identified in Tampa, Florida in June, 1953. Before 1953 came to an end, rabies was also reported in insectivorous bats in Pennsylvania and Texas. In the decade that followed, bat rabies was to be identified in all 48 states and southern Canada. Bat rabies is unknown, however, in Alaska and Hawaii. (No rabies in any species has ever been reported in Hawaii.) Vampire bat rabies has been reported in all of Latin America, it is a major cattle disease and the cause of human rabies.

The report of bat rabies in Texas and New Mexico led to investigations by Constanine and co-workers, who were to demonstrate that bat rabies could be disseminated by aerosols in caves where sunlight did not penetrate. The saliva of the insectivorous bats is the vehicle of the virus (see Chapter 17).

Webster and Clow were the first to propagate rabies virus in tissue culture as far back as 1936. The medium consisted of Tyrode solution containing normal monkey serum plus a suspension of minced mouse embryo brain. The inoculum consisted of brain from a mouse prostrate on the seventh or eighth day following an intracerebral injection of rabies virus. Material passed through such culture medium as often as 88 times, and the supernatant was still found to be virulent.

Galloway and Elford were the first to report on the size of the rabies virus, finding it about 100 to 150 μm. It thus falls among the larger viruses. In 1962 Almeida and colleagues reported 400-μm-diameter particles by negative contrast microscopy associated with fixed rabies virus-infected cell culture. Others later reported these findings with various rabies strains. Three groups in 1963, one headed by Matsumoto, Davies et al., and the other by Atanasiu et al. using different cell cultures, revealed the bullet-shaped morphology of the virus for the first time. A more detailed description of the virus was to come in 1966 by Pinteric and Fenje.

The growing of rabies virus in the developing chick embryos was a major breakthrough in 1940. Two groups of workers, Bernkopf and Kligler and Dawson, succeeded at about the same time in growing rabies virus in the chick embryo. Kligler and Bernkopf inoculated the chorio-allantois, Dawson the brain of the embryo. Bernkopf and Kligler in a later publication describe their work in more detail and point out that the chick embryo virus after many passages showed greatly reduced virulence for rabbits. Dawson also found the

* In 1989 to 1990 vampire bats caused 2 human rabies epidemics in 20 to 30 persons in Peru.
virulence greatly reduced for the rabbit. Later Koprowski and Cox\textsuperscript{95} attenuated Johnson’s avian brain-fixed Flury strain by chicken embryo passage, greatly reducing its deleterious neurotropic nature. This low egg passage (LEP) vaccine along with a high egg passage (HEP) variant would later be adapted to cell culture.\textsuperscript{96,97}

It would not be until 1955 that a similarly effective vaccine for human use would be produced in duck embryo by Peck.\textsuperscript{98} The duck embryo rabies vaccine (DEV) would be regarded as the standard prophylactic measure for 25 years. The combined work of Wiktor, Plotkin, and Koprowski resulted in a vaccine developed on a homologous human cell line (human diploid cell vaccine — HDCV) introduced in 1978.\textsuperscript{99} The primary advantages of the HDCV are greater immunogenicity, homogeneous antibody response and few allergic side effects.

The advent of monoclonal antibody (MAB) techniques opened new doors in the study of viruses and nowhere has the potential for this technology been better demonstrated than in rabies research. Wiktor et al.\textsuperscript{100} in 1978 were the first to describe rabies antigenic viral variation. Later these methods would be applied to the classification and diagnosis of rabies and rabies-related viruses. More recently MABs have been implemented in rabies epidemiology to describe viral variant geographic origin,\textsuperscript{101} species origin,\textsuperscript{102} and vaccine type,\textsuperscript{103} as well as the study of rabies pathogenesis.\textsuperscript{104}

The post World War II U.S. rabies problem was of great concern. With the coming of peace, people moved to new homes or were returning to where they came from, and the stray animal population exploded as pets were abandoned and multiplied. There was an urgent need to do something about the rabies problem.\textsuperscript{105} A national rabies program was inaugurated to attack rabies, beginning in 1947.

Educational materials were developed by the state and local health departments to fit the needs of the region or community, with materials for elementary, intermediate, and high school. Tierkel demonstrated in Memphis\textsuperscript{106} how all public agencies had a role. The local press support was essential, as well as the national news weeklies. Locally developed posters were excellent educational material.

