ORIGINAL ARTICLES

RABIES, AND ITS PRESENT STATUS IN CALIFORNIA.*

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Efforts to check the spread of rabies, or hydrophobia, among the dogs of California are greatly hampered by the difficulty in obtaining authoritative statements of fact regarding the present situation. Many controversial articles and conflicting theories are being read and discussed, and it is no wonder that the public and, to a large extent, the medical profession of California are unaware of the true state of affairs. This article will attempt to present the facts needed by those who are trying to check the spread of the disease among dogs and to make its transmission to people impossible.

The early part of the present epizoötic was reported by Black and Powers[1] in November, 1910, and the history of the disease up to April 1, 1911, was presented with the available statistics in an article published by myself[2] in July of that year. Since then the involved territory has been greatly enlarged and the most populous part of the state has been invaded. The center of maximum involvement has passed from Los Angeles to Fresno County and finally to San Francisco.

Figure 1 is a series of maps which shows at a glance how rapidly the disease has spread. The change in the shaded areas shows the increase in the number of counties involved, and the stippled counties represent an area invaded while the statistics here presented were being gathered together. It must be kept in mind that these maps, except some of the circles representing human deaths, are based on the results of laboratory examinations and not merely upon the interpretation of symptoms.

RESULTS OF LABORATORY EXAMINATIONS.

At the Hygienic Laboratory of the State Board of Health, in the year beginning April 1, 1911, and ending March 31, 1912, the heads or brains of 122 animals were received for examination. Five of the heads were in an advanced stage of decomposition and could not be examined. Sixteen gave negative results. Of the remaining 101 giving positive findings, 87 showed Negri bodies in the hippocampus or in other parts of the brain, and 14 others caused typical symptoms of rabies after inoculation into rabbits or guinea-pigs. The 101 positive cases were distributed among the different animals as follows: 2 men, 94 dogs, 2 cows, 1 horse, 1 cat and 1 ground-squirrel. Sixty-four people and seventy-eight dogs were reported as having been bitten by the animals which showed evidence of rabies on examination. As an indication of the increasing prevalence of the disease it will not be out of place to mention that in the two months following the period for which the statistics have just been given 55 examinations were made with positive results in 46 cases. The rapid increase of rabies is shown by the fact that 101 positive cases were examined in twelve months before April 1, 1912, and nearly half as many, 46, in the two following that date.

The specimens giving positive results during the year ending March 31, 1912, are divided between the counties as follows: Fresno, 29; Kings, 18; Tulare, 16; San Francisco, 12; Kern, 7; Merced, 4; San Bernardino, 3; Stanislaus, 3; Riverside, 2; Madera, 2; San Joaquin, 2; Imperial, 1; Contra Costa, 1; San Mateo, 1.

The number of positive examinations increased rapidly during the winter, which is our cool and wet season. This is sufficient answer to the very general superstition that the disease is caused by hot weather and to the claim frequently made that inability to get water is the cause of hydrophobia in dogs. By months the positive examinations are grouped as follows: in 1911, April, 3; May, 3; June, 4; July, 3; August, 5; September, 7; October, 10; November, 9; December, 9; in 1912, January, 15; February, 18; March, 15.

Many examinations for rabies have been made in municipal and private laboratories in California. Through the kindness of those in charge the results of these examinations have been obtained for publication and have been combined with the statistics of the State Hygienic Laboratory in the table below.

TABLE 1.
Results of Laboratory Examinations for Rabies, April 1, 1911, to March 31, 1912.

Name of Laboratory	Number of Examinations	Total Number Positive	Diagnosis from Negri Bodies	Diagnosis from Inoculation	Persons Reported Bitten by Positive Animals
State Hygienic Laboratory	122	101	87	14	64
Health Dept. of San Francisco	70	49	47	2	48
Health Dept. of Los Angeles	29	18	18	0	29
Health Dept. of Long Beach	2	1	1	0	1
Letterman General Hosp., San Francisco	11	8	8	5	0
Dr. W. Ophüls, San Francisco	5	5	5	5	4
Dr. H. Zinsser, Palo Alto	3	1	1	1	0
Dr. S. P. Black, Los Angeles	18	18	18	0	29
Dr. R. A. Archibald, Oakland	21	8	8	1	0
San Francisco Veterinary College	143	46	46	0	5
	424	255	239	28	180
Subtracted because examined in more than one laboratory	5	5	5	5	0
Corrected Total	419	250	234	23	180

POSITIVE CASES BY COUNTIES.

San Francisco	119
Los Angeles	30
Fresno	30
Kings	18
Tulare	16
San Bernardino	8
Kern	7
Orange	4
Merced	4

* Read before the Sacramento Society for Medical Improvement, June 18, 1912.

Stanislaus	3
Ventura	2
Riverside	2
Madera	2
San Joaquin	2
Imperial	1
Contra Costa	1
San Mateo	1
	250

POSITIVE CASES BY ANIMALS.

Man	2
Dogs	240
Cats	3
Cows	3
Horse	1
Squirrel	1
	250

Those who claim that the disease will soon die out if unopposed will find food for thought in comparing the 250 cases of proved rabies of the year beginning April 1, 1911, with the 164 similar cases collected in my report of a year ago [2] for the seventeen months preceding. This gives a total of 414 positive cases examined in laboratories during the present epizoötic.

DIAGNOSIS BASED ON SYMPTOMS ONLY.

There can be little doubt that the laboratory examinations represent but a small fraction of the total number of cases of rabies in the state. Unless persons or valuable animals have been bitten or unless the disease is new in a region, many animals die or are killed and buried without its being considered sufficiently important to warrant the trouble and expense of removing the heads, boxing and icing them, and shipping them by express to the laboratory. Diagnoses based on clinical symptoms are not apt to be reported to the State Veterinarian or the local health authorities unless the suspected animals have come under the observation of a veterinarian or physician who realized that the officials should be notified. Replies to a circular letter to the health officers of the southern two-thirds of the state did not show any territory to be involved except the counties already shown to be infected according to the laboratory records. The cases reported as being diagnosed as rabies from clinical symptoms alone are probably duplicated in the record kindly furnished by Dr. Keane, State Veterinarian. To his office between April 1, 1911, and March 31, 1912, 285 cases of rabies were reported. Of these, 120 were based on laboratory evidence and are probably included in the statistics already given. The remaining 165 are additional cases reported by veterinarians on the basis of clinical symptoms. These 165 cases came from territory shown on the maps in Figure 1 to be infected. They are divided among the various animals as follows: dogs 142, cows 12, hogs 6, horses 3, goat 1, mule 1.

RABIES IN MAN IN CALIFORNIA.

The mortality among human beings seems very small when comparison is made with the death rate among dogs, which are the chief sufferers. Previous to April 1, 1911, five human deaths had been reported.[2] These are briefly reviewed below. The first of these preceded the summer of 1909, when the disease began to be prevalent.

1. A man, H. M. S., died with the symptoms of rabies in Pasadena on March 10, 1899, five weeks after being bitten in the face by his dog. Inoculation with brain tissue of the patient produced rabies in rabbits.[3]

2. M. E. C., a man, aged 30, died with the symptoms of rabies, in Holtville, Imperial County, on Dec. 12, 1909. He had been bitten by a cat.

3. J. S., a boy of 10 years, died with symptoms of rabies on February 21, 1910, in Los Angeles.[4] He had been bitten in the leg by a stray dog. Negri bodies were found in his brain.

4. J. B., a man of 62, died of rabies at Rivera, Los Angeles County, as a result of being bitten in the face by his own dog.

5. E. L., a girl of six years, died of rabies on Dec. 2, 1910, in Los Angeles, seventeen days after being bitten in the lip and nose by a stray dog. Intensive Pasteur treatment was begun, but the unusually short incubation period did not permit its completion and therefore it did not have time to produce the immunity needed for protection. Negri bodies were demonstrated in the head of the dog and later in the brain of the girl. Inoculation with brain tissue of the girl produced rabies in a rabbit.[5] This case was described in greater detail in my previous article on rabies in California.[2]

During the year for which the laboratory statistics are being given, April 1, 1911, to March 31, 1912, there have been six human deaths from rabies, bringing the total of reported cases up to eleven. That there were not more fatalities can only be accounted for by the large number of persons who availed themselves of the Pasteur treatment for the prevention of rabies. The remaining six cases are given below.

6. A girl of three years, M. L. C., developed the symptoms of hydrophobia (rabies) and died on June 27, 1911, near Tulare, Tulare County. The typical symptoms, including the spasms of the throat on attempting to swallow, were present and left no doubt as to the diagnosis. The source of the infection was not ascertained although careful inquiry was made by the attending physician, Dr. John B. Rosson, to whom we are indebted for our information.

7. A boy, aged 15, C. V. B., died of hydrophobia on August 27, 1911, in Los Angeles. From the report [6] of this case published by Dr. W. V. Chalmers Francis, attending physician, and from information kindly furnished by him through correspondence, the following facts have been briefly gathered together:

About nine months before the boy's death his pet dog, as well as several other dogs in the neighborhood, had been bitten by a strange dog. One or two of the animals which had been bitten were later killed on the suspicion of having rabies. The boy's dog developed an acute illness, supposed at the time to be poisoning, and died five to seven

days after the first symptoms. Among the symptoms of the dog were rapid breathing, salivation and weakness of the hind legs. The boy took entire care of the sick animal. Whether the boy was actually bitten is not clearly remembered, but one of the boys in the family was bitten by the dog at about this time, and the boy who died had open wounds on his hands when he was caring for the animal. The boy was a strong healthy youth who attended school during the day and acted as life-saver and swimming expert at one of the public baths in the evening.

On August 22, he began to feel feverish. The next day he took to his bed and complained of stiffness in his legs. He had no appetite. The following night he was unable to sleep. On the third day, August 24, he disliked to drink on account of trouble with his throat. He dressed himself and walked stiffly. The following day he became much excited and easily angered. His flushed face wore an expression of fear and anxiety. He complained of slight pains in throat, chest, and abdomen and of difficulty in swallowing. He could not sleep. He answered questions rather clearly, but contradicted himself frequently. Occasionally he had outbursts of passion followed by expressions of regret and apology. He had fear that he would be forced to drink and he exclaimed that he would not drink because it choked him. Drafts of air precipitated spasms of the face so painful that when the door was opened, the patient screamed in terror.

Other prominent symptoms were loss of power in the legs, loss of the patellar reflex, irregular breathing, irregular and rapid heart action and elevation of temperature to 102° F. Sometimes the patient would not breathe during a period as long as forty seconds. During the remaining two days of life the patient had frequent convulsions and fits of anger. There were noisy delirium, delusions, hallucinations, and unreasoning fear. At times he became rational and complained of burning in his throat, but he would refuse angrily to try to drink. Toward the end he developed emphysema of his face, neck and chest. He died on the 27th of August, the sixth day of his illness.

An examination of his brain performed by Dr. Stanley P. Black, revealed the presence of Negri bodies, and confirmed the diagnosis based on symptoms.

8. A man of 30 years, W. L. L., died of rabies on September 1, 1911, in Los Angeles. We are indebted to his attending physician, Dr. H. A. Johnston of Anaheim, and to Dr. Anders Peterson of the Los Angeles County Hospital for the following information: On June 15, 1911, the man was bitten on the hand by his own pet dog. There were about four small deep wounds. These were cauterized with nitric acid. A veterinarian who examined the dog stated that he suspected rabies and advised observation of the animal. The owner killed the dog against this advice, thus destroying further evidence, and refused to take antirabic treatment.

On August 30, 1911, 59 days after he was bitten, the man began to feel sick and tired and to yawn frequently. The following night severe symptoms began. He was taken to the Los Angeles County Hospital on August 31. When he arrived, he was semi-conscious and the spasms in his throat were so severe that he could not swallow or speak. He died on September 1, the third day of his illness.