The success of the field operations was measured by the control of urban rabies epizootics in Memphis, Tennessee (1949), St. Louis (1950), El Paso (1951), Chicago (1952), Houston (1953), and subsequently the disappearance of urban epizootics, to be replaced by county wide situations that involved animals other than dogs.

The chicken embryos (CEO) live rabies virus vaccine was first tested in 1948 and for decades was the preferred vaccine for dog rabies control.\textsuperscript{107} It has now been replaced by safer and equally effective inactivated vaccines.\textsuperscript{108} (See Chapter 22.)

In Japan a decree to eliminate all stray residential and feral (semi-wild) dogs was diligently applied throughout the 1950s. Within a few (3 to 4) years there was a dramatic drop in rabies, the first in decades. The authorities said dog populations in some areas were reduced by 70 to 80%. Vaccination was made compulsory for all remaining dogs; the vaccine was an 0.5% phenolized Fermi vaccine first used by Umeno and Doi in 1921.\textsuperscript{109} The last case of rabies occurred in 1956;\textsuperscript{110} rabies had existed in Japan for a thousand years, dating back to the 10th century.

Another country to eliminate rabies was Taiwan, initiated by the rabies control efforts of the civilian government in the 1950s. The health authorities used epidemiological procedures in finding the rabies foci. In these pockets dog control was intensified, followed by vaccination of the local dog population. This procedure was very successful and by the end of the 1950s, Taiwan was rabies free. The absence of a wild life reservoir was confirmed by the present rabies-free status of Taiwan.\textsuperscript{111}

Malaysia has successfully controlled rabies since the early 1950s; Tierkel, as a World Health Organization (WHO) consultant, assisted the national health services on how to deal with the problem. The same approach was used as that recommended in the U.S. National
Rabies Program\textsuperscript{110} and the WHO Expert Committee on Rabies\textsuperscript{112} namely: (1) education, (2) dog control, and (3) vaccination. Malaya has maintained rabies control successfully for more than 30 years, in spite of border outbreaks.

Singapore, an independent city state, has eliminated canine rabies and maintained a disease-free state since the 1950s.\textsuperscript{113}

Hong Kong was able to eliminate rabies at the same time and remained free until the eruption of rabies in neighboring South China in 1981 to 1982. The recognition of Hong Kong rabies brought attention to a greater problem in the Canton region. The Hong Kong\textsuperscript{114} veterinary authorities under the Director of Agriculture and Fisheries were able to stop the epizootic in Hong Kong and help the Chinese government deal with the south China problem.

The subcontinent of India, Pakistan, and Bangladesh has the largest rabies problem in the world. The estimates of annual human rabies fatalities vary from a few hundred to 50,000 (see Table 1).

\section*{CONCLUSION}

The above data and mention of earlier experiences of global aspects of rabies\textsuperscript{113} emphasize the basics of rabies control, which is education to accept control. Animal (dog) control is the first step. If dog control is not accepted by the public, or if the opposition is not educated early, there is trouble. All societies have problems with dog control but they can be solved by education and giving leaders responsibility in rabies control.

Human behavior scientists can be of great help in identifying problems and dealing with the opposition.

The U.S. spends tens of millions of dollars on animal control annually. The world dog population is difficult to estimate but if we use a ratio of one to ten for 5 billion people, the estimated dog population may approach 500 million — an awesome number. This is a very costly problem to contemplate. Education, research, and vaccination are the trinity. All are pertinent, but how to get a world program moving is our concern.\textsuperscript{115}

The Pan American Health Organization (PAHO) rabies control is a model continental program and is in an advanced state of development; a model for the WHO regional offices. The cost to get programs started is not prohibitive, but funds are needed to place trained public health veterinarians in the five WHO regional offices in Europe, Africa, the Middle East, Southeast Asia and the western Pacific; initial costs would be about $100,000 per region. The programs developed in the Americas are an example from which the world can learn.