9. A boy six years old, C. W. B., died of hydrophobia on February 15, 1912, in Santa Maria, Santa Barbara County. Dr. R. W. Brown of that city is to be thanked for furnishing us the important facts in the case.

On January 12, 1912, this little boy was playing in the road in the country near Santa Maria when a small black dog attacked him and bit him in the face and on the hand. The dog then went on its way and was not seen again. Four hours later the wounds were cauterized. On February 14th, one month after the biting, the boy was visited by Dr. Brown, who found his patient on the bed with an expression of extreme terror on his face. For four or five days the child had not been himself, being at first peevish and disinclined to play and later having spells of choking and of "seeing things" on the wall. During the doctor's visit the boy complained of thirst and asked for water, but, when given as little as a teaspoonful, he fell backward suffering agony from the spasm in his throat, and swallowing was impossible. Early the following morning the little fellow died.

10 A man of 21 years, F. A., died of hydrophobia on March 9, 1912, in San Francisco. Through the courtesy of Dr. F. R. Dray, attending physician, the following facts have been learned regarding this case. The young man was the owner of four dogs. One of these was bitten by a dog supposed to be "mad." The dog which was bitten developed rabies and bit one or more of the other three before it died. All four of the animals finally succumbed to the disease. While attempting to give the last of his dogs castor oil, the owner was bitten in the right thumb near the nail. This occurred on February 3, 1912, before the outbreak of rabies in San Francisco had received sufficient publicity to be generally recognized. The young man contented himself with cauterizing the wound with phenol two days after it had been inflicted.

On March 2, four weeks after the bite, he began to have pain in the right arm. Two days later he became very nervous and troubled and consulted a physician. He was unable to swallow some pills intended to quiet him. On the same day he was sent to the German Hospital. On admission he was unable to swallow liquids except with greatest difficulty. During the following night he was rational, but after that he had frequent periods of intense excitement, delirium, and convulsive twitching. He had hallucinations leading him to believe that there were various animals in his bed, and his face bore a peculiar drawn expression resembling a smile. Noises or contact precipitated attacks of twitching and rigidity of his muscles. There were no true convulsions. There was moderate fever. As he was unable to swallow,

nourishment was maintained by rectal feeding. I was invited to visit the patient on March 8th. The disease was far advanced and death was evidently not far away. The patient's face wore a markedly drawn and worried, or frightened expression and his open mouth was filled with foamy saliva. There was moderate cyanosis and the breathing was heavy. He was unable to articulate. The extremities were very weak and somewhat rigid. The patient died early on the morning of March 9th, eight days after he began to feel pain in his shoulder and six days after symptoms of nervousness began.

A post-mortem was performed and parts of the brain were sent to several laboratories for diagnosis. The results were uniformly positive for rabies. At the State Hygienic Laboratory, Negri bodies were demonstrated in the hippocampus. A rabbit and a guinea-pig were inoculated and both developed rabies. The guinea-pig showed symptoms of furious rabies for five days.

11. A man of 63 years, J. M., died of rabies on March 21, 1912, in San Francisco. On February 25th this man was bitten deeply in the left wrist and more superficially in the left foot by a dog on the streets of San Francisco. The wounds were cauterized half an hour afterward. The brain of the dog inflicting the wounds was examined at the laboratory of the San Francisco Health Department and was found to contain Negri bodies. After a delay of five days the patient came to the Laboratory of the Health Department on March 1, and was put under the Pasteur treatment with virus distributed through the State Hygienic Laboratory. On the 17th day of treatment, four days before the treatment would have been finished, the patient complained of pain in his arms and chest, but especially in his left shoulder. The location of the pain was probably due to the fact that the more serious wounds had been inflicted in the left wrist. He also complained of a general aching. The next day he took to his bed. His chief symptoms were loss of appetite, insomnia, nervousness, and pain in his left shoulder and chest. He had a mild fever reaching a maximum temperature of 99.2° F. The next day I had the privilege of seeing the patient. The symptoms were much as already described. The patient's mind was clear and he did not seem specially apprehensive. On the evening of the following day, March 20, more characteristic symptoms developed. There was difficulty in swallowing. The next morning he had convulsions and spasms. Chloroform was given for relief. The patient finally became comatose and died at noon, March 21, 1912. A portion of the brain was examined at the State Hygienic Laboratory and Negri bodies were found in the hippocampus. Animal inoculations were impossible as the specimen had been sterilized by embalming.

We are indebted to Dr. W. H. Kellogg of the San Francisco Health Department and Dr. Paul Castelhun, attending physician, for information regarding this case.

This is the second case in California where the Pasteur treatment was begun but was unable to save the patient because the incubation period was much shorter than usual and not sufficient for the development of immunity.

COURSE OF THE DISEASE IN MAN.

The chief symptoms of rabies in human beings have most of them been depicted in the cases already described. In the majority of the people bitten by rabid animals the disease does not develop even without treatment, but all of the cases which advance to the point of showing symptoms are fatal in spite of any treatment as yet known. By taking an average of a large number of cases it has been found that about 15 per cent of untreated people, who have been bitten by rabid animals, develop the disease, while all but 1.3 per cent[7] could have been saved by treatment. These figures are based only on cases of persons receiving significant bites from animals conclusively shown to be rabid. The mortality is highest from bites which are most severe and those inflicted nearest the central nervous system or large nerve trunks and from virus of special virulence for man, as, for example, the virus received from wolf bites. The wound inflicted by a rabid animal heals or fails to heal without being noticeably affected by the presence or absence of the virus. After an incubation period varying in man from 14 days to a year, or even longer, but in the great majority of cases lying betwen thirty and seventy days, symptoms make their appearance. There may be redness, pain, numbness, or itching at the wound or near it. Nervousness, irritability, and inability to sleep may be the only symptoms for a day or two. A moderate elevation of temperature is a fairly constant symptom. These earliest symptoms are usually followed within a day or two by marked nervous excitability and sensitiveness to external stimuli. A draft of air, a touch, or a noise may cause painful local spasms of the facial or other muscles, or general muscular spasms. Moderate difficulty in swallowing is followed, as the symptoms develop, by excruciating pain due to spasms of the throat brought on in greatest severity by any attempt to drink. The dread of these spasms will sometimes lead patients to scream at the sight of a glass of water or at the suggestion of drinking. These symptoms were early interpreted as fear of water and the disease was named hydrophobia. There are hallucinations and there may be violent fits of anger and even furious mania, but intervals usually occur in which the mind is clear. The breathing becomes irregular and the heart action is rapid. Finally paralysis becomes the predominant symptom and convulsive seizures, controllable only by general anesthetics, cease, and death ends the suffering. The course of the disease is usually between three and eight days from the first symptoms. The duration of the disease is shorter in the more severe form, known as the dumb or paralytic type, where the stage of excitement is not very marked, than in the furious type of the disease.

COURSE OF THE DISEASE IN THE DOG.

In dogs, as in man, the incubation period is long, varying from 8 days to one year, but seldom exceeding six months and usually lying between 15 and 60 days. As in man, about 15 per cent of the dogs bitten by rabid animals develop the disease. The symptoms in the dog resemble those of man in being chiefly the effects of greatly increased susceptibility of the nervous system to external stimuli. The first symptoms noticed are apt to be a change in behavior. The animal may be more affectionate than usual, but he is more apt to be morose and agitated. He tends to snap and bite, probably because of hallucinations. The voice is frequently changed. Soon difficulty in swallowing appears and paralysis of the jaws and hind legs is apparent.

Dogs fairly well advanced in the disease will frequently try to drink and they succeed in wetting their dry noses and tongues, but are usually entirely unable to swallow. The water runs back out of their open mouths. The paralysis gradually spreads to the whole body and the animal dies in a few days after the first symptom, usually in 4 or 5 days, possibly in 2 to 10 days. The symptoms of rabies vary greatly, and frequently some characteristic symptoms, such as the hanging of the jaw, may be absent.

The cases of rabies in dogs are arbitrarily divided into two merging types, furious and dumb rabies. This classification only serves to indicate whether the nervous symptoms show themselves chiefly in excitement and activity or in helpless paralysis. The dumb form is as a rule the more severe and more rapidly fatal.

Fig. 2. Dogs showing symptoms of rabies.

The jaw is allowed to hang down and can be closed with difficulty, if at all. Figure 2 shows pictures of three dogs suffering from rabies.

They all show the dropping of the jaw, and some of the pictures suggest the muscular weakness, especially of the hind legs. The swollen dry tongue, the bleary eyes, and the emaciation cannot very well be made out in the pictures. The first in the series of four pictures shows a dog which came down with rabies at the Presidio of San Francisco, and I am indebted to Dr. John R. Barber for the opportunity of securing the photograph. The other three pictures were taken in Riverside and were kindly furnished by Dr. Geo. H. Tucker, Health Officer of Riverside County.

In the furious type the dog is apt to leave home and to travel long distances, running along aimlessly and attacking without warning animals or persons who may happen to be in his path. Such rabid animals usually look dirty and tired, and the beginning muscular weakness may show itself in a wavering gait. The dog may travel for many miles and for a couple of days before weakness brings it to the ground to die. Attempts to treat such dogs have resulted frequently in their biting the persons attempting to relieve their suffering.

As an example of the distances which rabid dogs

sometimes run, introducing their disease into new territory, the following case is of interest. A bull terrier left his home in San Francisco at 10 a. m. on April 21, 1912. No abnormality was noticed by his owners. The next day he killed and tore a dog and attacked a woman in Half Moon Bay, twenty-five miles or more from his home. The dog was shot and the head was sent to the State Hygienic Laboratory, where Negri bodies were demonstrated in the brain tissue.

CHARACTERISTICS OF THE DISEASE.

Rabies, or hydrophobia, is a specific infectious disease to which all warm blooded animals are susceptible. The disease can only be contracted through the introduction of virus from a previous case of rabies into a wound which enters or penetrates the skin and thus permits the infectious agent to come in contact with nerve filaments. The infectious agent, differing in this respect from other known causes of disease, spreads slowly up the nerves to the central nervous system, where it develops and produces characteristic symptoms leading in almost all cases, at least in all human cases and probably in all canine cases infected in the usual way, to death in from two to eight (or possibly ten) days.

The organism causing this disease has not been isolated, but many of its characteristics are known. It is small enough to pass through the coarser Berkefeld filters. Many consider the characteristic Negri bodies found in the brain tissue to be forms of the parasite and point to the evidence of internal structure shown by the grouping of the granules within these bodies.

The dog is the principal factor in the spread of rabies. Remlinger[8] tells us that the dog transmits the disease to man in 93% of the human cases. The virus is present in the saliva and is introduced by the teeth in biting, although it may be introduced into existing wounds. The virus may be present in the saliva for two or three days before the onset of definite symptoms, as has been shown by the experiments of Roux and Nocard.

The most virulent tissues of a rabid animal are the brain and spinal cord. The peripheral nerves and several of the glandular structures (salivary glands, pancreas, lachrymal glands, suprarenal capsules, and rarely the mammary glands) are infectious, but other parts of the body do not contain the virus. Most of the period of incubation is taken up by the traveling of the virus along the nerves to the central nervous system and, as a result, the incubation period, when inoculation has been made into the extremities, is longer than when the virus has been introduced near the brain.

METHODS OF DIAGNOSIS.

The diagnosis of rabies in man or animals can usually be based, with a small percentage of error, on clinical symptoms alone when the disease has advanced to a point where marked symptoms are shown. After death, examination of the body does not reveal any gross changes sufficiently characteristic to warrant the making of a diagnosis. There is apt to be marked rigor mortis. In dogs the stomach frequently contains foreign bodies such as grass, sticks, and stones, but this may occur in other diseases. The only conclusive post-mortem evidence is found through microscopic examination of nervous tissues. Important, chiefly as confirmatory evidence, are the multiplication of the cells of the endothelial capsule in certain of the nervous ganglia with more or less destruction of the ganglion cells. These lesions were described by Van Gehuchten and Nélis. Other changes of similar importance were described by Babès. They are the accumulations of newly formed cells around the ganglion cells in certain parts of the central nervous system.