As a working figure, the number of 500 million dogs is based on their experience in the U.S. when the national rabies control program began in 1947; at that time the U.S. population was less than 200 million so we estimated the dog population to be less than 20 million. In 1990, the U.S. dog population is reported as 55 million, with a human population of 250 million, or a ratio of about 1:5. Rabies control is possible worldwide but there is a need for promotion and planning by the WHO regional offices, using the model of the PAHO in cooperation with national foreign assistance programs. As the century closes, now is the right time to start planning with the cooperation of foreign aid programs in the U.S., Canada, Europe, Asia, and the Middle East for the respective WHO regional offices to make a goal of world rabies control a reality in the 21st century.

The research needed is in place on many continents. How to transfer this to the field should be of great concern to all of us. We have many avenues — literature, symposiums, and consultants — but permanent staff in the WHO regional offices is urgently needed.
### TABLE 1
Classification According to the Animal Which was the Source of Exposure to Patients from 1908 to 1972 (Scientific Report of Central Research Institute, Kasauli for 1972 to 1973)

<table>
<thead>
<tr>
<th>Species of animals</th>
<th>No. of persons infected and taken full treatment</th>
<th>Percentage to total</th>
<th>Death</th>
<th>Percentage of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ape</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Buffalo</td>
<td>12,461</td>
<td>0.810</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Badger</td>
<td>60</td>
<td>0.004</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Bear</td>
<td>115</td>
<td>0.007</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Bijjoo</td>
<td>2</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cow, calf, bullock, ox</td>
<td>17,470</td>
<td>1.136</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Camel</td>
<td>831</td>
<td>0.054</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cock, hen, fowl?</td>
<td>9</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cat</td>
<td>3,769</td>
<td>0.245</td>
<td>2</td>
<td>0.053</td>
</tr>
<tr>
<td>Deer</td>
<td>17</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Dog</td>
<td>1,380,920</td>
<td>89.817</td>
<td>2,567</td>
<td>0.186</td>
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<tr>
<td>Donkey, ass, mule</td>
<td>2,995</td>
<td>0.195</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Duck?</td>
<td>5</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Eagle?</td>
<td>3</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
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<td>2</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Fox</td>
<td>320</td>
<td>0.021</td>
<td>1</td>
<td>0.312</td>
</tr>
<tr>
<td>Goat/sheep</td>
<td>1,695</td>
<td>0.110</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Guinea pig</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
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<td>4</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Human</td>
<td>21,566</td>
<td>1.403</td>
<td>2</td>
<td>0.009</td>
</tr>
<tr>
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<td>4,013</td>
<td>0.251</td>
<td>—</td>
<td>—</td>
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<td>Hyena</td>
<td>552</td>
<td>0.036</td>
<td>17</td>
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<td>4.901</td>
<td>903</td>
<td>1.196</td>
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<td>8</td>
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<td>—</td>
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<td>Kite?</td>
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<td>—</td>
<td>—</td>
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<tr>
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<td>5</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Lion</td>
<td>42</td>
<td>0.003</td>
<td>—</td>
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<tr>
<td>Laboratory infection</td>
<td>16</td>
<td>—</td>
<td>—</td>
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<tr>
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<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Monkey</td>
<td>8,550</td>
<td>0.556</td>
<td>—</td>
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<td>3,024</td>
<td>0.197</td>
<td>2</td>
<td>0.066</td>
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<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
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<td>65</td>
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<td>—</td>
<td>—</td>
</tr>
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<td>Owl?</td>
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<td>—</td>
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<td>Other rodents</td>
<td>3</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pig, boar, sow</td>
<td>521</td>
<td>0.034</td>
<td>—</td>
<td>—</td>
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<tr>
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<td>449</td>
<td>0.029</td>
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<tr>
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<td>36</td>
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<td>—</td>
<td>—</td>
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<td>110</td>
<td>0.007</td>
<td>—</td>
<td>—</td>
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<td>Squirrel</td>
<td>17</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Tiger</td>
<td>368</td>
<td>0.024</td>
<td>—</td>
<td>—</td>
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<tr>
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<td>357</td>
<td>0.023</td>
<td>7</td>
<td>1.961</td>
</tr>
<tr>
<td>Vulture?</td>
<td>14</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Wolf</td>
<td>1,558</td>
<td>0.101</td>
<td>69</td>
<td>4.429</td>
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<tr>
<td>Zebra</td>
<td>2</td>
<td>—</td>
<td>—</td>
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**TOTAL** 1,537,477 — 3,579 0.232
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