Of far greater practical importance are certain small round or oval bodies which were discovered and described by Negri and bear his name. They are found chiefly and characteristically within the ganglion cells of the brain, but frequently are seen away from those cells. The finding of Negri bodies alone is considered by the highest authorities to be sufficient evidence on which to base the diagnosis of rabies. As a rule they are found most easily in the hippocampus but they can be discovered in other parts of the brain. The simplest way of demonstrating them, and the method used in most cases at the State Hygienic Laboratory, is to make, on glass coverslips, smears of gray matter

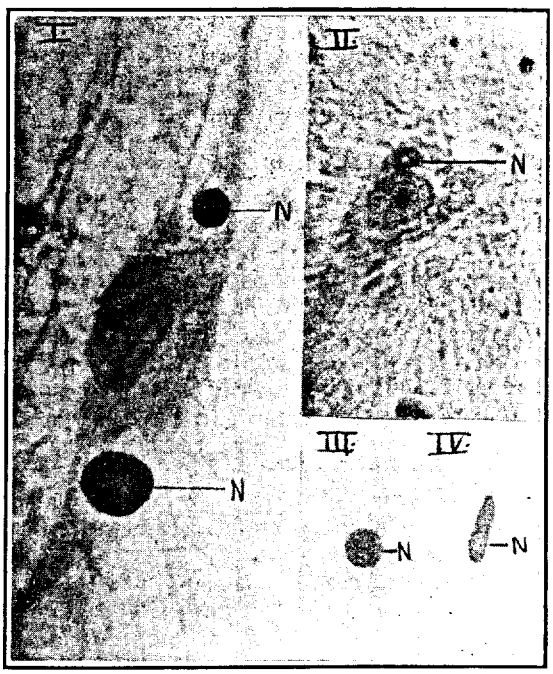

Fig. 3. Negri bodies (marked N) within ganglion cells and free. Magnification 800. Photomicrographs by Sawyer.

from the hippocampus, and to stain with methylene blue and fuchsin according to the method of Williams. The coverslips are then mounted in balsam and are carefully searched, for several hours if necessary. Figure 3 shows photomicrographs of preparations made in diagnostic work at the State Hygienic Laboratory.

In the first picture is a large ganglion cell from the hippocampus from a dog's head which was sent to the laboratory from San Francisco. In each

end of the cell is seen a large round body. These are Negri bodies and are an indication that rabies is present. As already stated, many suppose that the Negri bodies are the actual pathogenic organisms, but others consider them to be structures produced by the action of the toxin of rabies on tissue cells. The second picture is a photograph of a ganglion cell in a stained paraffin section from the hippocampus of one of the human cases which died in San Francisco. The Negri body is shown in the protoplasm close to the cell nucleus. The third and fourth pictures show free Negri bodies, one having the usual round shape and granules, which are indistinct in the picture, and the other having the more unusual oval shape.

Although Negri bodies, when found, are proof of the presence of rabies, failure to demonstrate them does not completely rule out the existence of the disease. The Negri bodies may be so few or so small, either because the animal was killed early in the disease or because of factors which we do not know, that their detection is not accomplished in several hours' search. In order to be able to make an absolute diagnosis, which in many cases is very important to persons who have been bitten or who own animals which have been bitten, it is necessary to inoculate brain tissue from the negative cases into laboratory animals, usually rabbits or guinea-pigs. The material in small quantity (0.1 to 0.2 c. c. of the suspension in physiological salt solution) can easily be injected through a small trephined opening into the space between the skull of the anesthetized animal and the brain. The animal should not be noticeably affected by this operation. If the brain tissue contains the virus of rabies, the animal will come down with the disease and exhibit symptoms in a varying length of time, usually 15 to 30 days in rabbits, although in some cases the incubation period is several months.

The laboratory examination for diagnosis is carried on at several points in California. The State Board of Health does this work at its Hygienic Laboratory in Berkeley, when the specimens are properly iced in some watertight container and are sent by express prepaid. When the head arrives in the laboratory the top of the skull is removed and the brain taken out. By dissection the hippocampus is secured and smear preparations are made as already described.

It is advisable, when animals are under suspicion of having rabies, not to kill them if they can be safely captured and confined for a period of ten days. The symptoms usually develop rapidly and are in most cases sufficiently characteristic to leave no doubt, and at least to enable a decision with regard to the advisability of Pasteur treatment for any persons bitten. A decisive diagnosis is also important so that dogs which were bitten by the suspected animal can be killed in order to prevent their developing the disease later and spreading it further. If the animal dies, the laboratory examination is apt to be more conclusive than when it is killed early in the disease.

TREATMENT OF RABIES.

When the symptoms of rabies have once made their appearance, the disease cannot be checked and treatment is of no avail except for the amelioration of suffering. The agony of the few days of intense suffering can be lessened by careful protection of the patient from noises and drafts and, in the early stages of the disease, by the administration of sedatives, but when the agonizing spasms are frequent and severe it is only humane to bring about relaxation and unconsciousness by means of ether or chloroform.

In the absence of a cure for rabies, the preventive treatment becomes very important. Cauterization of the wound has been found through long experience to diminish the chances of development of the disease, and this has been confirmed by experiment. The most practical and efficient method of cauterization is the application of concentrated nitric acid to the wound with a small stick or swab, as soon as possible after the biting. If the wounds are very large, as in the case of severe lacerations of the face, cauterization may be unwise and it may be necessary to depend on careful washing with bland sterile solutions and the intensive Pasteur treatment.

No method of cauterization saves a large enough percentage of cases to warrant the neglect of further preventive treatment. Fortunately, an efficient method of immunization was found for us by Pasteur. Soon after Pasteur began his studies on rabies he discovered that the virus was located chiefly in the central nervous system, and, after failing to grow the microörganism of rabies on artificial culture media, he conceived the idea that it could be grown in pure culture in the living animal. He therefore inoculated the brains of rabbits with brain tissue from rabid animals and kept his culture alive by transplanting it from rabbit to rabbit. The virulence for rabbits increased rapidly with these serial passages until the incubation period in rabbits became as short as six or seven days. Then no further change in virulence was apparent on further transplantation and the virus was known as fixed virus for rabbits, in contrast to the virus found in nature and called street virus. In several infectious diseases, for example, anthrax and chicken cholera, Pasteur had been able to produce immunity in animals by treating them with cultures of the infectious agent after the microörganism had been rendered less virulent by being grown on artificial media under unfavorable circumstances. Pasteur took the pure culture which he had produced for rabies, i. e., the spinal cords of rabbits which had just died of rabies, and attempted to render it less virulent in various ways, finally adopting as most practical a method of drying the cords in glass bottles over sticks of potassium hydroxide. After a cord has been dried in this way for eight days, it is no longer able to produce the disease, even in rabbits, which are specially susceptible to the fixed virus. Inoculation with such cords gives no symptoms but makes the person or animal inoculated resistant to a stronger virus, i. e., a cord which has dried a shorter time. By gradually increasing the strengths of the attenuated virus injected under the skin a considerable degree of immunity can be developed in an animal or person in from

eighteen to twenty-one days. This immunity continues to increase after treatment and as a rule reaches a high level fifteen days after the end of treatment. In order, therefore, to give the highest protection, the Pasteur treatment must be begun about thirty-six days before symptoms would develop; if that can be done, the treatment is practically certain. But as incubation periods shorter than 36 days are not very rare, the importance of losing no time between being bitten by a rabid animal and receiving treatment is apparent, although very few persons develop rabies if they have had time to finish the 21 days of treatment.

The duration of decided immunity after the Pasteur treatment probably averages about two years. Experiments on dogs have shown that 33% of them are immune after two years. Remlinger [8] concludes that persons who have taken the Pasteur treatment and are bitten more than one and one-half years later should again be immunized. He cites a case of death from rabies in a man who was bitten by a rabid dog four years after he had taken the Pasteur treatment.

Calmette has made a valuable addition to the Pasteur method. He introduced the keeping of antirabic virus in pure, sterile glycerin, thus making it possible to use fewer rabbits than before in manufacturing virus and to have nevertheless a sufficient amount on hand for emergencies. In glycerin the unground virus will remain practically unchanged in virulence for a month.

There are a number of radical modifications of the Pasteur method in use. Perhaps the most important of these is the method of Högyes who, instead of using virus attenuated by drying, dilutes fixed virus and begins treatment with extremely small doses, increasing them gradually. This method has been found to produce results almost identical with those of the classical Pasteur method. Other deviations from the usual methods differ chiefly in the way in which the cords are attenuated.

Much hope for a cure for rabies has been placed in the fact that the serum of animals immunized by the Pasteur treatment, especially when it is followed by injections of virus of full strength, has considerable power of destroying the virulence of fixed virus. Unfortunately the most potent serum yet tried has been unable to cure rabies and its best use at present is in the serum-virus mixture of Marie. He mixes fixed virus with not quite enough immune serum to neutralize it. A dose of this mixture immunizes patients more rapidly than the usual Pasteur treatment. Marie [9] has used this mixture during the first three days of the Pasteur treatment in the more severe cases under his care. In this way, he has shortened the course of treatment by five days, and has probably saved lives by hastening full immunity. Serum alone has failed to immunize or cure, and in the serum-virus method it acts probably chiefly by attenuating the fixed virus.

The Pasteur method, according to Remlinger [8] had been applied before 1907 to 131,579 cases with only 549 deaths occurring more than 15 days after the end of treatment. This indicates that the true failures were 41 hundredths of one per cent. of the total number of treatments. When it is considered that approximately fifteen per cent. of all untreated persons who are bitten by dogs known to be rabid, develop the disease, it is apparent, even when liberal allowance is made for the number of persons who take treatment without definite proof that the biting animal was rabid and also for the few persons dying during treatment or within fifteen days of the end of treatment, that many thousands of people have already been saved.

With these figures in mind, it would be surprising if any one bitten by a rabid animal failed to report for treatment. There is no question that all persons bitten far enough into the skin to draw blood should take Pasteur treatment. When the saliva of rabid animals has entered fresh wounds, treatment should be taken. If small, partially healed wounds of several days standing are wet with the virus of rabies the question of treatment is not so easily settled, for Babès and Vasilu [10] have shown by experiment that such wounds cannot be easily infected. When there is serious doubt, treatment should be advised.

PASTEUR TREATMENT IN CALIFORNIA.

The accepted methods of preventing dogs from spreading rabies, although proven by experience to be efficient, have not been applied with sufficient thoroughness to give the people of California the protection they need and should demand. As a result, it has been necessary for many persons, who have been bitten by animals which were either proved to be rabid or strongly suspected, to undergo the Pasteur treatment. The treatment usually involves an expense of about a hundred dollars, when obtained privately, and, when the patient cannot afford to pay for treatment, he is subjected to the expense of traveling to a branch of the State Hygienic Laboratory as well as the loss of time and cost of board during the three weeks of treatment. The economic loss due to rabies is therefore far in excess of the value of the cattle, horses, and dogs which die from the disease. In my previous article,[2] I collected the following statistics regarding Pasteur treatment in California from the entrance of rabies into California to March 31, 1911. One hundred and forty-one treatments were sent to California by the government and at least 20 came from other sources. Definite information was obtained regarding the administration of 125 treatments, 105 with government virus. One patient in the series died of rabies because the incubation period was so short that the treatment with government virus could not be completed. One patient showed a slight transient paralysis. With these exceptions the treatments were succcessful and free from complications.

During the period for which we are reporting in detail in this article (April 1, 1911, to March 31, 1912,) many Pasteur treatments have been given in the state. After September 1, 1911, all government virus sent to California for administration by the State Board of Health was ad-

ministered by the State Hygienic Laboratory and its branches. Therefore the statistics of the laboratory regarding Pasteur treatment begin with that date. Except for emergency purchases of parts of a few treatments, all virus used by the State Hygienic Laboratory came from the government. The chief facts regarding Pasteur treatments at the State Hygienic Laboratory during the year under consideration are given below.

TABLE 2.
PASTEUR TREATMENTS BY THE STATE HYGIENIC LABORATORY.
Sept. 1, 1911, to March 31, 1912.

Where and by Whom Administered	No. of Cases	Treatments Completed	Deaths	Diagnosis in Biting Animals Based on: Negri Bodies or Inoculation	Observed Symptoms	Suspicious History
Southern Branch, Los Angeles	5	4	0	5	0	0
San Joaquin Valley Branch, Fresno	6	6	0	6	0	0
City Health Dep't, San Francisco	22	16	1	18	1	3
City Health Dep't, Los Angeles	2	1	0	2	0	0
Letterman Gen'l Hosp., Presidio, S. F.	4	4	0	3	0	1
Total	39	31	1	34	1	4

The 39 cases came for treatment from the several counties as follows: San Francisco, 26; Los Angeles, 5; Tulare, 2; Fresno, 2; Orange, 1; Kern, 1; Ventura, 1; and Merced, 1.

The infection came from the bites of dogs in 35 instances, and in two cases from the bites of cats. The two remaining cases were inoculated with virus from a human case. In one instance the nurse attending this case of rabies accidentally injured his thumb while it was covered with the patient's saliva, and in the other instance the inoculation happened through an accident in one of the laboratories which examined the patient's brain after death. The one fatal case developed symptoms before the treatment was completed. There were no complications in any of the cases, except an abscess at the site of inoculation in one instance. This was not serious beyond the temporary inconvenience. A certain amount of local reaction usually occurs at some time during the treatment and most of it is probably due to anaphylaxis. In our experience this reaction has been most marked between the 7th and 11th days of treatment. There may be malaise and slight elevation of temperature for a day or two when the local redness and soreness is at its height.

The time between the infliction of the bite and the beginning of treatment averaged 7.1 days. The longest delay was 21 days and the shortest, one day.

The following table shows all cases for which full statistics could be obtained and which were treated in California between April 1, 1911, and March 31, 1912. The facts were kindly furnished by the physicians administering the treatment.

TABLE 3.
PASTEUR TREATMENTS ADMINISTERED IN LABORATORIES IN CALIFORNIA,
April 1, 1911, to March 31, 1912.

Where and by Whom Administered	No. of Cases	Treatments Completed	Deaths	Diagnosis in Biting Animals Based on: Negri Bodies or Inoculation	Observed Symptoms	Suspicious History
State Hygienic Laboratory of California State Board of Health.	39	31	1	34	1	4
Dr. S. P. Black,* Los Angeles	58	56	0	43	13	2
Dr. W. W. Cross,* Fresno	22	22	0	22	0	0
City Health Dep't,* San Francisco	4	2	0	3	0	1
Total	123	111	1	102	14	7

* Treatments additional to those officially administered with government virus for the State Hygienic Laboratory.

The 123 patients came from the various counties of California as follows: Los Angeles, 40; San Francisco, 30; Fresno, 23; Tulare, 10; Orange, 5; Kern, 5; Ventura, 3; San Bernardino, 2; Riverside, 2; Merced, 1; Kings, 1; Santa Barbara, 1.

The infection came from the various animals as follows: dogs, 112; horses, 4; man (not from biting), 4; cats, 2; and ground-squirrel, 1.

The longest delay before beginning treatment was 70 days and the next in length was 49 days. Excluding these two extreme figures the length of time betwen the biting and the beginning of treatment ranged from 1 to 29 days and averaged 6.6 days.

Between April 1, 1911, and March 31, 1912, the United States Hygienic Laboratory sent to California virus for 99 treatments. This virus was probably all used for patients included in the statistics just given. During the same period, three commercial houses, to whom I am indebted for these figures, distributed virus in California for 63 cases. Of these at least 54 are not included in the statistics already given. The 54 cases treated were situated in the following counties: San Francisco, 26; Los Angeles, 11; Fresno, 7; Tulare, 2; Orange, 2; Modesto, 2; San Joaquin, 1; Stanislaus, 1; Imperial, 1; Kern, 1.

Adding together the 123 treatments given in the last table and the 54 treatments sent out by commercial houses, we find that 177 patients were treated in the year ending March 31, 1912. Previous to that year at least 125 treatments were administered as already stated. This gives a total of 302 treatments in California since March 13, 1910, when, as far as I have been able to ascertain, antirabic treatment was first administered in California. Of the 302 persons treated, two developed rabies before the treatment was completed, giving a mortality of 66 hundredths of one per cent. No deaths occurred among those completing treatments.

CHART
SHOWING THE SPREAD OF
RABIES IN CALIFORNIA
BY COUNTIES
EXISTENCE OF RABIES PROVED BY STATE HYGIENIC LABORATORY.
ADDITIONAL COUNTIES, RABIES PROVED BY OTHER LABORATORIES.
NEW AREA, APRIL 1, TO MAY 31, 1912 PROVED BY STATE HYGIENIC LABORATORY.
HUMAN DEATHS FROM RABIES.
NOV. 2, 1909, TO DEC. 31, 1910
JAN. 1, 1911, TO AUG. 31, 1911.
SEPT. 1, 1911, TO MAR. 31, 1912.
DEL NORTE
SISKIYOU
MODOC
HUMBOLDT
TRINITY
SHASTA
LASSEN
TEHAMA
PLUMAS
MENDOCINO
GLENN
BUTTE
SIERRA
COLUSA
SUTTER
YUBA
NEVADA
LAKE
YOLO
PLACER
EL DORADO
SONOMA
NAPA
SOLANO
AMADOR
CALAVERAS
SAN FRANCISCO
TUOLUMNE
MONO
STANISLAUS
MARIPOSA
MERCED
MADERA
FRESNO
INYO
SAN MATEO
SANTA CLARA
SAN BENITO
MONTEREY
TULARE
KINGS
SAN LUIS OBISPO
KERN
SANTA BARBARA
VENTURA
LOS ANGELES
SAN BERNARDINO
ORANGE
RIVERSIDE
SAN DIEGO
IMPERIAL

As an indication of the increasing need for Pasteur treatment it is of interest that during the two months (April and May, 1912,) immediately following the period for which statistics have been collected, the State Hygienic Laboratory treated 66 cases in the several laboratories where antirabic treatments are administered for the State Board of Health.

THE PASTEUR INSTITUTE.

The large number of Pasteur treatments needed in California by the State Board of Health for administration to people who are financially unable to secure the treatment from their physicians, and the disadvantages of depending for virus on a source so far away as the government laboratory in Washington, D. C., led the State Board of Health to pass a resolution on May 18, 1912, authorizing the State Hygienic Laboratory to manufacture antirabic virus. On June 3, 1912, Dr. Donald H. Currie of the United States Public Health and Marine-Hospital Service inspected the Pasteur Institute, which had been established as a department of the State Hygienic Laboratory, and approved of the equipment and methods in use. Since that date all virus used by the laboratory has been of its own manufacture.

The virus is produced by inoculating anesthetized rabbits intracranially with fixed virus, chloroforming them when paralysis is almost complete and removing their spinal cords by pushing them out of the canal in accordance with the method of Oshida.[11] The cords are hung from silk threads over sticks of potassium hydroxide in Pasteur drying bottles and are kept in a dark cabinet. The temperature in the cabinet is maintained at 20° C. by an electric regulator. As the cords are cut day by day, the segments are immediately placed in glycerin and are stored in an ice chest until needed for administration or shipment to one of the branches. The virus is discarded if unused at the end of three weeks.

The treatments are administered at the State Hygienic Laboratory in Berkeley, at its Northern Branch in Sacramento, at its San Joaquin Valley Branch in Fresno, at its Southern Branch in Los Angeles, and also by deputized bacteriologists in the City Health Departments of San Francisco, Sacramento, and Los Angeles, and in the Letterman General Hospital at the Presidio of San Francisco. In order to receive free antirabic treatment from the State Board of Health, it is necessary to make application to the local health officer. He will apply by telegraph to the Secretary of the State Board of Health, vouching for the suitability of the case, financially and otherwise, for free antirabic treatment. If the Secretary approves, he will give instructions as to the branch laboratory to which the patient is to be sent.

METHOD OF SPREAD OF RABIES.

Rabies in California is harbored and carried chiefly by domestic dogs, but it is possible that wild animals will take a greater and greater part as the disease becomes thoroughly established. Coyotes are under heavy suspicion and there is strong testimony that the disease in California has been conveyed in a few instances by these animals, but laboratory proof is still lacking. The skunk, known to carry the disease in Arizona, has not been convicted in California. The only wild animals of California so far definitely proved to carry rabies are a ground-squirrel, which bit a girl in San Bernardino County, and a large gray fox which was killed in the mountains of Ventura County about the middle of April, 1912. This fox entered the tent where several campers were sleeping and ran over the bed, pulling the covers. The animal bit a man, who tried to push him away, and then escaped, but the next night the animal returned and was killed. The fox's head was examined in Los Angeles and showed many large characteristic Negri bodies. Dr. R. B. Durfee was good enough to send me the story of this case. Coyotes seem to have played a larger part in the spread of rabies in Oregon than in California. Dr. Calvin S. White, State Health Officer of Oregon, informs me that between April 1, 1911, and June 10, 1912, the thirteen animals whose brains were examined and found to contain Negri bodies were classified by kinds as follows: Five coyotes, five horses, two pigs, and one dog.

The rapid distribution of rabies by rabid dogs who run for long distances has already been illustrated. Much more rapid is the conveyance of the disease through the transportation of dogs during the incubation period over the railroads or in automobiles. Two recent examples of this method are striking and will be cited.

On May 7, 1912, a bull dog went mad in Berkeley and bit four children and a woman and was finally shot on the street in Oakland by a policeman. Three of the children were bitten in the face. Examination of the animal's brain at the State Hygienic Laboratory revealed Negri bodies. The dog's license tag made it possible to find the owners, from whom it was learned that the animal had been brought by train six weeks before, from Fresno, a heavily infected region, to Berkeley, which had previously been free from rabies.

On April 1, 1912, a San Francisco dog, which was known to have played with a dog proved rabid at the city laboratory, was taken approximately 300 miles to Likely in Modoc County by his owner, who was later joined by a brother. On May 7th, the dog began to show symptoms of rabies, and the next day he bit both men. The dog's head was sent to the University of Nevada where Negri bodies were found in the brain and rabies was produced by inoculating some of the brain tissue into an animal.

The stories of these two dogs show how rabies can jump over long distances and start outbreaks in new territory. When once established in a region containing many dogs, the disease spreads rapidly from animal to animal.

CONTROL OF RABIES.

In order to protect dogs, cattle and people from rabies several precautions should be taken. The roaming dog population should be diminished as

much as possible and every dog at large should be muzzled with a well fitted metal muzzle which projects beyond the end of the dog's nose and absolutely prevents biting. If the disease is thoroughly under control within a certain area, quarantine against dogs from infected areas should be considered. It has been proved possible to keep rabies out of isolated countries, such as Great Britain and Australia, by a six months' quarantine on all dogs.

Rabies is a disease very easily held in check by simple measures directed toward the control of the chief reservoir and distributing agent of the disease, the domestic dog. It is therefore a disgrace for any community to permit rabies to become prevalent within its boundaries.

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